COLLEGE OF FAMILY PHYSICIANS SINGAPORE

The SINGAPORE FAMILY PHYSICIAN

UPDATE IN NEUROLOGY

- Human Prion Diseases
- Numbness
- Tremor
- Parkinson's Disease
- Cerebrovascular Accidents
- Migraine
- Diabetic Neuropathy
- Motor Neurone Disease

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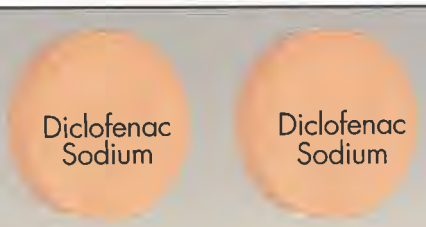

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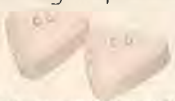

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NEUROLOGY IN FAMILY PRACTICE

"Medicine is not only a science, but also the art of letting our own individuality interact with the individuality of the patient." ***Dr Albert Schweitzer***

Neurology in family medicine is the most intriguing, yet fascinating aspect of family practice. The scope of neurology in family practice ranges from the daily complaints of headaches, giddiness and numbness, to the more complicated problems of peripheral nerve syndromes, motor neurones diseases, and the intracranial pathologies leading to tremors, seizures, dementias and neurovascular conditions.

While many conditions in neurology require secondary and tertiary care, the minor but more intriguing symptoms offer the family physicians the challenges of the basic neurological workout through the time-tested method of a thorough medical history and systematic clinical examination. Simple laboratory and radiological investigations offer further insights into the intrinsic pathology of the disease, but for the intracranial problems, the ultimate procedure that often lead the physician to the diagnosis lie in the CT scan and the MRI's.

With this in mind, this month's issue offers the reader a sampling of the subject by discussing a range of topics that spans the scope of neurology in family practice. The basic problem of "Numbness" that confronts the family physicians daily in his practice is best discussed by our unique pair of authors, a consultant neurologist and his family physician son, Drs S C Loong and T W Loong.

The complicated "Motor Neuron Diseases" that offers the challenge of the diagnostic workout is only possible if the physician is familiar with the various pathologies and this is discussed by Dr Pavanni, consultant neurologist at SGH.

Two common conditions that extend the two ends of the scale of neurology are included in the form of updates, "Cerebrovascular Accidents" by Dr M C Wong, head and senior consultant neurologist at SGH, and "Migraine" by Dr K F Tang, a consultant neurologist in private practice.

"Diabetic Neuropathy" encompasses the composite picture of a multipathological condition with predominant neurological symptoms and is precisely presented by Dr H S Lim, senior consultant and head of the Diabetic Centre at SGH.

I had lined up two current topics that were both discussed in Parliament, the controversial "Bovine Spongiform Encephalopathy" (mad-cow disease) with its human counterpart, the "Cruetzfeldt-Jakob Disease" by Dr B Ong, consultant neurologist at NUH, and "Dyslexia"; the latter unfortunately did not materialise.

Finally, I managed to persuade a group of neurologists to contribute their presentations on "Common Movement Disorders", which were presented at a symposium organised by the Training & Education Centre, Tan Tock Seng Hospital. These consist of a series of four short articles followed by a discussion and conclusion by the chairman of the symposium.

In conclusion, I must record my appreciation to all the authors of this issue for their tremendous response to my request for these articles, not to mention their submitting the work well on time! I am also pleased to note that one of the authors is a practising family physician.

Dr Arthur Tan Chin Lock

HUMAN PRION DISEASE:

An Update in the Light of the Bovine Spongiform Encephalopathy Epidemic

B K C Ong, MBBS, M Med (Int Med), FAMS

SUMMARY

Human prion diseases may present as sporadic, inherited and transmissible neurodegenerative disorders. Reasonably well characterised clinical phenotypes include Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker disease (GSS), kuru and fatal familial insomnia (FFI). The transmissible agent in these disorders is unique, in that it is probably devoid of nucleic acid content, does not invoke an inflammatory response in the brain and is a protease resistant abnormal isoform of a protein normally expressed in the brain; a prion or proteinaceous infectious particle. Of these, CJD is the commonest and has been described throughout the world largely in its sporadic form. This disease generally manifests as a rapidly progressive dementing illness associated with ataxia, multifocal myoclonus and typical periodic triphasic slow sharp wave complexes on electroencephalogram. Iatrogenic human to human transmission has been reported, but the current concern is whether cross species transmission can occur from the food chain in the light of the British epidemic of bovine spongiform encephalopathy (BSE).

Keywords: *Prion diseases, prions, spongiform encephalopathies, Creutzfeldt-Jakob disease, bovine spongiform encephalopathy*

INTRODUCTION

The prion diseases have seen an explosion of knowledge in the understanding of both pathogenesis and aetiology. Prions appear to affect both humans and animals, and are unique in that they can be sporadic, inherited and transmissible. The infectious agent also has unique properties and probably lacks nucleic acid[1]. Hence, the old practice of referring to this group of disorders as 'slow virus diseases' is inaccurate and outdated. This brief article will attempt to outline the principal advances in our understanding of prion diseases and the infectivity of prions.

Associate Professor & Consultant Neurologist
Department of Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 119074

CREUTZFELDT-JAKOB DISEASE

This can occur in sporadic, iatrogenic and familial forms. The sporadic form is the commonest of human prion diseases, accounting for >80% of cases. Creutzfeldt-Jakob disease (CJD) generally occurs at a mean age of 60 years, with an age range of 16 to 82 years. Males and females are equally affected and the occurrence is worldwide, with an annual incidence of about 1 per million population. Affected patients can have prodromal symptoms that include fatigue, depression, weight loss, sleep disorders and poor appetite lasting several weeks. Subsequently, the patient develops a progressive dementia over weeks to months, marked by behavioural, emotional and intellectual decline. In almost all patients,

myoclonus develops and later becomes generalised. Some cases develop cerebellar signs and visual disturbances at the outset of the disease. The electroencephalogram (EEG) typically shows slow sharp wave periodic complexes but may only reveal non-specific diffuse slowing. The blood and cerebrospinal fluid are normal and imaging is usually unhelpful, although a recent report suggests that MRI may reveal altered signal areas in the basal ganglia[2]. CJD is almost invariably fatal, usually within a year of onset, and no treatment is available at present.

Familial CJD is most commonly linked to two point mutations at PRNP (human prion protein gene) codon 178[3] and 200[4]. The former mutation results in a CJD phenotype that has a more protracted clinical course. Even mutation at codon 200 has produced some atypical clinical features in affected patients. Iatrogenic CJD will be further discussed below.

OTHER HUMAN PRION DISEASES

Kuru, the Gerstmann-Straussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI) are three other well characterised human prion diseases. GSS was first observed in a large family in Austria in 1936 but has subsequently been described in Japan and the United States. Patients generally present between 30 to 60 years of age with progressive cerebellar signs with the later development of parkinsonism and pyramidal release. Dementia is a late feature and the condition tends to progress over 2 to 10 years with typical massive multiform ('kuru') plaques mainly in the cerebellum[5]. GSS is usually familial with mutation at codon 105[6] of the PRNP gene most often described. Sporadic GSS does occur.

FFI has only been relatively recently characterised, typically progressing to death over 1 to 3 years and manifesting as a sleep disorder with autonomic failure, myoclonus, ataxia and late dementia[7]. Here the neuropathology is confined to the thalamus which is atrophied. All patients with FFI have a mutation at codon 178 of the PrP gene with substitution of asparagine for aspartic acid. FFI has not, to date, been successfully transmitted to animals as of yet. Kuru will be discussed in more detail below.

THE PRION PROTEIN AND INFECTIVITY

It may surprise the uninitiated that cellular prion protein (PrP^C) is a plasma membrane glycoprotein that is highly expressed in neurons and encoded in humans by a gene located in chromosome 20[8]. The function of this normal PrP^C remains unclear at present, but there are experimental clues that it is necessary for normal synaptic function[9]. Pathogenic prion protein, or Prp^{Sc}, is an abnormal isoform of PrP^C and arises from conversion from the latter by a conformational change[10], in the process becoming infective. This could occur spontaneously in the sporadic prion diseases, be induced by exogenous PrP^{Sc} in the transmitted forms, or result from a mutation in the gene for PrP^C in the familial forms. PrP^C, therefore, plays a pivotal role in prion replication, and involves a PrP^C-Prp^{Sc} interaction. Many lines of evidence suggest that PrP^{Sc} is the infective agent and that somehow, the abnormal conformation of this agent determines infectivity[10,11]. Such 'infectivity' challenges traditional notions that infective agents require nucleic acid to replicate but it is important to realise that some controversy persists as there are unanswered questions with regard to distinct 'strains' (diversity) and that PrP^{Sc} does not co-distribute with the infectivity. Additionally, the mechanism of Prp^C to PrP^{Sc} conversion remains unexplained, as does the mode by which PrP^{Sc} targets and spreads within the central nervous system when inoculated peripherally.

INFECTIVE OR TRANSMISSIBLE HUMAN PRION DISEASES

Kuru is the historical example of a transmissible prion disease and was once the commonest cause of death amongst women of the Fore people in Papua New Guinea. Affected individuals developed progressive cerebellar dysfunction and at death, usually a year after disease onset, autopsy demonstrated widespread spongiform changes with gliosis and prion protein (PrP) amyloid plaques in the cerebral hemispheres and cerebellum[12]. A veterinary pathologist noticed neuropathological similarities between scrapie and kuru[13], and transmission studies to laboratory primates were later

successfully carried out. The prevailing theory is that kuru likely originated as sporadic CJD in a tribe member and ritualistic cannibalism subsequently transmitted it to other members. Creutzfeldt-Jakob disease was also transmitted to laboratory primates in 1968[14], followed by GSS in the 1970s[15]. It is noteworthy, however, that the ease of transmission to laboratory primates varies considerably, being easiest with sporadic CJD.

Besides being the essential infective agent, PrP^{Sc} appears directly responsible for the pathology seen in the CNS of affected animals as it accumulates in neurons. This accumulation precedes neuronal vacuolation and astrocyte gliosis, and the formation of amyloid plaques[10].

What chiefly concerns us, though, is the risk of iatrogenic transmission of CJD in humans. Accidental transmission has been documented from corneal transplantation (initial report in 1974)[16], contaminated electroencephalogram needles[17], dura mater grafts[18], pericardium grafts and apparently contaminated surgical instruments[19]. Animal corneas have significant levels of PrP, making infection from corneal transplants plausible. Additionally, the spectre of transmission of CJD from human growth hormone (HGH) preparations was raised when some of these HGH recipients developed a progressive cerebellar syndrome with later dementia and/or myoclonus[20]. As about 10,000 human pituitaries are required to produce a single HGH preparation, and sporadic CJD occurs in 1 to 2 per million population per annum, it is not inconceivable that prion contamination can occur. It is known that degenerative changes include the hypothalamus and pituitaries of sheep infected with scrapie, and there is little reason to doubt that there would be prions in human pituitaries as well. In fact, CJD has even been reported in women who received human pituitary gonadotrophins[21]. The issue of exposure also concerns health care workers. At least thirty cases of CJD have been reported in health care workers[22] although no clear pattern of infection is evident and the link to exposure to infective cases is not a strong one.

BOVINE SPONGIFORM ENCEPHALOPATHY (BSE) AND THE RISK OF HUMAN INFECTION

Veterinarians in Britain first noticed signs of a neurological disorder in cattle in 1985 and BSE was subsequently characterised in 1986. Since then, an epidemic has occurred in British herds and this was traced to contaminated animal feed made from sheep parts which included brain and nervous tissue[23]. Scrapie-infected brain was somehow not excluded from the raw material and the sequence homology between sheep and bovine PrP (differing at only 7 positions) allowed cross-species spread[24]. In fact, this species barrier is an important factor and made transmission of scrapie from sheep to rodents very difficult. Human and bovine PrP differ at more than 30 positions and, theoretically at least, the likelihood of transmission of BSE to humans would seem remote. No epidemiological studies have as yet linked CJD occurrence to scrapie in sheep farming communities.

Nevertheless, there have been reports of farmers developing CJD who had herds with BSE affected cattle. The overall incidence of CJD has also risen in Britain in the 1990s although this is due largely to an increase in cases over 75 years of age and improved case ascertainment in the elderly secondary to publicity about BSE[25]. Additionally, at least 10 cases of variant CJD have been reported in the United Kingdom since 1990[26]. These cases were felt to be unusual because of the young onset (19 to 41 years), the clinical findings with early neuropsychiatric features and ataxia, and the absence of typical EEG features usually seen in CJD. This contrasted with 185 other sporadic cases reported since May 1990, which had a mean age of 65 years at disease onset. Neuropathologically, these variant CJD cases also showed unusual kuru type plaques not seen in 175 other sporadic CJD brains studied. However, the exposure histories were unhelpful, although nine reported having eaten beef products, none had eaten brain and one was a strict vegetarian since 1991.

Taken as a whole, no definite link has yet been found that links the epidemic of BSE to increased occurrence of CJD in humans. Given the long incubation period and the recent report of variant young onset CJD, however, lingering doubts about the safety of beef products remain.

It would be wise to avoid consuming products that are made of brain or nervous tissue of bovine origin until the issue is clarified.

CONCLUSION

The human prion diseases present as neurodegenerative disorders that can be sporadic, familial or transmissible. The culprit agent appears to be PrP^{Sc} which seems to cause neurological damage by in some way inducing a conformational change in native PrP^{C} that becomes self-replicating. PrP^{Sc} can arise from chance mutation of the PRNP gene or can be inherited. Most significantly, PrP^{Sc} is potentially 'infective' and iatrogenic human disease is well described. Given the fact that destruction of prions is difficult, stringent sterilization precautions should be maintained with surgical instruments. Brain and ocular material from patients with CJD should be considered highly infectious and should be contained or incinerated and these patients should not be considered as organ or tissue donors[27]. The issue of transmission via the human food chain remains unresolved and unproven to date.

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NUMBNESS: A PRACTICAL APPROACH

*S C Loong, MBBS, FRACP
**T W Loong, MBChB, M Med (FM)

SUMMARY

Numbness is a common presenting complaint. Vague psychosomatic symptoms are sometimes described by the patient as "numbness". However, true numbness always points to some disturbances of the sensory system. Methods of sensory testing are described. Patterns of numbness and their most common causes are then discussed.

Keywords: *numbness, paraesthesia, dysaesthesia, sensory testing, sensory nervous system*

INTRODUCTION

Numbness, like pain, is a common symptom. However, unlike pain which may arise from a disease of the cardiovascular, gastrointestinal, renal or other systems, numbness points specifically to a disturbance of the sensory pathways of the nervous system.

ANATOMY OF THE SENSORY NERVOUS SYSTEM

Although we talk of nerve supply *to* a particular part of the body, sensory nerve impulses really travel in the opposite direction, from sensory receptors towards the CNS.

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If the receptor is on the limbs or trunk, nerve impulses follow this route:

receptor → peripheral nerve → dorsal root → sensory tract in spinal cord → thalamic nuclei → sensory cortex.

If the receptor is in the face:

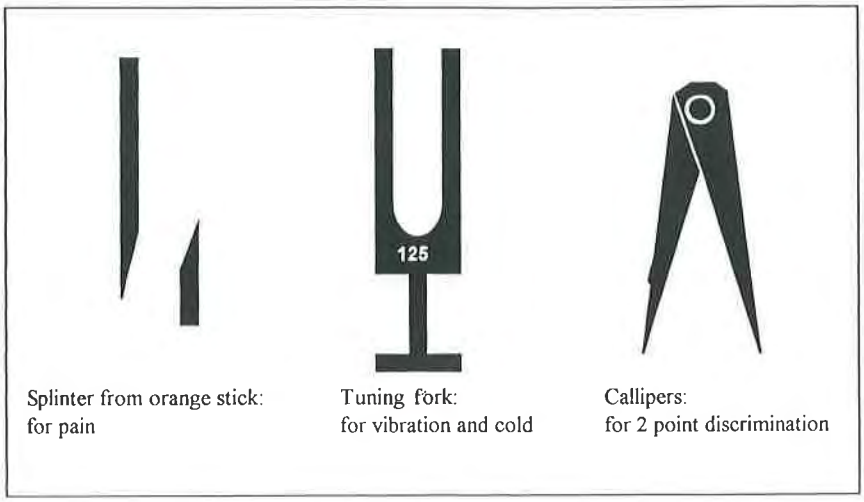
receptor → cranial nerve (trigeminal) → sensory nuclei in brain stem → thalamic nuclei → sensory cortex.

SENSORY TESTING

The following sensations can be tested in the clinic:

1. **Superficial sensations**: light touch (tested with cotton wool or tissue paper), pain (pin or splinter from an orange stick) and temperature (hot or cold objects – most conveniently a tuning fork kept in an air-conditioned room)
2. **Deep sensations**: position sense (passive movements of digits, Romberg's test) and vibration sense (125 Hz tuning fork).
3. **Cortical sensations**: 2-point discrimination (callipers) and stereognosis (by asking the

Figure 1: Some Equipment Used in Sensory Testing



patient to identify an object by feeling it's shape).

There are two methods of sensory testing which are extremely useful but under-utilised. These are elicitation of dysaesthesia and determination of two-point discrimination threshold.

Dysaesthesia is elicited by simply rubbing the patient's skin and asking the patient if it feels abnormal. It can be used to 'map out' areas of sensory disturbance. For example carpal tunnel syndrome causes so-called sensory 'splitting' of the ring finger as the median nerve supplies only the radial (lateral) aspect of this finger. Rubbing the sides of the digit will therefore evoke an abnormal sensation on the radial side but not the ulnar side.

Although ***two-point discrimination*** is traditionally used to assess cortical sensory function it can also be used to assess peripheral sensory impairment in the limbs. The area of skin to be tested (usually on a digit) is touched with the two points of a calliper and the patient asked if one point or two is felt – this is much easier for the patient than deciding whether that area feels more or less painful than another area. The minimum distance between calliper points at which the patient can still feel two separate sensations is the two-point discrimination threshold. Taking carpal tunnel syndrome again, the two-point threshold for the radial (lateral) side of the ring finger may be 0.4 cm compared to 0.2 cm on the ulnar side. This is significant although both thresholds are within the normal upper limit of 0.5 cm. Used in this way two-point discrimination provides a quantitative assessment of the degree of superficial sensory loss and thus can be used to monitor a patient's progress.

THE TERMINOLOGY OF SENSORY DISTURBANCE

Some neurological terms used to describe sensory disturbance may be confusing and require definition. "***Paraesthesia***" refers to any abnormal sensation which occurs spontaneously. Paraesthesia is commonly described by the patient as a feeling of numbness, pins and needles, tingling or crawling. "***Dysaesthesia***", already described above, is an abnormal sensation which is evoked by stimuli such as rubbing the skin. "***Hypesthesia***" is decreased sensitivity to stimuli (increased sensory threshold) – it may be accompanied by "***hyperpathia***", an unpleasant sensation evoked by stimulation of an hypesthetic area (hyperpathia is classically encountered in thalamic lesions). "***Hyperesthesia***", on the other hand, is increased sensitivity to stimuli (decreased sensory threshold).

A PRACTICAL APPROACH TO NUMBNESS

History Taking

This begins with clarification of the *exact nature*

of the abnormal sensation that the patient describes as "numbness". Some patients may say that a limb is "numb" when in fact it is weak. Others may use it to describe any of a variety of vague psychosomatic symptoms. The first question to ask the patient is therefore "What do you mean by 'numbness?".

Three more questions help to distinguish "true" numbness from the psychosomatic variety:

- *"Is the numbness inside or outside?"*
  Because sensory receptors giving rise to numbness are located in the skin, true paraesthesia is felt superficially ("outside") whereas most psychosomatic discomfort such as "sourness" (the "xuan" discomfort that Chinese patients may describe) and "tiredness" is felt deep in the muscle.
- *"Does the numb area feel abnormal when I rub it?"*
  True paraesthesia is almost accompanied by dysaesthesia on rubbing the "numb" area. Therefore, if the patient complains that a hand is numb and yet it feels no different from the other hand when the skin is rubbed the numbness is unlikely to be of neurological significance.
- *"Does the numbness shift from place to place?"*
  Numbness which is evanescent and shifting in location from hour to hour or day to day is almost always psychogenic.

However, numbness that is fixed in location but intermittent is not necessarily psychogenic – disease of the peripheral nerves (e.g. carpal tunnel syndrome), TIAs and sensory seizures may all cause intermittent symptoms.

The next step is to determine the distribution or pattern of numbness. This will allow us to localise the lesion and decide what the probable causes are.

Numbness in the Head

The most benign and common cause of numbness in the head is ***tension-anxiety***. This is typically intermittent and shifting and may be part of the hyperventilation syndrome.

The most sinister cause of numbness in the head is the ***"numb chin" syndrome***. This is fortunately rare and is due to involvement of the mental nerve by metastasis to the mandible. This syndrome demands a search for occult malignancy.

Facial numbness due to a ***trigeminal nerve*** lesion is not difficult to recognise. The corneal reflex will be absent when the ophthalmic division is affected. Important causes of pure trigeminal sensory neuropathy are collagen vascular disease and a space occupying lesion in the paratrigeminal region. If numbness is confined to the maxillary division, nasopharyngeal carcinoma must be excluded.

Isolated facial numbness is rarely caused by a central (thalamic or cortical) lesion.

Numbness in the Upper Limbs

The two most common causes of numbness in the upper limbs are ***carpal tunnel syndrome*** in females and ***cervical spondylotic radiculopathy*** in males.

Patients with carpal tunnel syndrome often complain of numbness in all digits of one or both hands. However, examination will reveal dysaesthesia that involves the lateral $3^1/_2$ digits only, with sensory "splitting" of the ring finger – that is, dysaesthesia on the radial (lateral) side of the ring finger but not on the ulnar side.

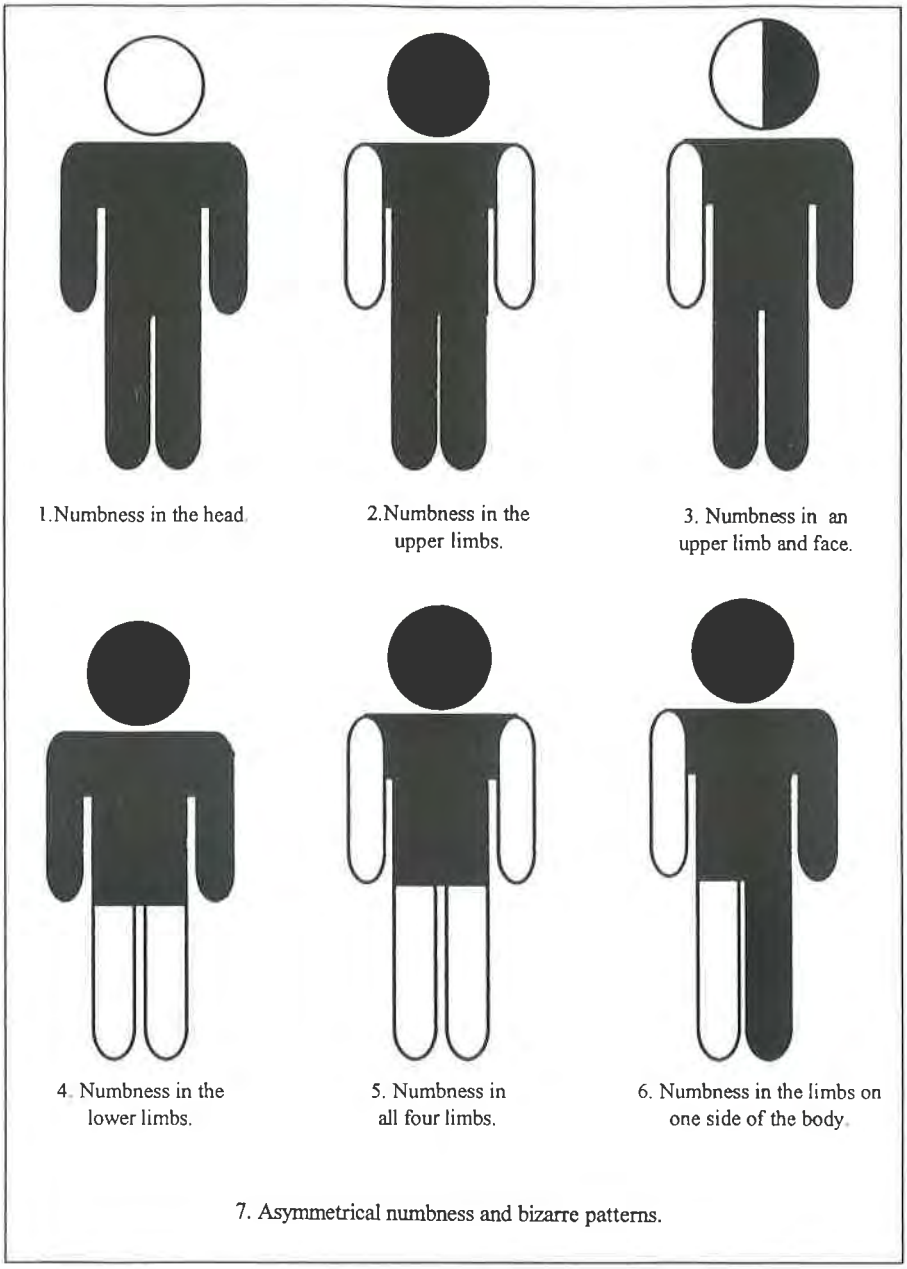
Other typical features of the numbness due to carpal tunnel syndrome include:

- its occurrence on waking up at night or in the morning.
- its occurrence with manual activities such as holding up the newspapers for reading ("morning papers sign").
- it can be "flicked away".
- it is never felt above the wrist.

Wasting of the thenar eminence is seen only in severe long standing cases. Phalen's and Tinnel's sign may be present but false positives are common.

By contrast, cervical spondylotic radiculopathy (unless accompanied by cervical myelopathy) rarely causes numbness in all the digits of a hand; the numbness is usually also felt above the

Figure 2: Patterns of Numbness



wrist – the patient often describes it as radiating down the forearm to the hand. On examination, there may also be a positive foraminal compression test and diminution of the biceps jerk if it is the C6 level or diminution of the triceps jerk if it is at the C7 level.

Numbness from an ***ulnar nerve*** lesion is confined to the medial $1^1/_2$ digits. It is usually due to nerve entrapment at the elbow. Interestingly it may not occur until several years after injury to the elbow ("tardy ulnar nerve palsy").

Numbness due to a ***radial nerve*** lesion is restricted to the snuff box area. It is commonly due to prolonged pressure on the nerve in the upper arm – for example an intoxicated patient who has lain unconscious with an arm draped

over the back of a chair ("Saturday night palsy").

Numbness in an Upper Limb and Face

Numbness of a hand and ipsilateral face (cheiro-oral) is typical of a ***cortical*** lesion. When persistent, it is usually caused by a stroke or space-occupying lesion. If transient, the causes to consider are TIAs, migraine and simple partial seizures.

Numbness in the Lower Limbs

The commonest cause of numbness in a lower limb is ***lumbrosacral spondylotic radiculopathy*** – usually L5 or S1 root. An S1 root lesion causes numbness on the sole of the foot and is almost invariably accompanied by diminution or loss of ankle jerk. An L5 root lesion causes numbness on the lateral aspect of the leg and dorsum of the foot; it will also cause weakness of ankle dorsiflexion. Ankle and knee jerks will be preserved.

A ***lateral popliteal nerve*** palsy can cause numbness rather similar in distribution to that of an L5 root lesion apart from causing weakness of ankle dorsiflexion too. The two lesions can be distinguished by the fact that internal rotation of the hip will be weak in an L5 root lesion only. Lateral popliteal nerve palsy is usually idiopathic but diabetes may be a predisposing factor.

A benign but troublesome cause of numbness on the anterolateral aspect of a thigh is ***meralgia paraesthetica*** due to entrapment of the lateral femoral cutaneous nerve as it passes under the inguinal ligament. It may be accompanied by pain. The condition usually occurs without any identifiable cause although obesity, diabetes, pregnancy or prolonged squatting may be predisposing factors. It is differentiated from an L3 root lesion causing similar numbness and pain in the thigh by the presence of a normal knee jerk and normal power in knee extension.

A rare but treatable cause of intermittent numbness in the sole of the foot is ***tarsal tunnel syndrome***. This is due to entrapment of the posterior tibial nerve in the tarsal tunnel behind the medial malleolus.

If the numbness affects both lower limbs symmetrically the likely cause is a thoracic cord, lumbar cord, or a cauda equina lesion. A cauda equina lesion will also cause "saddle anaesthesia" (numbness in the sacral area). Cervical myelopathy and polyneuropathy may initially cause numbness in the lower limbs only, but the symptoms will eventually spread and involve all four limbs.

Numbness in All Four Limbs

Symmetrical numbness in all four limbs is usually due to either a ***polyneuropathy*** or ***cervical myelopathy***. Differentiation is not difficult as polyneuropathy causes hyporeflexia in all limbs while myelopathy causes hyperreflexia.

The commonest cause of chronic polyneuropathy is diabetes while the most important cause of acute polyneuropathy is Guillain-Barre syndrome.

In cervical myelopathy two other signs may also be present:

- 'Lhermitte' sign – an 'electric' sensation radiating down the body or limbs on sudden neck flexion.
- Inverted supinator jerk – an exaggeration of finger flexion accompanied by a diminution of elbow flexion on eliciting the supinator jerk; it indicates a lesion a the C6 cord level.

Numbness of Limbs on One Side

Numbness of the upper and lower limbs on one side of the body (hemiparaesthesia) is usually due to a thalamic or brainstem lesion, and occasionally a cord lesion. If the lesion is in the thalamus (or higher), the hemiparaesthesia will be accompanied by ipsilateral facial numbness. If it is in the brainstem (medulla), there will be contralateral facial numbness. If in the cord, there will be no facial numbness and the hemiparaesthesia will invariably be part of the Brown-Sequard syndrome – this syndrome results from a hemicord lesion and consists of (i) loss of pain and temperature sense contralateral to the lesion (ii) ipsilateral loss of proprioception and (iii) ipsilateral spastic weakness.

Asymmetrical Numbness and Bizarre Patterns of Numbness

Asymmetrical limb numbness is likely to be due to multiple peripheral nerve lesions (mononeuropathy multiplex) or multiple root lesions. The common causes of mononeuropathy multiplex

are diabetes, leprosy and collagen vascular disorders.

If the distribution of numbness does not correspond to a peripheral nerve, root, tract, thalamus or cortical distribution it does not mean that it is functional. Thalamic lesions are notorious in causing 'bizarre' pattern of sensory disturbance.

LABORATORY TESTS

For numbness due to a probable peripheral nerve dysfunction, EMG (nerve conduction) is extremely useful for confirming diagnosis and determining prognosis. For numbness due to root lesions plain X-rays of the spine are usually adequate (mainly to exclude malignancy). For suspected cord lesions or intracranial lesions CT or MRI is necessary. EEG is recommended for suspected partial seizures and carotid ultrasonography for probable sensory TIAs.

CONCLUSION

With a systematic approach, a clinical diagnosis can be made in most patients presenting with "numbness".

A PRACTICAL APPROACH TO TREMOR

A Tan, MRCP (UK), FAMS

INTRODUCTION

Tremor is a rhythmic, oscillatory movement produced by alternating or synchronous contractions of antagonist muscles. It is the most common involuntary movement and includes physiological tremor, essential tremor, Parkinson's disease (PD) tremor, and cerebellar tremor amongst others.

CLASSIFICATION

There are three ways of classifying tremor – according to phenomenology, anatomic distribution and frequency of tremor[1]. The easiest and most practical classification is the phenomenological one, and it is basically divided into rest tremor and action tremor. In action tremor, one can subdivide it into postural, kinetic, task-specific and isometric.

CLINICAL ASSESSMENT

Several methods are available for quantifying tremor. There are accepted tremor clinical rating scales, and using accelerometers to measure the frequency of tremor. However the simplest way of assessing the tremor in the clinic is visually and getting the patient to write a sentence and draw a spiral. The patient's response to treatment can be easily monitored using these methods.

Senior Registrar
Head, Movement Disorders Programme
Department of Neurology
Tan Tock Seng Hospital
Moulmein Road
Singapore 308206

MECHANISMS OF TREMOR GENERATION

There are two broad mechanisms of tremor generation. Using microelectrodes and sophisticated imaging with positron emission tomography (PET), researchers have found two prominent central brain oscillators in the ventral thalamus and inferior olives[2]. Mechanical reflex pathways such as the heart beat, stretch reflex and muscle mechanical properties also contribute to tremor generation. Thalamotomy or thalamic stimulation, by jamming the central oscillators in the ventral intermediate nucleus, can relieve many types of drug-resistant tremor.

CLINICAL SYNDROMES AND TREATMENT

Rest tremor is typically seen in Parkinson's disease (PD), although it can be present in severe essential tremor or cerebellar tremor. In PD, it has a 'pill-rolling' character and tends to disappear when the arms are outstretched. The tremor is produced by alternating contractions of antagonist muscles. Treatment of PD rest tremor involves the usual medications used for treating PD like levodopa, anticholinergics and dopamine agonists. Levodopa is by far the more effective drug, although some feel that anticholinergics may be more effective for tremor. Clozapine, a relatively new dopamine D4 receptor antagonist, has also been shown to improve resistant PD tremor[3]. A last resort would be to do a thalamotomy or thalamic stimulation. It can provide major relief in about 85-90% of patients[4].

Postural tremor (when the arms are outstretched) is commonly due to enhanced physiological tremor or essential tremor. Physiological tremor

occurs in normal individuals and is aggravated by stress, steroids, caffeine, xanthines, amphetamines, valproate and in thyrotoxicosis. Essential tremor occurs in 0.3-1.7% of the general population. The amplitude of tremor increases with age. There is a bimodal peak of onset in the 2nd and 6th decades. It has been found that there are spontaneous discharges in the inferior olives bilaterally in essential tremor patients. Treatment of essential tremor includes Propranolol (80-240 mg/day), Primidone (25-250 mg/day) and some even advocate an occasional prophylactic intake of alcohol just before an important function. Other drugs which are less useful include benzodiazepines, methazolamide, phenobarbitone and botulinum toxin.

Kinetic tremor occurs when the limb is performing an action. This can be demonstrated by the finger to nose test. This is often due to disease affecting the cerebellum or its outflow tracts. Sometimes titubation of the head may be seen. Cerebellar, brainstem and midbrain tremors are very resistant to drug therapy. Medications which have been tried include isoniazid, carbamazepine, clonazepam and glutetamide, but these are not very effective. Weights can be attached to the limbs to dampen the tremor. VIM thalamotomy or thalamic stimulation are quite effective for relieving the kinetic tremor, especially the distal aspects.

There are other less common tremors due to midbrain stroke, head injury[5], multiple sclerosis and peripheral neuropathy. These are more difficult to treat and the underlying pathology must be attended to.

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THE CLINICAL ASPECTS OF PARKINSON'S DISEASE

C B Tan, M Med (S'pore), FAMS

INTRODUCTION

Parkinson's disease (PD) is a degenerative condition characterised pathologically by degeneration of pigmented neurons of the substantia nigra and locus ceruleus resulting in loss of striatal dopamine. Lewy bodies which are eosinophilic, intracytoplasmic inclusions present in degenerating neurons are also present. While Lewy bodies are considered histologic hallmark of PD, their role in the pathogenesis of the disease is unknown. The incidence rate of PD varies from 5 to 24 per 100,000 population and the mean age of onset is between 58-62 years. Less than 10% of patients with PD have their onset before the age of 40 years.

CLINICAL FEATURES

The onset of PD is usually unilateral with involvement of the other side after an average of 3 years. Although a resting unilateral tremor is the most common initial presentation, vague symptoms like arthralgia, constipation, depression, easy fatiguability, olfactory dysfunction and cognitive decline may precede by years the cardinal manifestations of PD. In PD the sense of smell is sometimes lost early. Resting tremor, bradykinesia and rigidity are the 3 cardinal features of the disease. The diagnosis of Parkinson's disease is based on the presence of at least 2 of the 3 cadinal features and a predictable response to levodopa therapy. Impaired postural reflexes, considered to be a characteristic feature of PD, is a late manifestation of the disease and may not be helpful as a diagnostic aid at the onset of the disease.

Consultant Neurologist
Department of Neurology
Tan Tock Seng Hospital
Moulmein Road
Singapore 308206

Tremor

Tremor is often the earliest manifestation of PD and occurs in 75% of PD patients. The tremor of PD occurs at rest and typically the distal portions of the limbs are involved. In the early stage of the disease the tremor may be localised to a single finger before evolving to the more familiar pin-rolling movements of the thumb and fingers. The tremor may precede other manifestations of PD by several years. Usually the tremor begins in one upper limb and increases during periods of stress and anxiety. The usual tremor frequency is 3-5 cycles per second. Since the tremor disappears with action, it seldom causes any motor disability although many patients with PD are embarrassed by it. The tremor when it involves the lower limbs is seen when the patient is sitting or supine and abates with weight bearing. Less commonly and usually in the later stages of the disease, tremor may affect the jaw, lips and tongue. In addition to resting tremor, a disproportionately high number of patients with PD also have a postural essential tremor when compared to a similar age-matched control group.

Rigidity

Rigidity refers to the resistance to passive movements that occurs in PD and can affect axial, proximal and distal muscles. The sustained

increase in muscle tone is seen equally in both agonist and antagonist muscles and may be characterised as smooth (lead pipe) or rachety (cogwheeling). Cogwheel rigidity can usually be elicited when rigidity and tremor are both present. Rigidity can be tested with passive flexion extension movements at the wrist or by supination pronation of the forearm. The rigidity is often enhanced when the patient actively moves the contralateral limb during testing of the ipsilateral limb. Rigidity probably contributes to motor impairment by reducing speed of voluntary movement.

Akinesia / Bradykinesia

Akinesia refers to the inability to initiate and carry out movement. Bradykinesia is used to describe slowness of movement while hypokinesia refers to a diminution in movement. This group of symptoms is perhaps the most disabling feature of PD. The severity of bradykinesia correlates well with the degree of striatal dopamine loss. The masked facies and reduced blink rate are facial manifestations of hypokinesia. Pharyngeal hypokinesia leads to reduction in voice volume and sialorrhoea. When the small muscles of the hand are affected loss of finger dexterity and micrographia are seen. There is difficulty in initiating walking with loss of normal associated movements like arm-swing.

Gait and Postural Instability

The posture in patients with PD is unmistakable. The spine, hips, knees and elbows tend to flex forward. There is difficulty in initiating walking. The gait is characterised by slow velocity, short shuffling steps and a tendency to festinate. Walking can be further disrupted by sudden episodic freezing and turn hesitation. Impaired postural mechanism frequently co-exist leading to falls forward (propulsion) or backward (retropulsion). Postural instability can be tested simply be giving the patient a modest pull forward after assuring the patient that he or she will not be allowed to fall during the test. The test is considered positive if the patient loses balance or falls without support from the examiner or if she takes four or more steps forward. In most patients with PD, the gait and balance difficulty usually evolve about 5 years after the onset of the disease. Severe postural instability can be catastrophic giving rise to frequent falls and traumatic fractures. In the more advanced stages, patients are literally confined to a wheelchair or bed with the attending complications like pneumonia and thromboembolism.

DIFFERENTIAL DIAGNOSES

Drug-Induced Parkinsonism

Drugs which block dopaminergic receptors like the neuroleptics are most commonly implicated. Other drugs known to induce Parkinsonism include metoclopramide, reserpine and illicit drugs (MPTP). It is important to identify drug-induced Parkinsonism since the symptoms and signs can remit if the offending drug can be withdrawn. Occupational exposure to heavy metals like manganese should also be ascertained. Exposure to carbon monoxide or anoxic injury, either during suicidal attempts or accidental exposure can also produce Parkinson-like features in survivors. These patients often response to levodopa therapy and have a relatively more benign prognosis compared to PD.

Parkinsonian-Plus Syndrome

The diseases referred to collectively under the term parkinsonian-plus syndrome are not usually responsive to treatment with levodopa and tend to have a poor prognosis compared to PD. They are distinguished clinically from PD by the presence of a variety of symptoms and signs that occur in various combinations. These disorders include striatonigral degeneration, progressive supranuclear palsy (PSP), multisystem atrophy and corticobasal ganglionic degeneration. Tremor is typically absent in these disorders. The chronology of symptoms is important to distinguish these degenerative disorders that may mimic PD. Gait and speech difficulties, for example, are early manifestations of PSP. Impaired upward and horizontal gaze with normal oculocephalic reflexes is the hallmark of PSP. Eyelid apraxia which refers to the inability to open the eyelid voluntarily is also seen. The rigidity of PSP tends to affect the axial musculature, and dystonia may also be present. Severe postural instability and autonomic symptoms as the initial symptoms suggest multisystem atrophies, another degenerative

disorder of unknown etiology. Autonomic symptoms include syncope, urinary complaints, constipation, impotence and disorders of sweating. Postural hypotension is indicated by a drop of greater than 20 mm Hg of systolic blood pressure after standing for 5 minutes. Hyperreflexia, extensor plantar response and cerebellar signs reflect the multisystem involvement in this disorder. Striatonigral degeneration and corticobasal degeneration are largely pathological diagnoses and are difficult to distinguish from idiopathic PD apart from the absence of tremor and unresponsiveness to levodopa therapy.

Other Parkinsonian Syndromes

Postencephalitic parkinsonism is extremely rare. Apart from a propensity to oculogyric crisis, the symptoms and signs are similar to idiopathic PD. Juvenile parkinsonism is characterised by a slower progression of symptoms, tendency to develop focal dystonia early in the course of disease and prone to levodopa-induced dyskinesia. A diagnosis of juvenile parkinsonism should only be made after exclusion of Wilson's disease and the rigid form of Huntington's disease. In young patients, serum and urinary copper and serum caeruloplasmin must be done. A slit lamp examination for Kayser-Fleischer ring is also mandatory.

PROGNOSIS

The mortality rate for untreated patients with PD is three times that expected in the general population of the same age and sex. Since the introduction of levedopa therapy, the mortality rate has decreased to 1.3-1.9 times that expected in the general population. This can be attributed partly to the lower incidence of pneumonia and thromboembolic episodes prevalent in the era before the advent of levodopa. Adverse prognostic factors, associated with more rapid progression of the disease and shorter survival time include the presence of dementia, older age at onset of disease and postural instability and gait disturbance manifestations early in the course of the disease.

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MEDICAL TREATMENT OF PARKINSON'S DISEASE

A Tan, MRCP (UK), FAMS

PRINCIPLES OF EFFECTIVE THERAPY

There are several principles of effective therapy in Parkinson's disease (PD). The first is to keep patients functioning independently as long as possible. As medications are only symptomatic, one should avoid prescribing them if the patient has good functional capability. After 5 years of levodopa therapy, 75% will develop complications of motor fluctuation.

The next principle of therapy is that management must be individualised. As low a dose as possible of medication is used to keep patients functioning adequately.

MANAGEMENT STRATEGIES

Many medications are available for treating PD and these include:

a) Dopamine precursors – levodopa (Madopar, Sinemet)

b) Dopamine agonist – bromocriptine (Parlodel), pergolide (Celance), apomorphine, cabergoline

c) Dopamine releaser – amantidine (Symmetrel)

d) Monoamine oxidase B inhibitor – selegiline (Jumex)

Senior Registrar
Head, Movement Disorders Programme
Department of Neurology
Tan Tock Seng Hospital
Moulmein Road
Singapore 308206

e) Anticholinergics – trihexyphenidyl (Artane), benztropine

f) Catechol-O-Methyl tranferase inhibitors.

There are also surgical options such as thalamotomy, pallidotomy, thalamic stimulation and, in future, foetal cell transplants.

The importance of physiotherapy cannot be under emphasized. It keeps muscles and joints supple and promotes good health. Speech therapy helps in the problems of communication and swallowing, which are common problems in PD.

MEDICAL TREATMENT

At an early stage of PD, when there is no disability, it may not be necessary to prescribe medications. In the large multi-centre DATATOP study[1], the investigators showed that **selegiline** may slow down disease progression. However, this is hotly debated and some researchers disagree with the conclusions. 10,000 I.U. of **vitamin E**, an antioxidant, has not been shown to delay PD disease progression. Other antioxidants are being studied because of the postulation that an excess of free radicals may be destroying the substantia nigra in PD patients.

Symptomatic treatment of PD is required when there is a threat to employment, activities of daily living or an appreciable worsening of gait or balance. Although levodopa is the most powerful medication in treating PD, many avoid using it as a first-line drug in the younger-onset PD patients because of the motor fluctuations it can cause several years later[2]. **Artane**, an anticholinergic, improves parkinsonian symptoms

by 20-30%. It may be useful for tremor. Because it can cause memory disturbance, confusion, bladder and bowel dysmotility, it is generally not recommended in patients above the age of 70 years. **Amantidine** works by increasing dopamine release and blocking dopamine re-uptake in the synaptic vesicles. It has a mild action and benefits 60-70% of patients. The effect may wear out in 6-12 months. One of its unusual side effects is a skin rash called livedo reticularis.

Dopamine agonists are more efficacious than anticholinergics or amantidine, but less powerful than levodopa. It may be employed as monotherapy or as an adjunct to levodopa. Rinne and co-workers showed that a combination of bromocriptine and low-dose levodopa may delay the onset of levodopa complications compared with using levodopa alone[3]. As monotherapy, it can be effective for up to a year. Side effects include nausea, vomiting, giddiness, inflamed skin and confusion. Because of the side effects, dopamine agonists must be started and increased in dosage very gently.

Levodopa is the most potent anti-parkinsonian medication. It is converted by dopa decarboxylase into dopamine, which is the neurotransmitter deficient in PD. The lowest dose possible should be used to achieve symptom control. There are two preparations of levodopa: the standard form and the long-acting types. The long-acting preparations (Sinemet CR, Madopar HBS) are useful when the patient has motor fluctuations such as wearing off. They smoothen out clinical fluctuations and dosing is less frequent. Some patients complain of a lack of rapid response with the long-acting levodopa. This is easily circumvented by prescribing a small dose of standard levodopa together with the long-acting form as the first dose in the morning.

Motor fluctuations in PD occur after several years of levodopa therapy. These include wearing off, random off, delayed on, response variations to meals, peak-dose dyskinesias and off dystonia. The wearing off phenomenon occurs when the levodopa benefit ends before the next dose. One of the best ways to treat wearing off is by using a long-acting levodopa preparation. In patients with advanced PD, meals delay gastric emptying and interfere with the absorption of levodopa. The aminoacids in the meal compete with levodopa for absorption in the small intestine[4]. The patient should be advised to take levodopa at least half an hour before each meal and, if possible, to reduce the protein intake during breakfast and lunch, and compensate by taking more protein during dinner at night. Cisapride may help by accelerating gastric emptying.

Peak-dose dyskinesia consists of abnormal involuntary movements (chorea or dystonia) which occur when levodopa levels are too high. One strategy is to reduce the levodopa dose at the expense of increasing off periods. A good method of handling this problem is to add a dopamine agonist and gradually reduce the dose of levodopa. Clozapine, an atypical neuroleptic, may be useful for peak-dose dyskinesia. Off dystonia is a painful dystonic cramp that usually occurs when waking up in the morning. This is due to low levels of levodopa. A bed-time dose of long-acting levodopa helps greatly in this situation.

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SURGICAL APPROACH IN TREATING PARKINSON'S DISEASE

T T Yeo, FRACS (Neurosurgery)

Summary

There has been a worldwide resurgence of interest in the surgical treatment of Parkinson's disease in recent years. The growing realisation of the limits of medical therapy and an improved understanding of the neurophysiology and pathways of the basal ganglia in health and disease has led to a revival of a more rational surgical treatment for Parkinson's disease. Postero-ventral pallidotomy or pallidal stimulation is an effective operation for Dopa-induced dyskinesia, while bilateral subthalamic nucleus stimulation is suitable for the akinetic rigid type of Parkinson's disease and thalamic stimulation (in the Ventro-intermediate nucleus) is indicated for tremor-predominant Parkinson's disease. Neural fetal mesencephalon transplantation is also promising as a therapeutic option but remains experimental at this stage as double-blind clinical trials are presently in progress in the USA.

Keywords: *basal ganglia, movement disorder surgery, neural transplantation, pallidotomy, Parkinson's disease, subthalamic nucleus stimulation, thalamic stimulation*

INTRODUCTION

Surgery for Parkinson's disease is enjoying an unprecedented revival of late. While it was commonly performed in the 1950s and 1960s before L-dopa was discovered, it went through a long and steep decline in the 1970s and 1980s before becoming popular again in recent years. This has come about because of a variety of factors. Firstly, neurologists became more aware of the limits of medical therapy and its associated complications, realising that L-dopa was not a cure for Parkinson's disease. Secondly, tremendous advances have been made in basic neuroscience research with regards to the neurochemistry, neuroanatomy and neurophysiology of the basal ganglia and its functions. This had led to a better understanding of the pathophysiology of Parkinson's disease and the consequent abnormalities in the various pathways and provides us with a more rational and scientific foundation for the surgical treatment of Parkinson's disease. Thirdly, the operation of postero-ventral pallidotomy, popularised by Laitinen[1], has been much hyped about in both the scientific literature and the lay press, perhaps unjustifiably receiving widespread media exposure throughout the world as a 'miracle' operation for Parkinson's disease. It is this operation that has led the way to the recent renaissance of neurosurgery for Parkinson's disease.

Ten percent of patients with Parkinson's disease are said to be suitable surgical candidates. It is

Consultant Neurosurgeon
Movement Disorder Programme
TTSH Brain and Spine Centre
Department of Neurology
Tan Tock Seng Hospital
Moulmein Road
Singapore 308206

the purpose of this article to acquaint the reader with some of the exciting recent advances in the surgical treatment of Parkinson's disease.

OPERATIONS FOR PARKINSON'S DISEASE

These operations are almost always done under local anaesthetic for placement of a stereotactic frame on the head and the making of a burr-hole. The patient is awake and cooperating with the neurosurgeon throughout the operation and this is essential if the operation is to be successful. A probe is normally advanced to the selected target site in the brain and some neurophysiological testing is then usually done to ensure that the target site reached is indeed the optimal one. Once this is ascertained, the cells there are either destroyed with radio frequency lesion to a defined volume, or a deep brain stimulator (DBS) is implanted. The latter functions as a "pseudo-lesion", as it has been shown that high frequency stimulation mimics the effects of a lesion, with the advantage of not permanently destroying cells or tissue. Hence DBS eliminates the possibility of inadvertently destroying normal cells and tissues if the targeting is inaccurate. The likelihood of serious permanent complications is lower with DBS than with radio frequency lesioning and is one of its prime attractions accounting for its surging popularity.

Four neurosurgical options for the patient with Parkinson's disease will be described:-

(i) postero-ventral pallidotomy (PVP), or pallidotomy for short (and its equivalent operation pallidal stimulation)

(ii) subthalamic nucleus (STN) stimulation

(iii) thalamic stimulation, usually in the ventro-intermediate nucleus (Vim) of the thalamus, or thalamotomy in the same nucleus, and

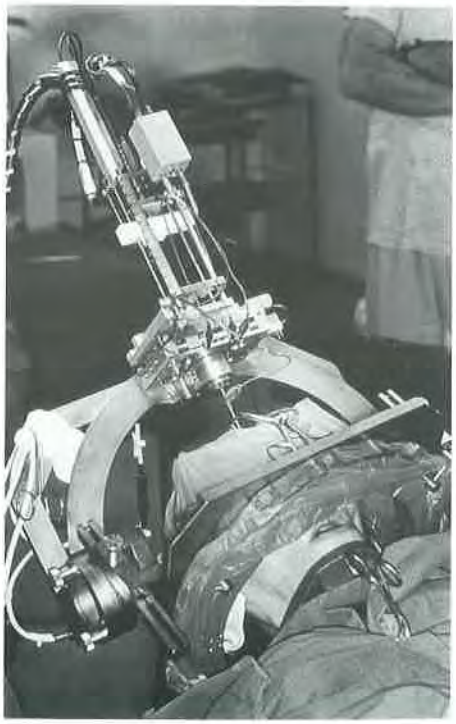
(iv) neural transplantation using fetal mesencephalon, as well as the possible future use of implanted polymer-encapsulated cell populations genetically engineered to secrete growth factors or neurotransmitters in the brain for treatment of Parkinson's disease.

Posteroventral Pallidotomy (PVP)

The positive clinical effects of a posteroventral pallidotomy in improving all 3 cardinal symptoms of Parkinson's disease as well as dopa-induced dyskinesia has resulted in the present revival of interest in the surgical therapy for Parkinson's disease. It is the present consensus that this operation is most effective for ***dopa-induced dyskinesias***[2,3], abolishing this disabling complication of long-term L-dopa therapy very strikingly on the side contralateral to the surgery and sometimes on the ipsilateral side as well. Its effects on the other symptoms of Parkinson's disease are more modest but nevertheless significant.

The main complication is that of hemianopia from inadvertent lesioning of the optic tract, which is very close to the ventral border of the globus pallidus. This varies from 14% in Laitinen's initial series[1] to 0%[4] in centres which use specialised single-unit microelectrode techniques (see Figures 1 and 2). In an effort to avoid this complication, some centres have inserted

Figure 1: Patient undergoing awake stereotactic microelectrode-guided postero-ventral pallidotomy for Parkinson's disease



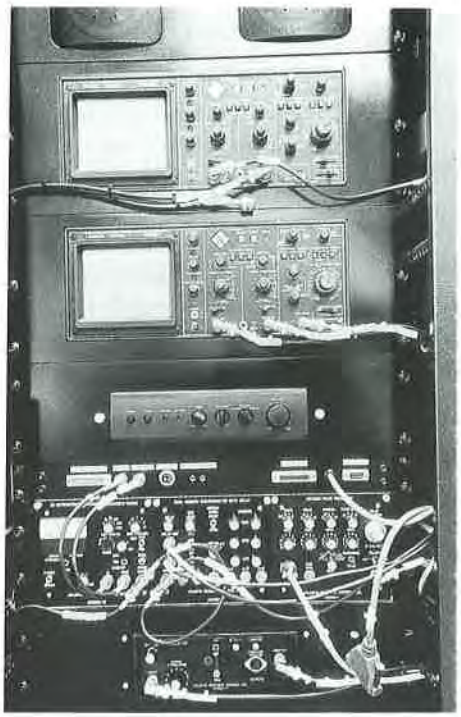


Figure 2: Microelectrode-guided movement disorder neurosurgery: The complex set-up for microrecording (and microstimulating) from single neurons in the basal ganglia and thalamus during awake stereotactic operations for Parkinson's disease

deep brain stimulators (DBS) in the postero-ventral pallidum and avoided radio frequency lesioning. Another reason for using pallidal stimulation is in bilateral cases, where it is known that the risk of neurocognitive deficit is high with bilateral radio frequency lesioning. In an effort to avoid this complication, some centres have lesioned one side only and placed stimulators on the opposite side[5].

Subthalamic Nucleus Stimulation

Bilateral subthalamic nucleus (STN) stimulation has been recently championed by Benabid and his colleagues[6]. Their results have been spectacular for patients with the ***akinetic-rigid type of Parkinson's disease***, and STN is now the exciting new target in movement disorder surgery. STN lesioning has been done by one group[7] but there is the potential danger of hemiballismus occurring should the wrong part of the STN be lesioned. This risk can be especially high since STN is a very small target. Hence the attractiveness of stimulating rather than lesioning in STN.

Thalmic Stimulation / Thalamotomy

Thalmotomies have a long history and have been done for the last 30 to 40 years for Parkinson's disease. Presently, their main indication seems to be for ***tremor-predominant Parkinson's disease***. It is less effective for the other symptoms of Parkinson's disease. The target is usually the Ventro-intermediate (Vim) nucleus of the thalamus, which lies immediately anterior to the ventro-caudal (Vc) or chief sensory nucleus of the thalamus. Patients with bilateral thalamotomies done for bilateral tremors have a high incidence of neurocognitive deficit as well as cerebellar symptoms like ataxia and dysarthria. (These side effects are less common with unilateral thalamotomy). In an effort to avoid these complications, Vim thalamic stimulation has been pioneered by Benabid[9] who has shown that the benefit is sustained on long-term follow-up of up to 8 years[10]. The results of thalamic stimulation are superior to thalamotomy[11] and this is now the treatment of choice for tremor-predominant Parkinson's disease.

Neural Fetal Mesencephalon Transplantation into the Putamen

Neural transplantation was very much in the medical limelight a few years ago, but initial media hype has now been replaced with a more scientific appraisal. Adrenal transplants have proven to be a failure and only multiple fetal grafts in the putamen have shown clinical benefit in patients with Parkinson's disease. There are now double-blind controlled trails in North America going on at the present moment on fetal transplantation, and the results are eagerly awaited and will hopefully be announced in a year or two. Until then, it is still an ***experimental therapy*** presently, and it remains to be defined what types of patients and what symptoms are improved by the operation. As well, there are controversial ethical aspects to the issue of fetal harvesting and transplantation, and it remains to be seen whether fetal transplantation will attain the popularity of the previously described operations above as it also requires a good basic

neuroscience laboratory set-up working closely with the clinical team, an uncommon combination in most clinical centres worldwide. Nonetheless, there is undoubted clinical benefit seen in some patients undergoing fetal transplantation so there may well be cases of Parkinson's disease that are not suitable for conventional stereotactic operations as listed above but who may be suitable candidates for fetal transplantation (although their numbers are likely to be small given that the other operations have such good results).

In an effort to avoid the ethical problems involved in fetal transplantation, recent experimental work in primates have used polymer-encapsulated cell populations producing specialised trophic factors (e.g. GDNF, glial-derived neurotrophic factor, putative dopaminergic trophic factor)[12]. Transplantation of cells isolated within a permselective polymer capsule restricts cell growth to the capsule space and protects them from immune destruction while allowing exchange of molecules between the entrapped cells and host tissue. This form of gene therapy will shortly be tried in humans and the potential seems very exciting.

CONCLUSION

While there is presently no true cure for Parkinson's disease, some of the surgical techniques outlined above are proving to be very effective therapy in cases where medication has failed. It is hoped that the reader is now better acquainted with what some of these newer therapeutic modalities are, and has a better appreciation of the surgical options available to sufferers of this oftentimes very disabling disease.

Acknowledgements

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CEREBROVASCULAR ACCIDENTS: AN UPDATE

* ***H M Chang,*** *MBBS (S'pore), MRCP (UK)*
** ***M C Wong,*** *MBBS (Aust), M Med (S'pore), MRCP (UK), Dip Amer Bd Neur (USA), FAMS*

BACKGROUND

Stroke is the leading cause of serious, long term morbidity and the third leading cause of mortality locally. Like coronary disease, its incidence has reared in the face of an affluent and aging society. In the past, it was viewed as an untreatable and irreversible process, being fodder for neurologists to discuss about cerebral functions, with treatment often ending with diagnosis. There have been dramatic advances in recent years, and we now appreciate that a brain attack should be accorded equal if not more importance and urgency as a heart attack if we are to salvage ischemic brain. The window of opportunity is short, probably measured in terms of hours. In order to treat any disease process, we need to understand the underlying mechanism and etiology. For instance a person who presents with right hemiparesis and a history of recurrent left transient monocular blindness (TMB) likely has significant left carotid disease. Stroke could have been due to poor blood flow in the carotid system (hemodynamic/hypoperfusion) or a small carotid plaque could have embolised distally (artery-to-artery embolism). Rational management includes a good history and examination, appropriate initial investigations and treatment, and subsequent planning for long terms goals.

APPROACH TO STROKE

Most strokes are due to occlusive diseases. In the SGH stroke data bank, 80% were ischemic, and 20% intracranial haemorrhage. The focus of this discussion will be on ischaemic strokes. Ischemic strokes generally occur when there is:

- thrombotic occlusion of a vessel by an atherosclerotic plaque,
- embolic occlusion, from either an arterial (e.g. aortic arch, subclavians, carotids, vertebrals) or cardiac (clot, vegetations, paradoxical embolus) source, and
- hypoperfusion (either due to focal severe vessel stenosis or systemic hypoperfusion) which usually results in a watershed infarct.

Large and small vessel disease, as their designations imply, refer to involvement of size of cranial vessels (and hence the cerebral territory at risk). The former usually results in large infarcts with multimodal neurological deficits (motor, sensory, cognitive and behavioural), an example of which is carotid artery stenosis, more commonly seen in whites than blacks or Chinese. The latter causes small infarcts, usually involving motor, cerebellar and/or sensory systems without significant higher function derangement, and are frequently called lacunar strokes. The type of stroke is influenced by the underlying mechanism, for instance: carotid disease and cardiogenic emboli rarely causes lacunar strokes.

* *Registrar*
** *Senior Consultant and Head*
Department of Neurology
SGH Brain Centre
Singapore General Hospital
Outram Road
Singapore 169608

As anginas are harbingers of heart attacks, so are transient ischemic attacks (TIAs) harbingers of brain attacks. Recognition allows early interventive procedures. Symptoms and signs vary with the territory at risk. In the anterior circulation, transient monocular blindness, mono or hemiparesis, and language disturbance may precede a stroke. Patients with TIAs related to severe carotid disease have a 12-13% risk of stroke within the first year. The risk is influenced by other factors such as "crescendo TIAs", severity of stenosis and ulcerated plaques. For patients who have had stroke, the risk of subsequent stroke ranges between 5-9% per year. In the posterior circulation, symptoms are usually more vague and misleading, with dizziness, nausea, vomiting, generalised limb weakness, visual, speech and auditory disturbances. In the elderly, it is often difficult to differentiate posterior circulation TIAs from other pathologic processes. The history guides the neurological examination, as one looks for signs to confirm or refute a working diagnosis. Besides motor and sensory examination, language, behaviour, eye movements and visual fields should be checked.

Stroke risk factors, hypertension, diabetes, hyperlipidaemia, obesity, smoking and excessive alcohol consumption should be actively identified and aggressively modified via education, life style changes and medications. These patients often have concomitant coronary and/or peripheral vascular disease which may require evaluation and treatment.

Some patients are found incidentally to have carotid or vertebrobasilar disease (i.e. asymptomatic) whilst being evaluated for other medical conditions. This has been studied for carotid stenosis, where stroke risk ranges from 2-5% per year, with variables such as severity, ulceration of lesion and scan evidence of infarcts influencing outcome. Risk stratification as above should be evaluated.

INVESTIGATIONS

Confirmation of an infarct or exclusion of bleed is done with neuroimaging. CT head is useful in differentiating acute bleeds from an acute infarct, however, it frequently does not show an acute infarct in the first 4-5 days, though occasionally positive scans may be present in the first 12-24 hours. MRI allows superior visualisations, particularly of posterior circulation infarcts, small and acute infarcts (as early as 6-12 hours after onset).

The cerebral circulation can be quickly and conveniently studied with ultrasound. The duplex scan of the neck and transcranial doppler assess the extracranial and intracranial, anterior and posterior circulations. The aortic arch, however, is not well visualised, and probably best studied with the transesophageal echocardiogram. Interpretation of results varies with operator experience and skill. Cerebral circulatory imaging with CT angiography (CTA) and Magnetic Resonance Angiography (MRA), are complementary and also allow visualisation of the cerebral circulation. Ultrasound provides useful adjunctive information about the vertebral origins (a common site of disease in the posterior circulation, but not well seen on both CT and MRA), flow directions and severity of stenosis or occlusion. Ultrasound, CTA and MRA, unlike the cerebral angiogram, allow the circulation to be assessed *non invasively*, though contrast needs to be administered for CTA. Angiography remains the gold standard for defining the vasculature, though it carries a small risk of complications.

Xenon CT scan, single photon emission computed tomography (SPECT), positron emission tomography (PET) and developing MRI techniques may also provide information on blood flow and metabolism.

Cardiac evaluation, starting with the humble electrocardiogram should always be done. Transthoracic or transesophageal echocardiogram are usually performed when a cardiogenic embolic source is suspected. Arrhythmias can be identified with continuous monitoring. Atrial fibrillation, global or segmental hypokinesia, cardiac thrombus, right to left shunts, valvular vegations and septal aneurysms are recognised potential sources of emboli.

Routine tests such as haemoglobin, haematocrit, lipid and fibrinogen level should not be neglected. Other investigations are guided by the circumstances, (e.g. screening for coagulopathies, hyperviscosites, vasculitis and dissections).

TREATMENT

Treatment for stroke has come a long way. In the secondary prevention of stroke, antiaggregates like aspirin are frequently indicated. Doses from 75 mg to 1200 mg are used. Data suggests that low dose may be as efficacious as high dose, with reduced complications such as intracranial or gastrointestinal bleeding. Generally, coumadins and heparin have been used in aspirin failures, severe large vessel stenotic lesions, embolic sources of strokes (cardiac and arterial sources). In particular, atrial fibrillation secondary to rheumatic heart disease or associated with risk factors has significant stroke risk that is decreased with anticoagulation. Duration of therapy depends on the underlying condition.

Amongst Caucasians, the origin of the internal carotid artery is a common site of disease. Surgical options includes carotid endarterectomy for *symptomatic* (i.e. TIAs, TMB or non-disabling strokes) extracranial carotid disease. Two large studies[1,2] have shown the superiority of endarterectomy for symptomatic (defined as a non-disabling stroke, TIA or TMB) severe (over 70%) carotid stenosis in secondary prevention of stroke, despite the risk of preoperative angiography and early peri/postoperative complications, stroke and mortality. These studies showed reduction of ipsilateral stroke risk in the subsequent years. This is conditioned upon a good, experienced surgeon with low surgical complication rate. No such benefit was seen for patients undergoing surgery for mild (<30%) carotid stenosis, the risk of ipsilateral stroke being low to begin with, and easily outweighed by early risks of surgery. Recently published interim results for moderate (30-69%) stenosis also did not show any beneficial results, with a trend against surgery. Pecutaneous carotid angioplasty (PTCA) with or without stenting is less invasive than endarterectomy. There have been no studies to compare the efficacy or surgery vs PTCA, but most patients recruited for PTCA have generally been high risk candidates for surgery. Results so far are optimistic.

Another group of patients are those with *asymptomatic* carotid stenosis. Is there any medical or surgical therapy that can influence their stroke risk? A recent study[3] looking at asymptomatic 60% or more carotid stenosis showed a lower stroke rate in patients receiving endarterectomy than medications alone. However, the risk of stroke in this group of patients is low to begin with, unlike the symptomatic group, and in order to realise this benefit, complications from angiography and endarterectomy have to be kept low. Until further data is out, it is prudent to assess these patients carefully before considering endarterectomy.

Recent interest has focused on treatment for acute stroke. A study in Hong Kong[4] using low molecular weight heparin in all types of ischemic strokes within 48 hours, showed reduced death and dependency from stroke. Clot lysing agents to re-establish blood flow have been tested in various clinical trials[5-8]. Different trials have used different criteria with respect to the acute stroke population studied, drug and route administered, complications and end points evaluated. Attention has focused on the "therapeutic window", within which the neurons are mostly stunned with chance of recovery if circulation is established, but yet complications of haemorrhage are low. Most studies, depending on the drug used, show higher adverse outcomes of bleed and death, but when subgroup analysis was performed, benefit was seen in some groups. The clinical and radiological features of these subgroups need to be further defined. A large study[8] using intravenous tissue plasminogen activator in all types of acute ischemic strokes under 3 hours showed decreased morbidity despite a higher rate of symptomatic haemorrhage. Overall mortality between 2 groups was similar. At present, thrombolytic therapy is best administered at specialised centres, by trained physicians.

Rehabilitation and education during the acute stage, after stoke, is very important. It should be started early, and requires a multidisciplinary approach, with the input of nursing staff, physiotherapists, occupational therapists, speech therapists, social workers, psychologists, doctors, patients and relatives. Patients are taught to understand their condition and be as independent as their deficits allow them, using correct techniques, exercises and aids. Facilities are also available for further inpatient and outpatient rehabilitation, depending on the level of disability and home support.

CONCLUSION

It has become clear to us that stroke is a heterogeneous disease. Our understanding of the pathophysiologic process is improving, so that therapy is becoming increasingly less empirical and more rational. Improved brain and vascular imaging have helped. Risk modification, secondary prevention are crucial. Cardiogenic embolism is potentially preventable. Thrombolytics, anticoagulants, neuroprotective agents, endovascular and surgical techniques are increasingly finding their place. The next few years are full of promise for stroke treatment.

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MIGRAINE: A PRACTICAL VIEWPOINT

K F Tang, *MBBS (S'pore), MRCP (UK), MSc Nuclear Medicine (London)*

Migraine is a very common disorder: usually under-diagnosed and under-treated

INTRODUCTION

Migraine is a common disorder characterised by benign recurrent headaches. Surveys of adult urban population revealed that 15% of females and 5% of males have headaches satisfying the usual diagnostic criteria for migraine. Therefore at least 10% of the population would at any one time be considered to be migraine sufferers. It is therefore one of the most common acute presenting symptoms in any family practice, second perhaps only to febrile illness.

DEFINITION AND CLASSIFICATION

Migraine has been defined as an idiopathic, benign, recurring headache disorder characterised by unilateral headaches often pulsating in quality. The headaches may be moderate or severe in intensity and are often aggravated by physical activities and may be associated with nausea, photophobia and phonophobia. There is often a family history of migraine. In recent years an attempt had been made to include the need to exclude a structural lesion of the central nervous system in any definition of migraine but this produced enormous logistical problems because of perceived need to perform expensive imaging studies.

Types of Migraine

- Migraine without aura (common migraine)
- Migraine with aura (classical migraine)

3 Mount Elizabeth #14-01
Mount Elizabeth Medical Centre
Singapore 228510

It is common to classify migraine into 2 broad groups: common migraine i.e. migraine without aura and classic migraine or migraine with aura. Common migraine probably accounts for 85% of all migraine sufferers. Patients with common migraine suffer episodes of moderate to severe pain which may affect one or both sides of the head. They are often throbbing in nature and often but not always associated with a sick feeling in the stomach or being sensitive to light, sound or movement. The sufferer feels better after lying down in a dark and quiet room. Sleep may bring relief.

In classical migraine however there is an aura and this aura consists of a disturbance of the central nervous system which may be referable to the cerebral cortex or the brain stem. The typical disturbance is visual with bright flashing lights, black spots, fortification spectra or partial loss of vision. Sometimes there is sensory disturbance with pins and needles moving over one or more limbs. These disturbances are short-lived, usually lasting less than one hour and resolve without any permanent deficit.

PATHOGENESIS AND CLINICAL PRESENTATION

Although we know that there are genetic as well as environmental factors in the pathogenesis of migraine, we still do not know what really causes migraine. There is therefore no complete "cure" for migraine. Fortunately our understanding of the pain mechanisms in migraine is much better. There have always been two rival theories on the mechanism of migraine headaches. These are the vascular theory (i.e. the disorder starts in the blood vessels) and the neurologic theory (i.e. the disorder starts with groups of nerve cells and fibres in the central

nervous system exerting some of their influence via the trigeminal nerves). There is experimental and clinical evidence for both.

Since animals do not suffer from migraine (or at least we cannot know if they suffer from headaches or not) the condition has to be studied only in man. Since it is almost never a fatal condition, it is not possible to have pathological study or to do invasive study. Most of our advances have therefore come from non-invasive study of cerebral blood flow. The group headed by Olsen have shown a focal reduction of regional cerebral blood flow when migraine attacks with aura are provoked; the areas of reduced cerebral blood flow are usually in the posterior parts of one or more hemispheres. These studies were mainly done with semi-quantitive radio-isotope inhalation on intra-arterial injection methods with external detectors. A recent case report has shed more light on the pathogenesis of migraine. A woman who was undergoing a Positron Emission Tomographic (PET) brain scan for another purpose developed migraine without aura. Twelve successive PET scan images in her case showed a reduction in cerebral blood flow was present bilaterally in the visual associated cortex. This decrease in regional cerebral blood flow spread forward across the cortical surface towards the parietal and occipital-temporal areas at a relatively constant rate. The maximum decrease in regional cerebral blood flow was about 40%. Recovery was excellent by 12-15 minutes later.

It is now clear that brain peptides play a critical role in the pathogeneis of migraine. The central role of serotonin (5HT) has been known since the day when an intravenous infusion of serotonin was shown to dramatically stop migraine headaches. This treatment was complicated by intolerable side effects: flushing and diarrhoea. The central role of serotonin has been further strengthened by the success of 5HT receptor agonist like Sumatriptan in the treatment of clinical migraine attacks.

DIAGNOSIS

The first major problem in migraine management is how to make a confident diagnosis. A history of many years of typical throbbing headaches with side-to-side shift and progression from one area to another in association with nausea, vomiting or visual symptoms is suggestive. If there is a family history of migraine and the headaches have identifiable triggers (external or internal) then the diagnosis of migraine can be confidently established.

Warning Flags in Migraine Diagnosis

Special care must be taken in the following circumstances:

- *The first severe attack*
  A "never before in my life" headache with very acute onset (as if someone had "struck my head with a hammer") is the hallmark of acute subarachnoid haemorrhage. CT scan of the brain to identify blood in the subarchnoid space would be indicated. If the history is typical, a normal CT scan would not be sufficient to exclude the diagnosis.

- *The presence of neurologic symptoms or signs*
  A progressively more severe headache followed by numbness or weakness of a hand must ring warning bells for intracerebral haemorrhage.

- *Pain lasting many consecutive days*
  This is suggestive of severe sinusitis or meningitis even in the absence of fever. Torula (crypotcoccal) meningitis is the most often missed diagnosis in this setting.

- *Involvement of extraoccular muscles*

- *Onset in the elderly or in midlife*

TREATMENT

How do we treat acute migraine headache and then prevent them from recurring so that the patient can continue to live a normal and pain free life? Treatment may be drug or non-drug in nature. Increasing publicity about the side effects of medications in general and disappointment with the perceived failure of pharmacological treatment in patients with severe migraine have resulted in a profusion of non-drug treatments for migraine. Few of these have stood the test of scientific trials but remain popular because of isolated reported cases of "cure" or "dramatic

relief". It is difficult to say if the efficacy of these treatments in some patients can be fully explained by the placebo effect. We must admit they have been inadequately studied.

Non-Drug Treatment

These non-drug treatments include the following:

- Biofeedback and relaxation therapy
- Acupuncture
- Foot reflexology
- Aromatherapy
- Herbal teas
- Transcendental meditation and hypnotherapy
- Magnetic chairs and beds
- Special elimination or inclusion diets
- Exercises e.g. Yoga

Some of these have powerful psychological effects which may be beneficial in the total management of the migraine patient although some have felt they are more likely to succeed in tension-type headaches rather than classical migraine.

Drug Treatment

Drugs useful in migraine are divided into those that abort the acute migraine attack and those used prophylactically (interval treatment) to reduce the frequency and severity of migraine attacks.

Drugs Used in Acute Attacks

Agents used in the treatment of acute attacks act on the 5-hydroxytryptamine (5-HT) receptors or other pain receptors. These include:

- Simple analgesics (with or without muscle relaxants):
  Acetaminophen, Acetaminophen plus Chlromezanone (Beserol), Acetaminophen plus Orphenadrine (Norgesic)

  In practical terms the first line management of the acute migraine attack is the mildest analgesic that can produce good pain relief. Finding a drug that does this consistently for any one patient is the problem. It is good practice to start with the mildest drug and then move up the ladder when necessary. Starting with acetaminophen and then trying a non-steroidal anti-inflammatory drug when this fails is a good way to start.

  The milder migraine headache often responds well to acetaminophen 500 mg to 1000 mg. Where there is significant muscle over-contraction or neck stiffness the use of combination drugs like Beserol or Norgesic may produce greater symptomatic relief. The addition of codeine increases its effectiveness and is available as Panadeine and Migraleve.

- Non-Sterodial Inflammatory Drugs
  Aspirin, Mefenamic Acid, Diclofenac, Naproxen, Indomethacin

  There is a wide range to choose from but unfortunately it is impossible to predict which patient would be more likely to respond to which of these NSAIDs. Intramuscular and rectal Diclofenac 25 to 75 mg are popular choices while oral Mefenamic Acid, Ibuprofen, Diclofenac, Naproxen etc. are often effective when administered soon after the onset of headache. Limitations to their usefulness would be allergic side-effects (often the patient who develops orbital oedema with one NSAID would also develop a similar reaction to another) and gastro-intestinal symptoms especially heartburn. Aspirin is an often forgotten but useful drug and intravenous forms of aspirin are used quite effectively in other countries.

- Ergotamine Tartrate

  Ergotamine tartrate is a 5-HT receptor agonist and has been used safely for more than 50 years. It constricts dilated vessels and dilates constricted vessels and hence can shorten the aura phase of classical migraine. Rectal and parenteral forms are useful if vomiting or nausea is a prominent symptom but these are not available in Singapore. Excessive use produces excessive vasoconstriction causing digital gangrene, and it is contraindicated in ischemic heart disease. Commercial preparations like Cafergot (maximum daily dose 6 tabs, maximum weekly dose 10 tabs) and Migril (maximum daily dose 4 tabs, maximum weekly dose 6 tabs because it contains 2 mg of ergotamine as compared to Cafergot's 1 mg) include

caffeine to improve gastric absorption of ergotamine.

- Sumatriptan

  This is the first of a new class of drugs acting on the 5-HT1 receptor. It probably acts by constricting cranial blood vessels and preventing the release of peptides from trigeminal nerve endings. Oral Sumatriptan 100 mg has been reported to produce pain relief in 50% of patients after 2 hours and in 75% of patients after 4 hours (provided 57% take a second tablet 2 hours after the first tablet). Subcutaneous Sumatriptan 6 mg is more efficacious – producing relief in 72% of patients after 1 hour (compared with 25% of those given placebo). The high cost of Sumatriptan is a limiting factor. It is difficult to ask the non-responder patient to pay $20 for each oral tablet and $50 for each injection when they are left with the same headache. New drugs of the same class in development may prove to be more efficacious.

- Lignocaine

  The use of intravenous Lignocaine can be greatly limited by the need to admit the patient for treatment. Recently there has been a resurgence of interest in Lignocaine nasal spray. In one study, patients were told to spray one half c.c. of lignocaine into their noses at the start of a headache. This stopped the pain completely in 50% while in another study, lignocaine also relieved the pain in 50%, but the relief was far less dynamic.

- Narcotics
  Pethidine, Morphine

  These medications are best avoided because of the risk of addiction. Most headache clinics throughout the world inform their potential patients that they do not carry narcotics in their clinic.

Drugs Used Prophylactically

Some form of prophylactic treatment is indicated when attacks are frequent. The threshold for starting prophylactic treatment varies from patient to patient and may be strongly influenced by the patient's concern about the side effect of frequent analgesic use. In general, a headache frequency greater than twice a month would be considered justification for prophylactic treatment. The patient, however, has to be psychologically prepared to take medications every day for weeks to months at a stretch. Agents with proven efficacy when used prophylactically include:

- Beta-blockers
  Propranolol, Atenolol, Nadolol, Metoprolol

  These are the first drugs of choice in a non-asthmatic patient and have a 20-year history of safety and efficacy. Long-acting propranolol is popular as a once a day dose in other countries but the common practice in Singapore is to use start with propranolol 20 mg bd or tds and gradually increase the dose up to 40 mg tds provided there are no side effects. Side effects like lethargy, vivid dreams or nightmares, chronic cough, postural hypotension, cold extremities, etc. necessitate withdrawal of therapy in as many as 30% of patients.

- Amitriptyline

  This tricyclic antidepressant blocks the reuptake of 5-HT at central synapses. Its antimigraine effect appears at doses way below that effective for the treatment of depression. Dry mouth, weight gain, drowsiness and dreamy state are common but may disappear with persistent use or at a lower dose.

- Calcium Antagonists
  Verapamil, Nifedipine, Flunarizine

  The older short-acting calcium antagonists are seldom used nowadays with the easy availability of longer-acting neuro-selective calcium antagonists like Flunarizine. Side effects of Flunarizine include weight gain, drowsiness, fatigue, depression and even parkinsonism in the elderly.

- Anticonvulsants
  Sodium valproate, Phenytoin

  For many years the use of phenytoin has been restricted to the use for more complicated forms of migraine like basilar migraine. Recent reports suggest that sodium valproate is effective in migraine prophylaxis. Its use will always be tempered by the

very small risk of hepatotoxicity. It should not be used in children (with increased risk of hepatotoxicity in children below the age of 8 years) or women in the reproductive age group (because of teratogenesis i.e. spina dysraphism).

Table 1: Drugs Used in Migraine Treatment

Trade Name	Generic Name	Dosage Formulation
Adalat	Nifedipine	5 mg, 10 mg
Beserol	Acetaminophen Chlormezanone	500mg 100 mg
Betaloc	Metroprolol	100 mg
Biogesic	Acetaminophen	500 mg
Brexin	Piroxicam-b-cyclodextrin	20 mg
Brufen	Ibuprofen	200 mg, 400 mg
Cafergot	Ergotaime tartrate Caffeine	1 mg 100 mg
Cataflam	Diclofenac potassium	25 mg, 50 mg
Dilantin	Phenytoin	100 mg
Epilim	Sodium valproate	200 mg
Imigran / Imitrex	Sumatriptan	100 mg 6 mg (IV)
Inderal	Propranolol	10 mg 40 mg
Indocid	Indomethacin	25 mg
Migraleve	Acetaminophen Codeine phosphate Buclizine HCL	500 mg 8 mg 6.25 mg
Maxolon	Metoclopramide	10 mg (IV, IM, Oral)
Migril	Ergotaime tartrate Caffeine hydrate Cyclizine HCL	2 mg 100 mg 50 mg
Norgesic	Acetaminophen Orphenadrine	450 mg 35 mg
Orudis	Ketoprofen	100 mg
Panadol	Acetaminophen	500 mg
Panadeine	Acetaminophen Codeine phosphate	500 mg 8 mg
Periactin	Cyproheptadine HCL	4 mg
Pethidine	Pethidine HCL	50-75 mg (IM)
Ponstan	Mefenamic acid	250 mg, 500 mg
Prozac	Fluoxetin	20 mg
Sibelium	Flunarizine	5 mg
Synflex	Naproxen sodium	275 mg, 550 mg
Tilcotil	Tenoxicam	20 mg
Tramal	Tramadol HCL	100 mg (IM), 50 mg
Tryptanol	Amitriptyline	10 mg, 25 mg
Voltaren	Diclofenac sodium	75 mg (IM), 25 mg, 50 mg, supp. 12.5, 25, 50 mg

- Methysergide

  Methysergide has agonist properties on 5-HT receptors. It is not available in Singapore. The risk of retroperitoneal fibrosis makes this an unattractive option for anyone other than the most severe migraine sufferer.

- Newer antidepressants with selective serontonin re-uptake inhibition
  Fluoxetin

  Recent reports suggest that the new highly selective 5-HT re-uptake inhibitors (SSRIs or selective serotonin re-uptake inhibitors) are also effective in migraine prophylaxis. We have seen patients with debilitating common migraine who have responded only to this class of compounds.

Optimism in Migraine Treatment

There is good reason for optimism when faced with a patient with migraine. It is usually possible to find an effective drug for acute abortive therapy and another for long term prophylaxis in any patient with chronic severe migraine although it requires patience (on the part of both doctor and patient) and some "detective" work. There is reason to believe that new and more effective anti-migraine therapy will become available in the near future. However, it is by no means clear that these will be "affordable". It is the duty of the pharmaceutical industry as a responsible citizen of the world to make this possible.

DIABETIC NEUROPATHY

H S Lim, MBBS, M Med (Int Med), FAMS

INTRODUCTION

The prevalence of diabetic neuropathy varies from study to study depending on the criteria of diagnosis. Like retinoapthy and nephropathy it is less common at the time of diagnosis in IDDM than in NIDDM. This is because, being usually milder and asymptomatic, hyperglycaemia in NIDDM predates the diagnosis by a relatively longer period. Nevertheless it is often missed unless one actively looks for it. Diabetic neuropathy can be very debilitating with high mortality, especially when the autonomic system is involved. Prevention and early detection should therefore be an integral part of diabetes management.

It is generally accepted that the longer the duration of diabetes and the poorer the pre-existing glycaemic control the higher the incidence of peripheral neuropathy[1]. Severe weight loss may also precipitate neuropathic symptoms. In the Diabetes Control and Complications Trial (DCCT) IDDM patients who had peripheral neuropathy tended to be males, smokers, taller than average, have retinopathy, low insulin secretion, and have onset of IDDM after puberty. Height as a predisposing factor is also reported by Robinson, et al[2].

PATHOGENESIS OF DIABETIC NEUROPATHY

This is not completely understood. It is generally accepted that chronic hyperglycaemia and endoneurial hypoxia probably act in concert to produce the clinical and neurophysiological abnormalities.

In the sorbitol pathway theory, chronic hyperglycaemia promotes an increase in endoneurial production of sorbitol through the enzymatic action of aldose reductase. This leads to myoinositol depletion and altered Na^+-K^+-ATPase activity which ultimately leads to nerve dysfunction. It was therefore anticipated that aldose reductase inhibitors would be therapeutically useful. Unfortunately trials using a number of aldose reductase inhibitors have been generally disappointing.

Endoneuronial hypoxia is postulated to play a central role in diabetic neuropathy (Figure 1). A vital pathway leading to hypoxia is believed to begin with defective delta-6-desaturase activity[3]. The postulated mechanism involves decreased production of gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA), prostaglandin E1 (PGE1), arachidonic acid (AA). PGE1 and prostacycline deficiency causes hypoxia through microvascular and haemorheological factors.

Decreased arachidonic acid also leads to decreased polyunsaturated fatty acids (PUFA), key components of the myelin sheath and neuronal membrane-bound enzymes.

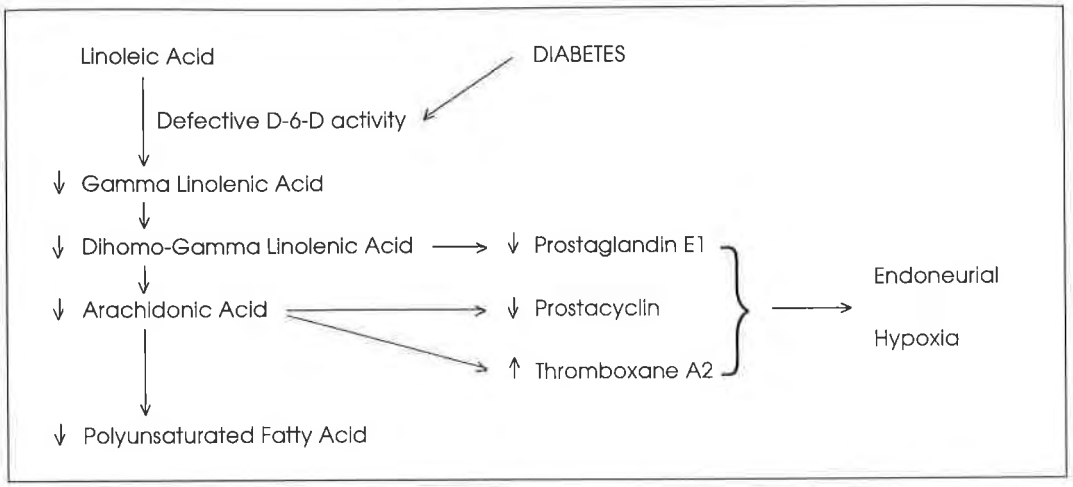
Glycosylation of nerve proteins and haemoglobin can also be expected to cause changes in protein function and structure and tissue ischaemia, and thereby contribute to nerve dysfunction.

CLASSIFICATION OF DIABETIC NEUROPATHY

A clinically useful broad classification into somatic neuropathy and autonomic neuropathy

Senior Consultant
Director, Diabetes Centre
Department of Endocrinology
Singapore General Hospital
Outram Road
Singapore 169608

Figure 1: Suggested Pathogenetic Mechanism in the Causation of Endoneurial Hypoxia



D-6-D = Delta-6-Desaturase
Adapted from Jamal GA[3]

Table 1: Classification of Diabetic Neuropathy

I.	Somatic Neuropathy
	• Distal symmetric polyneuropathy (sensory mainly)
	• Diffuse motor neuropathy
	• Mononeuropathy – Cranial nerve neuropathy Entrapment neuropathy Truncal neuropathy
	• Proximal asymmetric neuropathy
	• Acute painful neuropathy
II.	Autonomic Neuropathy

is shown in Table 1. However the two categories are not mutually exclusive, neither are the various subsets of somatic neuropathy, although occasionally pure forms are encountered. In general only the acute painful neuropathy and the proximal asymmetric neuropathy occur in relation to concurrent poor glycaemic control. For convenience of discussion the somatic and autonomic neuropathies will be discussed separately.

DIABETIC PERIPHERAL NEUROPATHY

Clinical Varieties

The commonest form of somatic neuropathy is the ***symmetrical predominantly sensory neuropathy***. The patient presents with insidious onset of loss of sensation and paraesthetic and various forms of painful sensations that may be described as numbness, pins and needles, aches, pulling and cramps. Varying degrees of hypoaesthesia and loss of ankle jerks are common findings. Muscle weakness and wasting is minimal, if any. Associated autonomic neuropathy is common. The course is variable but usually progressive.

The patient with ***diffuse motor neuropathy*** presents with insidious weakness of lower and upper limbs which are typically wasted and areflexic. Pain and sensory symptoms are almost always not an issue. It is unrelated to existing hyperglycaemia. This condition is very debilitating and progressive. It may resemble motor neuron disease.

In ***proximal motor neuropathy*** (formerly called Garlands diabetic amyotrophy), there is usually unilateral muscle weakness and wasting of the proximal parts of the limbs, more frequently the lower limbs, involving predominantly the quadriceps, iliopsoas and the adductor muscles. Pain in the affected area is variable. There are typically no sensory deficits. The patient is usually an NIDDM in the older age-group with

poor glycaemic control. He has difficulty standing without support, climbing stairs and rising from sitting and lying, and in raising his arms if the deltoid muscles are affected. Metabolic correction usually leads to a gradual improvement and the patient should be repeatedly assured.

When glycaemic control is poor, ***acute painful neuropathy***, due predominantly to small fibre neuropathy, may rarely develop, manifesting as excruciating pain in the trunk and legs, severe muscle weakness and wasting, and absent tendon reflexes. Sensory loss is variable. The term 'neuropathic cachexia' is sometimes ascribed to this condition because of the severe muscle wasting.

Focal nerve palsies are also relatively rare. They usually affect a single nerve at any one time (mononeuropathy) and bear no relation to concurrent glycaemic state. Simultaneous involvement of several nerves define mononeuropathy multiplex. Nerves prone to compression are especially vulnerable. The signs depend on the nerve affected. Median and ulnar nerve involvement presents with motor and sensory signs in the small muscles of the hand. The peroneal nerve at the fibula head and lateral cutaneous nerves of the thigh are sometimes affected. Affection of the third, fourth and sixth cranial nerves leads to various forms of eye movement dysfunction, usually accompanied by mild pain. Facial nerve palsy gives a typical Bell's palsy. In diabetic third nerve palsy, the pupils are spared, unlike third nerve palsy due to external compression. This is because the parasympathetic fibres that subserve the pupillary constrictors, being superficially placed along the third nerve, are not affected by the ischaemic process that is believed to be the underlying mechanism.

Other nerves that may be affected are the various nerve roots. This causes band-like pain around the trunk, easily confused with root compression by degenerative or other spinal conditions, or even the pre-vesicular stage of herpes zoster. Phrenic nerve affection raises the hemidiaphragm. Focal nerve palsies are usually self-limiting.

The Diagnosis of Peripheral Neuropathy

The diagnostic work up should seek not only to establish the diagnosis of diabetic neuropathy but also to rule out other causes of neuropathy, such as alcohol, nutritional deficiency states, autoimmune diseases, etc.

The detection of neuropathy begins with attentive sympathetic appraisal of the patient's symptoms coupled with relevant cross examination, bearing in mind that many symptoms may have a non-diabetic, non-neuropathic basis. Symptom appraisal and review should consider both the positive and negative aspects (Table 2). It should be recorded in the patient's own words for accurate subsequent review of progress, e.g. "my feet cannot feel the floor", "feet feel hot/cold", "prickling", "like ants crawling", "legs feel dead", etc. A general recording of "paraesthesia" may be misleading and is discouraged. Dysaesthetic pain generally has a superficial quality and shooting character and tends to have nocturnal exacerbation. Trunk pain is usually constant in nature and is aggravated by movements or stretching.

Looking for signs of peripheral neuropathy is no different from any neurological examination, but a knowledge of the common presentations and frequent practice shortens the procedure considerably. Muscle wasting and weakness of the main muscle groups of the limbs and tendon reflexes (with reinforcement if necessary) should be looked for. Finger spread and abduction of the thumb should not be passed over. Foot and toe deformities should be looked for. Sharp pain, touch, vibration and joint-position sense can be easily performed using a sterile needle, cotton wool or tissue paper, a 128 Hz tuning fork and by big toe positioning, respectively. Position sense can further be tested by the Romberg's test. In some centres a Biothesiometer (Figure 2) is used to quantitate vibration perception threshold. The Semmes Weinstein Monofilaments (Figure 3) each exerts a specific force depending on its thickness. This is unaffected by the examiner's exertion as the filament's bending with increased force maintains a steady pressure effect. Loss of appreciation of pressure with the 5.07 monofilament (number represents Log^{10} of Force in grams) suggests risk of developing pressure ulcers.

Special attention has to be paid to detecting the neuropathic foot at risk of or already afflicted by complications (Table 3). Some of these may be

Table 2: Symptomatology of Diabetic Neuropathy

SYMPTOMS			
POSITIVE		**NEGATIVE**	
Sensory	***Motor***	***Sensory***	***Motor***
Paraesthesia / Dysaesthesia *	Cramps	Loss of touch	Weakness
Trunk Pain **		Loss of pain	
Hyperaesthesia ***		Loss of temperature	
Thermal sensation		Unsteadiness#	

* *Paresthesia: tingling, buzzing*
Dysaesthesia: prickling, "pins and needles", burning, electric current

** *Aching pain*

*** *Hyperaesthesia: light touch by hand/fingers or ordinary materials like socks causes pain*

\# *Unsteadiness results from diminished / loss of proprioception*

Table 3: The High Risk Foot

Hypoaesthetic/anaesthetic foot
Dry cracked skin
Absent ankle jerks
Pressure points/callosities
Foot and toe deformities, e.g. claw toes
Past history of an ulcer(s) and/or amputations
Presence of an ulcer
Peripheral vascular insufficiency

Figure 2: Measurement of vibration perception threshold with the Biothesiometer

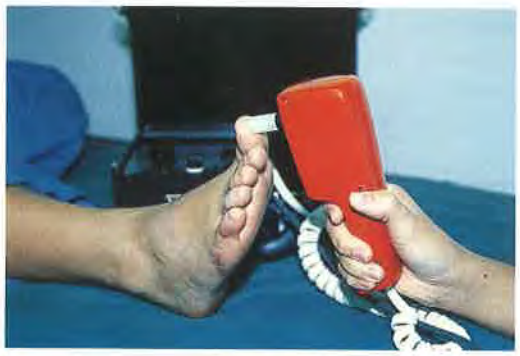
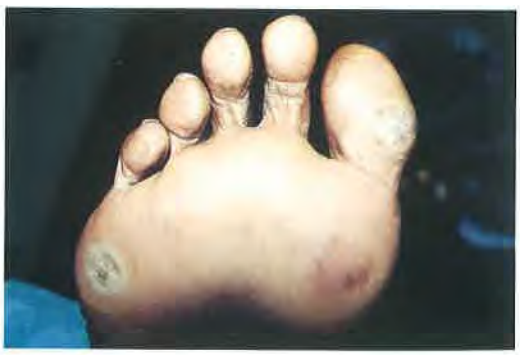


Figure 3: Measurement of pressure perception threshold with the Semmes Weinstein Monofilaments

Figure 4: Dry, cracked and thickened skin of diabetic neuropathic foot



early and subtle, such as thickened skin, corns, and dry cracked skin (Figure 4).

Is there a role for neurophysiological tests? The diagnosis of peripheral neuropathy can usually be made with confidence when there are unequivocal symptoms and signs. Even in the institutional context, non-clinical testing is only necessary in borderline situations or for research purposes. Nerve conduction velocities assess large fibre integrity while amplitude of the action potential gives an impression of nerve fallout.

Primary Prevention

The treatment of peripheral neuropathy and its complications really begins with prevention. The Diabetes Control and Complications Study (DCCT)[4] has proven unequivocally that long-term near-normalisation of blood glucose reduces by 60% the risk of its development and progression. The mere alleviation of symptoms of hyperglycaemia (polyuria, polydipsia, lethargy) is no longer enough. A team approach involving the doctor, diabetes nurse specialist, dietitian and the patient himself, to optimise metabolic control is crucial at this stage. The doctor is duty-bound to screen the patient for neuropathy so that early treatment and secondary preventive measures can be started.

Treatment of Peripheral Neuropathy

Once peripheral neuropathy has developed the management calls for a holistic approach. The doctor is then further supported by the podiatrist, the orthotist and the physiotherapist. The patient's family's role takes on an expanded dimension. Family members will have to inspect and trim the nails of the visually impaired.

Some forms of neuropathy constantly coexist with poor metabolic control (see above) and it is in this setting that euglycaemia has to be quickly established. However this may sometimes paradoxically cause temporary exacerbation of pain as improved nerve function may actually enhance transmission of painful signals.

Once neuropathy has been detected it behoves the doctor to not only to relieve symptoms but also to monitor the condition's progress by regular foot inspection, looking out for features that put the neuropathic foot at risk of complications. These features are listed in Table 4.

Table 4: Management Plan of Diabetic Neuropathy

Team approach	
Glycaemic control	
Whole patient support	
Pharmacotherapy:	Analgesics, Vitamin B's, Tricyclic Drugs (Amitriptylline, Imipramine), Antiepileptic Drugs (Carbamezapine, Phenytoin), Gangliosides, Capsaicin, Aldose Reductase Inhibitors, Gamma-linolenic acid

Poor glycaemic control, presence of other micro-angiopathic complications, visual impairment and social deprivation are the typical settings in which the neuropathic foot is at higher risk of ulceration.

Pharmacotherapy

Pain and paraesthesia can be initially treated with simple analgesics. If these prove ineffective one could use a tricyclic antidepressant such as amitripitylline at a dose varying between 50 to 150 mg per day. If symptoms are mainly nocturnal, the daytime dose is smaller to minimise daytime drowsiness. The pain relief afforded by these agents is believed to be independent of the drug's antidepressant effect; by blocking norepinephrine reuptake by neurons, desipramine, another tricyclic drug, has been shown to potentiate the inhibitory effect of norepinephrine on nociceptive pathways.

Antiepileptic drugs like carbamezapine 200 mg t.i.d. and phenytoin 200-300 mg/day are also effective but their use is limited by potential side effects. The anti-arrhythmic agent, mexiletine at a dose of 450 mg per day in divided doses has also been found effective[5].

A relatively new modality of treatment is capsaicin (0.025-0.075%) cream[6] which desensitises tissues to pain. Capsaicin, an active substance found in hot peppers, acts by initially releasing Substance P, a neurotransmitter of pain signals, from peripheral sensory fibres, and thus depletes it in the long term. It is more effective in relieving dysaesthetic than trunk pain.

Painful muscle contraction as a result of 'splinting' from neural pain may need muscle relaxants, non-steroidal anti-inflammatory drugs and muscle exercises.

Various preparations of vitamins comprising B1, B2, B6 and B12 are reportedly useful in nerve (axon and myelin sheath) repair and axonal transport, and personal empirical experience has been positive.

Supplementation with gama linolenic acid (GLA), such as found in Evening Primrose, has been recently found to improve symptoms, signs and electrophysiological abnormalities[7,8] (see Pathogenesis of Diabetic Neuropathy above).

As mentioned before the aldose reductase inhibitors (ARI's), despite theoretical promise, did not meet up to clinical expectations. Although improvement in nerve conduction velocities[9] can be demonstrated in neuropathic patients taking ARI's, symptom improvement has not been impressive, although it can be argued that at the symptomatic stage nerve damage has been too advanced for the ARI's to have any benefit. Perhaps they could have a place in prevention if given at an earlier stage. However this remains to be seen as side effects arising from their use have been prohibitive.

The Role of the Podiatrist and Orthotist

Once clinical peripheral neuropathy or complications have developed the active participation of the podiatrist and the orthotist is vital. They play a vital role in educating the patient on foot care. Preventive and local treatment of callosities, ingrown toe nails and superficial ulcers can by handled by the podiatrist in the first instance. Subtle high pressure points can be detected using sophisticated pressure analysis equipment. Special footwear and insoles could also be prescribed to take pressure off vulnerable parts of the foot.

Patient Education

It is outside the scope of this article to discuss in detail what the patient should know and do. In general he should be instructed with regards to inspecting his feet regularly, recognising warning signs, correct trimming of nails, simple skin care, proper footwear and appropriate exercise. For example, jogging would be inappropriate for the patient with diminished foot sensation, but bicycling and swimming would be suitable.

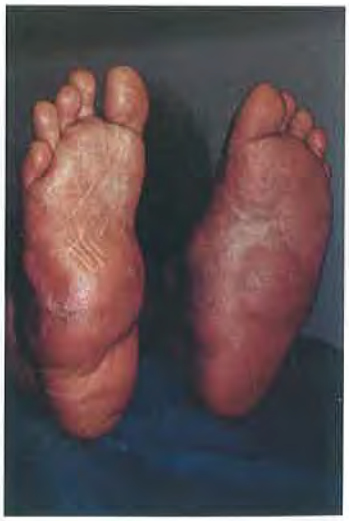
Charcot's Foot

A combination of severe peripheral and autonomic neuropathy leads to the so-called Charcot's foot which is characterised by destruction, disorganisation, collapse and subluxation of joint structures. It is initially painful but becomes painless in the chronic state. There is gross arteriovenous shunting due to opening up of normally collapsed AV shunts. There is therefore increased warmth as a result of hyperaemia. The bones become progressively osteopenic. Increase tracer uptake can be demonstrated on radionuclide bone scan. The affected foot ultimately becomes deformed with typically a rocker bottom and medial protuberance (Figure 5). Treatment consists of prolonged rest and NSAID's in the early stage, but once the condition is established prevention of ulceration, intensive foot care and education and the use of special shoes assumes paramount importance.

AUTONOMIC NEUROPATHY

Cardiac reflex testings show that up to 40% of diabetic patients have autonomic neuropathy, but much less have symptoms. Autonomic neuropathy can occur in association with any of the

Figure 5: Typical rocker bottom soles of diabetic Charcot's feet



somatic neuropathies aforementioned, but it is especially associated with the predominantly sensory neuropathy.

While any part of the widespread autonomic system can be affected, in practice only cardiac, gastrointestinal, urogenital and thermoregulatory manifestations are clinically assessable to diagnosis, then only in a setting of high suspicion index. The common symptoms that should alert the doctor to the problem are listed in Table 5. It can be easily appreciated that all these symptoms are often very non-specific and can be mistakenly attributed to other more common causes.

Table 5: Common Symptoms Suggesting Autonomic Neuropathy

Lightheadedness
Feeling of fullness of stomach
Vomiting of undigested food
Diarrhoea, especially at night
Loss of bladder and bowel sphincter control
Impotence

Cardiac Manifestations[10]

It is not uncommon to automatically attribute all complaints of giddiness to hypoglycaemia. Dizziness due to the ***postural hypotension*** of diabetic autonomic neuropathy is often missed because blood pressure is taken only in one position, usually the sitting position. It is due to sympathetic denervation resulting in loss of reflex vasoconstriction and diminished inotropic and chronotropic stimulation of the heart. It can be easily diagnosed by a fall in the systolic blood pressure of at least 30 mm Hg within 2 minutes after assuming the upright position. Before orthostatic hypotension is attributed to diabetes it is worthwhile excluding postural hypotension due to the effects of antihypertensive agents, dehydration and other hyponatraemic states, withdrawal from steroids and other hypocortisolaemic states like Addison's disease and hypopituitarism.

Simple advice like gradual getting out of bed and use of elastic stockings may be all that is needed to relieve symptoms. The use of antihypertensive agents and sedatives has to be judicious as they aggravate the problem. Severe cases can be treated with 9-a-fludrocortisone at a dose of 0.05 to 0.1 mg od. This mineralocorticosteriod increases vascular tone and blood volume.

Cardiac denervation, or specifically vagal neuropathy, is responsible for resting tachycardia, silent myocardial infarct and dysfunction of left ventricular filling and systolic ejection. Silent myocardial infarction occurs 6-7 times more commonly in the diabetics compared to non-diabetics. Affected patients also often have reduced exercise tolerance. Other associated signs of autonomic neuropathy are a persistent bradycardia with no change in heart rate with posture. Further confirmation can be made by measuring various cardiac reflexes, such as heart rate variation with deep breathing and during the valsalva manoeuvre. A specialised centre is usually but not necessarily the only place that these tests could be carried out. The technique could be learnt and applied in a GP clinic.

Gastrointestinal Manifestations

Gastrointestinal manifestations of autonomic neuropathy include postprandial fullness and vomiting due to gastroparesis, indigestion due to decreased biliary motility, and diarrhoea and constipation due to enteropathy. Attribution of these common symptoms to diabetes is by the associated presence of peripheral neuropathy, exclusion of other local gastrointestinal lesions and by abnormal cardiac reflexes mentioned earlier. Treatment is mostly symptomatic. Gastroparesis affects glycaemic control by upsetting the matching of meals to medications. In older patients it increases mortality from aspiration pneumonia.

Gastroparesis can be further confirmed by stomach emptying studies using radioisotope-labelled liquid or solid food. Treatment is largely symptomatic. Frequent small meals low in fat and non-digestible fibres helps. Erythromycin, which is a gastric motility receptor agonist, at 250 mg t.i.d. is useful for short-term and cisapride 10 mg t.i.d. for chronic use[11].

The diarrhoea of diabetic enteropathy is typically explosive, often accompanied by varying degrees of abdominal pain, intermittent, and

usually occurs at night as well, unlike irritable bowel syndrome symptoms of which are usually confined to the day. It is often aggravated by bacterial overgrowth. Treatment is largely symptomatic and if this fails a course of tetracycline, bactrim or metronidazole may prove effective.

Diabetic Impotence

Up to 75% of males with diabetes for 15-20 years have some degree of erectile impotence. A problem like impotence can masquerade as general weakness or depression or a general inquiry about vitamins and tonics to 'strengthen' the soma. Impotence in the diabetic patient may be functional. Apart from the usual stress that may overtake anybody, the anxiety created by the knowledge that diabetes may cause erectile failure and the demands of diabetes itself may precipitate functional impotence. Many diabetics are also on other medications that may cause erectile problems, such as methyldopa, prazosin and beta-adrenergic blockers. Concomitant hormonal problems such as hyperprolactinaemia and hypogonadism have also to be excluded. Other causes are vascular insufficiency from arteriosclerosis, spinal cord disease, alcoholism, radical pelvic surgery and prostate infections. These have to be excluded before erectile difficulty is attributed to diabetic neuropathy.

Nevertheless many diabetic men do suffer from organic impotence as a result of denervation or small vessel disease of the erectile muscles of the penis. This is often compounded by psychological factors and accelerated arteriosclerosis.

Functional impotence can be differentiated by its intermittent nature and the preservation of morning penile tumescence. Penile tumescence can be measured in a specialised centre by means of various equipment. One such instrument, the Rigiscan Plus (Figure 6), consists of 2 cables with flexible rings at their ends which are put round the penis. The ring circumference increases with penile tumescene. At fixed intervals, tautening of the rings is applied and the resistance to the tautening as tumescence increases gives a measurement of the radial rigidity of the penis. This high-tech instrument allows real-time recording of tumescene and rigidity on a PC using a special software programme. It has the capacity for 30 hours data storage which can be downloaded on to the PC in 5 minutes. Penile tumescence and rigidity can thus be measured in the overnight situation, after visual sexual stimulation and/or after an intracavernosal injection of a prostaglandin. By its anti alpha-1-adrenergic effect PGE1 relaxes penile smooth muscles. This dilates the penile arterioles. Expansion of the cavernosal sinusoids compresses the venules and retards venous outflow. Provided the vascular system is intact the resultant corporeal vascular engorgement produces penile rigidity.

Figure 6: The Rigiscan Plus

Approach to the Diabetic Man with Impotence

A conducive clinic setting is essential to allow the patient to introduce the subject. The approach should then proceed with a tactful review of the patient's general medical, sexual and drug history, including sexual experience, nature and degree of erection problem, followed by a clinical examination and selective laboratory investigations. This should be targeted towards looking for evidence of peripheral neuropathy and functional and non diabetes-related causes as mentioned above.

When there is a high functional

element, reassurance and general help in coping with stress may be all that is initially needed. If there is any doubt, the patient is then referred to the specialist for further evaluation and treatment. Further investigations would then incorporate the objective measurements of penile tume-scence and rigidity, if facilities are available.

Up to 35% of impotent patients taking Yohimbine reported partial functional improvement[12,13]. Yohimbine is an extract of the bark of the Yohimbine tree and has alpha-adrenergic antagonist effect that improves erectile function. A therapeutic trial of Yohimbine HC1 5.4 mg t.i.d. for 8 weeks could be given before more aggressive treatment is considered. In successful cases withdrawal of the drug causes a relapse, and hence the drug has to be continued on a long term basis. Long term side effects are thought to be minimal.

The options for more invasive treatment of diabetic penile erectile failure are (1) intracavernosal injection of PGE1[14] (2) vacuum suction device[15], and (3) penile prosthesis[16,17]. These methods of treatment should only be undertaken by endocrinologists and/or urologists trained in their use. They should be decided upon only in consultation with the spouse. Their use, especially self injection and vacuum suction device, requires a certain degree of dexterity on the part of the patient. The varieties of penile prosthetic implants include the (a) semi-rigid or malleable rods, (b) units that have inflatable balloon cylinders or chambers, and (c) units consisting of small plastic blocks so arranged that they can be bent to produce rigidity.

Retrograde ejaculation may be treated with antihistamine with anticholinergic activity such as brompheniramine 8 mg bd or the sympathomimetic agent, phenylpropanolamine 15 mg bd time-release capsules.

Thermoregulatory Problems

Sympathetic denervation is the mechanism behind the deranged thermoregulation seen in diabetics. Deficient sweating in the lower extremities results in cutaneous dryness predisposing to skin cracks and all its corollary. In some instances compensatory excessive sweating in the upper part of the body gives the impression of thyrotoxicosis or hypoglycaemia. Socially embarrassing hyperhidrosis can be treated with anticholinergic drugs such as benxhezol, but its adverse effect on bladder function has to be considered especially in the presence of neurogenic bladder and prostatomegaly.

Urogenital Problems

The patient with autonomic neuropathy of the bladder has weakened, and therefore prolonged, urine stream and post-micturition dribbling. Intervals between micturition get progressively longer such that the presence or absence of polyuria or nocturia assumes less importance in assessing control. Urodynamic studies and ultrasound imaging show increased residual urine and a thickened bladder wall. Progressive retention of urine ultimately leads to retention overflow. The bladder becomes palpable. Risk of urinary tract infection is increased. In the early stage manual bladder compression at regular intervals, and the use of a parasympathomimetic drug such as bethanechol chloride (10 mg qid) helps, but many patients eventually require intermittent self catheterisation or a permanent indwelling catheter.

Hypoglycaemia Unawareness

Although many patients who lose the classical warning signs of hypoglycaemia are found to have autonomic neuropathy, this is not invariably so. Hypoglycaemia unawareness is also related to the duration of the diabetes independent of autonomic neuropathy. The patient often lapses into neuroglycopaenic state of psychomotor dysfunction and even stupor without prior warning. An appreciation of this state of affairs on the part of family members and home blood glucose monitoring become more imperative than ever.

Prognosis of Autonomic Neuropathy

The presence of autonomic neuropathy carries a poor prognosis. Mortality goes up to 40% in five years in the presence of symptomatic autonomic neuropathy. In part this is because of the frequent coexistence of other micro and macroangiopathic complications. The risk of sudden death is increased. The cause of this is not well understood but may be due to cardiorespiratory arrest, sudden arrhythmia, or sleep apnea.

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MANAGEMENT OF MOTOR NEURON DISEASE

R Pavanni, *MBBS (S'pore), M Med (Int Med)*

INTRODUCTION

One of the first descriptions of motor neuron disease was based on Aran's report in 1850 of 11 patients with a progressive muscular wasting disease. Charcot was the first to give a complete clinical and pathological picture in 1874. The term "Amyotrophic Lateral Sclerosis" (ALS) has been used synonymously with motor neuron disease (MND) but ALS is a specific disease whereas MND is a more general term and will be used throughout. The clinical management and ultimate prognosis of a patient with MND will be discussed and what lies in the future for these patients.

CLINICAL PICTURE

MND generally starts as an asymmetrical, progressive muscular atrophy with fasciculations, cramping and weakness. The atrophy can begin in any striated muscle but the extrinsic eye muscles are generally not involved. Muscular cramping is very frequently the initial symptom and is seen in the muscles that are already weak or will become weak during the course of illness. Fasciculations are also seen in involved muscles but fasciculations alone are not equivalent to motor neuron disease if there is no denervation.

Muscular fatigue increases the weakness and these patients may have an unusual sensitivity to curare whereas neostigmine may give partial relief to their symptoms. Cold weather also sometimes increases the weakness.

Muscular atrophy begins in one hand in approximately one third of the patients, which is the classic form of the disease described by Charcot. The weakness, when it occurs in the hands as well as when it occurs in other parts of the body, involves muscles innervated in a segmental pattern and not in the distribution of a peripheral nerve. Thus in the hand, the atrophy and weakness eventually involve the entire hand, with flattening of both the thenar and hypothenar eminences and wasting of the interosseus spaces.

Characteristically, wasting begins in one hand and remains there for several months or occasionally a year before spreading to the other side. The reflexes in the involved limb are generally increased. The disease eventually spreads to involve the opposite side and other muscles, with the originally involved hand remaining the most severely involved until late in the disease. As the disease progresses, the patient becomes severely handicapped, whereby a characteristic appearance develops with the patient's arms dangling limply from sagging shoulder girdles. In about a fourth of the patients, weakness begins in the bulbar region and spreads to the rest of the facial muscles. Sometime during the course of the disease, patients may develop involvement of the pyramidal tract with clinical findings of spasticity, hyperreflexia, and the presence of the snout reflex or Babinski or both.

Disorders of eye movements are rarely seen and are usually found late in the course of the disease. Emotional incontinence is a common

Consultant Neurologist
Department of Neurology
Singapore General Hospital
Outram Road
Singapore 169608

accompaniment of pseudobulbar palsy. Fasciculations are a well known concomitant of muscular atrophy and by themselves are not diagnostic of denervation, but their widespread presence in a patient with obvious weakness suggests that the patient has motor neuron disease.

The predominance of MND in males has been seen in various studies and in about 5 to 10% of patients, a family history of the disease has been noted throughout the world. The clinical course is a progressive one, with eventual involvement of all the straited muscles other than the ocular ones. The patient becomes confined to bed and eventually his respiration becomes so laboured and compromised that he is unable to obtain adequate aeration of the lungs. This is usually the cause of death.

Table 1: Diagnostic criteria for MND (ALS)

The diagnosis of ALS requires the presence of:

- LMN signs (including EMG features in clinically normal muscles)
- UMN signs
- Progression of the disorder

Diagnostic categories:

- *Definite ALS:* UMN plus signs in three regions
- *Probable ALS:* UMN plus LMN signs in two regions with UMN signs rostral to LMN signs
- *Possible ALS:* UMN plus LMN signs in one region, or UMN signs in two or three regions, such as in monomelic ALS, progressive bulbar palsy, and primary lateral sclerosis
- *Suspected ALS:* LMN signs in two or three regions, such as in progressive muscular atrophy, and other motor syndromes

The diagnosis of ALS requires the absence of:

- Sensory signs
- Sphincter disturbances
- Visual disturbances
- Autonomic dysfunction
- Parkinson's disease
- Alzheimer type dementia
- ALS "mimic" syndromes

The diagnosis of ALS is supported by:

- Fasciculations in one or more regions
- Neurogenic change in EMG studies
- Normal motor and sensory nerve conduction (distal motor latencies may be increased)
- Absence of conduction block

DIAGNOSTIC CRITERIA

At the World Federation of Neurology consensus conference in 1990 at El Escorial, Spain, research diagnostic criteria for MND were suggested (Table 1). These criteria were based on clinical evidence with certain exclusive criteria. Although valuable as research criteria, the El Escorial criteria do not take into account the vagaries of clinical practice. Thus for clinical rather than research purposes the exclusion criteria should be interpreted flexibly and used to alert clinicians to rare and potentially treatable disorders.

In the differential diagnosis of MND a large number of disorders must be considered (Table 2), but in practice the diagnosis is usually

Table 2: Differential Diagnosis of MND

- Cervical spondylitic myelopathy and other cervical and lumbosacral radiculopathies
- Disorders associated with autoimmune processes
  - (a) Dysimmune lower motor neurone syndromes
  - (b) Monoclonal gammopathy with conduction block and motor neuropathy
  - (c) Lymphoma
  - (d) Paraneoplastic syndrome (encephalomyelitis with anterior horn cell involvement)
- Thyrotoxicosis
- Hyperparathyroidism
- Diabetic "Amyotrophy"
- Radiation-induced neurogenic disorders
- Post poliomyelitis progressive muscular atrophy
- Genetic enzyme defects: hexosaminidase A and (rarely) B deficiency
- Exogenous toxin disorders (lead, mercury, manganese toxicity)
- "Prion" disorders (amyotrophic forms of Creutzfeldt-Jakub disease)
- Certain myopathies, such as inclusion body myostis

straightforward by the time the patient is referred to a neurologist. Because the early symptoms may be ill-defined, or may be mistaken for localised lesions, it is common for patients to be referred first to rheumatology, orthopaedic, ENT or psychiatric departments.

PATHOLOGY

The essential pathologic feature is a loss of neurons in the ventral horn cells and degeneration and atrophy of those that remain. In general, this is apparent in the motor nuclei of the lower brainstem as well as the spinal cord. A common finding is that of extensive neuronal loss accompanied by astrocytic gliosis. The widespread sclerosis of the lateral columns is more severe at lower than at higher levels. There is much variability in the pathologic lesions of patients with motor neuron disease. A feature common to all is a loss of anterior horn cells. Most patients have changes in the rest of the spinal cord of varying severity which differs from patient to patient.

INVESTIGATIONS

The purpose of laboratory investigations is to exclude other diagnoses, and to support the diagnosis of MND. There are no specific biochemical or pathological markers of the disease.

Necessary Investigations

ESR, hematological and biochemical screen, chest radiographs and ECG should be undertaken. It is also wise to request for antinuclear antibody, thyroid function tests, vitamin B12 and folate levels, VDRL tests and protein electrophoresis. Electromyography and nerve conduction studies are important aids to the diagnosis of MND, and can exclude other neuromuscular disorders such as myopathy and motor neuronopathy. EMG furnishes evidence of widespread denervation and re-innervation from anterior horn cell damage that cannot be explained on the basis of a localised disease process. Important points to consider are that motor conduction velocity is seldom low enough to suggest demyelination and conduction block is not a feature of typical MND.

MRI is now regarded as mandatory in patients with possible MND; that is, where there is any possibility that the signs might be caused by a single lesion. Imaging may be focused on the head, neck, or thoracolumbar region, depending on the presenting symptoms and signs. Lumbar puncture with CSF analysis can be undertaken in atypical cases but in most cases, CSF analysis adds little and is generally not undertaken in most centres. A variety of conditions may mimic the clinical features of MND and further investigations like HIV screening, blood for lead and 24-hour urinary lead excretion may have to be done.

EPIDEMIOLOGY, RISK FACTORS AND PREVENTION

The incidence of MND is 1-2 per 100,000 and the prevalence is 4-6 per 100,000 in most parts of the world. The average general practitioner might expect to see a new case of MND once only in 25 years. Most surveys have found that the incidence of MND increases with age to a peak incidence between 60 to 70 years. In almost all studies, men are more commonly affected than women, with a ratio around 1.5:1.

PROGNOSIS

Median survival for all sporadic MND patients is about 3-5 years from onset of symptoms. A recent prospective study by Chancellor et at reported that overall, 50% survival from symptom onset was 2.5 years and 5 years survival rate was 28%. Bulbar onset is associated with a significantly reduced survival, with the median survival being about 2.2 years. Older age and female sex are adverse risk factors.

COMMUNICATION AND COUNSELLING

This is important and ideally should be a multidisciplinary approach. The care giver or close relatives should be informed of the diagnosis and allowed to explore all the implications of the diagnosis. They should be told that a normal life can be lead and various adjustments may have to be made along the way.

TREATMENT STRATEGIES

There have been various strategies and these include immunotherapy, vitamin and anti-free-radical therapy, agents modulating glutaminergic transmission and other miscellaneous agents.

These are all experimental and, at the moment, there is no definitive cure for these patients. Management at present is mainly supportive. Salivation and swallowing is a major problem and percutaneous endoscopic gastrostomy is helpful here for feeding. Ventilatory failure is a terminal event with superimposed infection being a problem at times. Home ventilation can occasionally be considered but this is a big burden on families. The terminal event should be explained carefully to the relatives and close physical and emotional support from both the medical and paramedical teams and counsellors is very much needed at this time. Management of MND still has a poor prognosis at the present time.

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COUNTER-TRANSFERENCE IN PSYCHOTHERAPY

G S Devan, MBBS, DPM, MRCPsych, FAMS

Summary

The concepts of counter-transference within a psycho-dynamic framework is discussed in relation to psychotherapeutic work with patients. The evolution of the concept from a traditional Freudian approach to an interpersonal approach to the subject is outlined. The paper outlines the various aspects of counter-transference that arise in clinical psychotherapy such as counter-transference and its role in projective identification, erotic transference and erotic counter-transference, management of counter-transference with borderline patients and counter-transference during termination.

Keywords: *Counter-transference, psychotherapy, projective identification, borderline patients, erotic counter-transference, termination*

COUNTER-TRANSFERENCE

The evolution of the concept of counter-transference ranges from the classical Freudian definition to later revisions which defined counter-transference in an interpersonal context. A knowledge of counter-transference enables the psychotherapist to do effective therapeutic work of interpretation, working through the transference and containment of patients' projections.

FREUDIAN CONCEPT

Freud introduced the concept of counter-transference and defined it as the analyst's transference to the patient or the analyst's reactions to the patient's transference. Freud considered counter-transference as a hindrance, and if it appears, the therapist is recommended further personal therapy for himself, in order to maintain the therapeutic alliance. One must remember that the Freudian era included mainly neurotic patients. Counter-transference from treating neurotic patients is not so intense compared to borderline patients. The Freudian definition will have to be modified to cater to the management of personality disorders.

INTERPERSONAL APPROACH TO COUNTER-TRANSFERENCE

By modern day standards, most psychotherapists will agree that the Freudian definition is too narrow. Kernberg considered counter-transference as the total emotional reaction of the therapist to the patient[1]. This is considered as a broad-based definition. Other post-Freudian contributors to the subject include Winnicott (objective hate)[2], Heiman[3], Little[4] and Hamilton[5]. Heiman and Little have both emphasized that counter-transference can be effectively utilised in psychotherapy – firstly, as a diag-

Consultant Psychiatrist
Department of Forensic Psychiatry
Institute of Mental Health
10 Buangkok Green
Singapore

nostic tool, and secondly as a mechanism whereby the therapist learns about the patient's internal world (internal object relations).

COUNTER-TRANSFERENCE SIGNALS

Greenson[6] has outlined the signals of counter-transference, referring to the therapist's affective state. This is outlined in Table 1.

Counter-Transference and Projective Identification

Projective identification is commonly used by borderline patients. Its mechanism involves both the patient and the therapist and has an intrapsychic and interpersonal component which involves counter-transference. Odden[7] has identified the different stages of projective identification as shown in Table 2.

Table 1:
Therapist's Affect and Counter-Transference

- Anger
- Sexual feelings
- Boredom
- Falling asleep
- Uncontrollable laughter
- Repeated dreams of patient
- Frequent slips of tongue
- Forgetting appointments
- Late coming

Table 2:
Stages of Projective Identification

- Patient projects self / object representation onto the treater
- Identification of the projection by the therapist who in turn is manipulated into behaving like the projected self of patient
- Detoxification and modification of projected material
- Reintroduction of detoxified material on the patient

In step 2, the patient identifies with the patient's projection through his counter-transference. However, to play an effective therapeutic role, the therapist must be able to contain or hold on to the patient's projection so as to allow detoxification rather than reproject without detoxification. The management of projective identification is an important step in the psychotherapeutic management of regressed states occurring in narcissistic and borderline personality disorders.

Counter-Transference and Erotic Transference

Recent emphasis has been given to counter-transference reactions to the erotic transference. Erotised counter-transference may lead to sexual misconduct by the therapist or violations of the boundary between the patient and the therapist[8,9]. In 1994, Gabbard[10] has described the type of counter-transference responses to the patient's erotic transference. A male therapist might diagnose erotic transference in an attractive female patient when none exists. This phenomenon could be explained by the therapist projecting his own sexual feelings towards the patient. When the patient wishes sexual closeness, the therapist might over-react by rejecting the patient through aloofness, silence or withdrawal of empathy. Rejection of the patient could be attributed to the fact that the therapist may fear that his own sexual feelings will get out of control. When erotic counter-transference appears, the therapist must seek consultation with senior colleagues. Sexual boundary violations by therapist are infringements of the doctor-patient relationship which can lead to litigation by patients, destruction of the psychotherapeutic relationship, or worsening of patient's mental state. A change of therapist is recommended when erotic counter-transference cannot be resolved.

MANAGEMENT OF COUNTER-TRANSFERENCE

One of the major obstacles to effective psychotherapy is the therapist's inability to analyse the negative transference. Therapists may avoid analysis of hostile feelings of patients because of their own insecurity about handling their own aggression. If the negative transference is not addressed, patients may not be able to terminate

or therapy will not progress. In Asian culture expression of aggression overtly may not be tolerated. This may lead to denial of hostile feelings in psychotherapy.

Self psychology informs us that when the mirror transference appears, the therapist may feel bored or ignored by the patient. On the other hand an idealising transference may provoke feelings of being admired by the patient which again must be avoided.

In the personality disordered patient, the therapist may try to deflate the balloon-like grandiosity of the patient by a premature irresistible urge to confront such grandiosity. Inability to contain patient's negative projections may also lead to disastrous interpretations. An aloof non-participating therapist may shut off the patient (due to insecurity) from projecting his internal object world onto the therapist. The rage reactions of borderline patients may at times become difficult to contain.

The management of counter-transference especially with borderline patients requires holding, containment, internal supervision[11], self-analysis, and silent interpretation[12]. Attending psychotherapy institutes, receiving personal psychotherapy, arranging consultation from senior colleagues and obtaining supervision, are some of the ways in which counter-transference could be dealt with effectively by the therapist. Even the best psychotherapist must receive help to deal with his counter-transference. Therapists should not isolate themselves and they should be partners of peer reviews. Searles[13] has reminded us that therapists may unwittingly use the patient as a receptacle for our unwanted personality components.

While transference is analysed, counter-transference should be monitored so as to prevent therapist's acting out. Such monitoring must take place in every session, while the therapist notes the moment-by-moment positive or negative feelings towards his patients, silently reflecting on these feelings and determining the historical determinants from the therapist's past. Masterson[14] reminds us that the most difficult skill to acquire in treating borderline patients is the ability to recognise and control one's identification with patient's projections.

COUNTER-TRANSFERENCE IN TERMINATION

Termination of psychotherapy is a difficult task for both patients and therapist. Counter-transference problems are rife during this period. Counter-transference feelings may get acted out; termination issues may be avoided by the therapist due to guilt. Sexual acting out may occur, with conversion of a psychotherapeutic relationship to a sexual relationship. All possible interventions should be taken to avoid such an event from occurring. Therapist over-disclosure may also occur. Unanalysed negative transference may hinder effective termination. Every psychotherapist must be prepared to lose his patient and bear the loss of a relationship so that the patient can terminate from a successful psycho-therapy.

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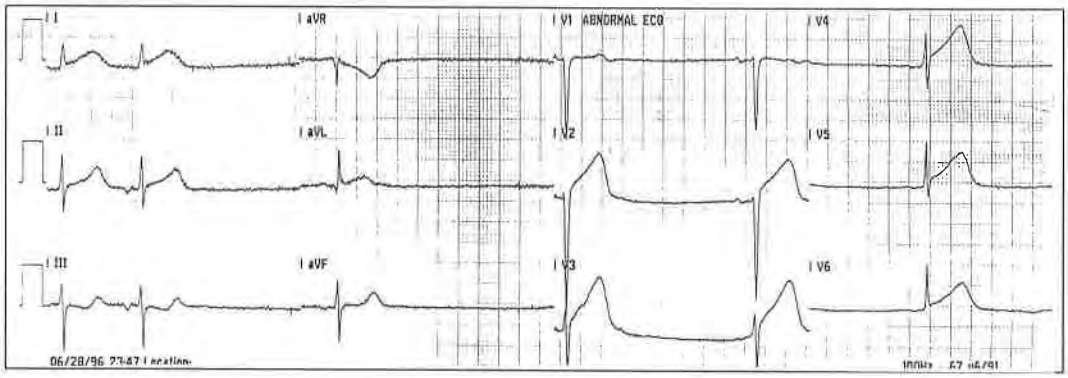
ECG QUIZ

CMC, F/80: non-insulin dependent diabetes mellitus, complained of vague abdominal discomfort and nausea but denied chest pain. Referred to gastroenterologist. Gastroscopy revealed gastritis.

ECG I



(a) What is the underlying rhythm?

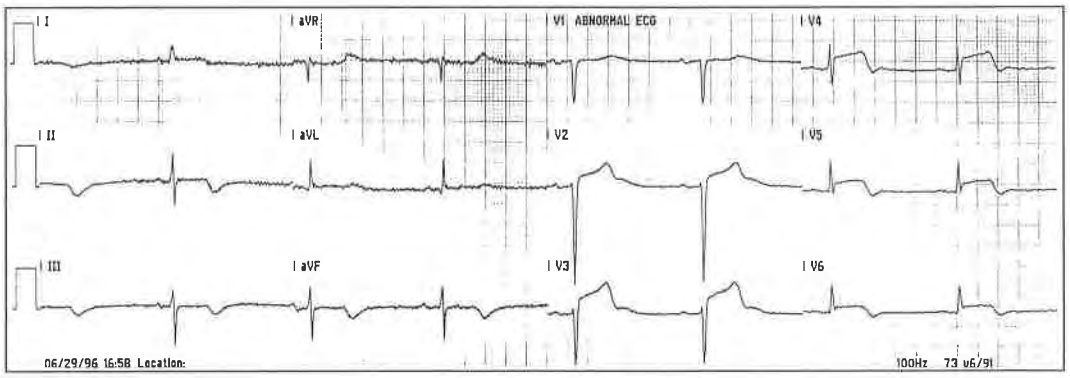
(b) Comment on the ECG complexes.

(c) What is your diagnosis?

(d) How would you further manage this patient?

The following day, she was referred to see the cardiologist because of further ECG abnormalities. She remained well and denied any chest pain throughout her stay.

ECG II



(a) What is your diagnosis?

(b) How would you manage this patient?

For answers to ECG quiz, please turn to page 182

ANSWERS

ECG I

(a) The heart rate is slow at 40 bpm. This is inappropriately slow. In the absence of medications that can slow her heart rate i.e. digoxin, beta blockers, calcium antagonists and amiodarone, it is important to rule out sinus node dysfunction. As she has no dizziness nor syncope, there is no indication for prophylactic pacemaker implant. However, the patient must be informed.

(b) The QRS complexes are narrow. However, there are ST elevations in the anterior leads I, AVL, V2-6 and reciprocal ST depression in lead III.

(c) This is consistent with the very early changes of anterior myocardial infarction. Note there are no Q waves in the corresponding leads. These usually occur much later.

(d) The clinical presentation of acute myocardial infarction can be atypical in the elderly and non-dramatic as indicated in this case. It is very unusual to have abdominal symptoms as a clinical presentation of anterior myocardial infarction. This is more apparent with inferior wall infarction. However, the ECG abnormalities should alert the attending doctor to refer the case to the cardiologist for further management.

ECG II

(a) The ECG has evolved with more pronounced ST elevation in the anterior leads V2-6 and T wave inversion in the inferior leads. The resting heart rate remained inappropriately slow as this is usually faster with anterior wall infarction.

(b) The absence of chest pain limited the timing of the onset of this anterior myocardial infarction. Hence, it was inappropriate to start her on thrombolytic therapy as there is an inherent risk of bleeding especially in the elderly. Instead, she was started on intravenous heparin and Ticlid to lessen the risk of extension of myocardial infarction. She was also on nitrates to prevent coronary arterial spasm. She had a coronary angiogram and this confirmed that she has only a 50% stenosis at the proximal segment of the left anterior descending and a 75% stenosis of the dominant right coronary arteries. She had balloon angioplasty and stenting of the right coronary artery. She has been well after her discharge. On retrospect, she may have coronary artery spasm of the left anterior descending artery with anterior wall injury.

Remember two points:

(a) Clinical presentation and ECG changes of acute myocardial infarction in elderly patients can be atypical.

(b) The pathophysiology and extent of underlying coronary arterial disease is unclear until the coronary angiogram. Hence, it is not always true that elderly patients will end up with coronary arterial bypass surgery although this is more likely than the younger age group.

* *Dr Koo Chee Choong*
6 Napier Road #02-15
Gleneagles Medical Centre
Singapore 258499

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The Whole Paper

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  Type throughout in upper and lower case, using double spacing, with three centimetre margins all round. Number every page on the upper right hand corner, beginning with the title page as 1.

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  Arrange the manuscript in this order: (1) title page, (2) summary, (3) text, (4) references, (5) tables, and (6) illustrations.

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* Insert at the bottom: name and address of institution from which the work originated.

The Summary

* The summary should describe why the article was written and give the main argument or findings.

* Limit words as follows: 100 words for major articles; 50 words for case reports.

* Add at end of summary: an alphabet listing of up to 8 keywords which are useful for article indexing and retrieval.

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The text should have the following sequence:

* Introduction: State clearly the purpose of the article.

* Materials and methods: Describe the selection of the subjects clearly. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known. Describe new or substantially modified methods, giving reasons for using them and evaluate their limitations. Include numbers of observations and the statistical significance of the findings where appropriate.

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  Laboratory values should be in SI units with traditional unit in parentheses.

  Do not use patient's names, initials or hospital numbers.

* Results: Present results in logical sequence in the text, tables and illustrations.