THE SINGAPORE FAMILY PHYSICIAN

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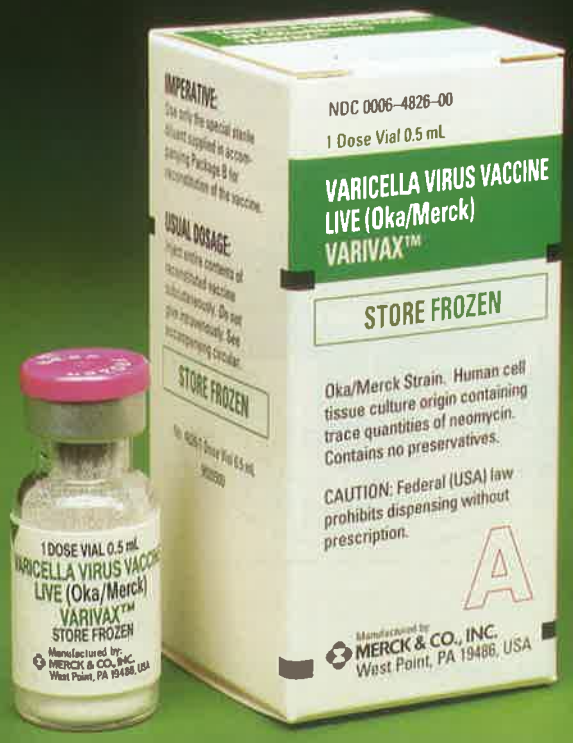

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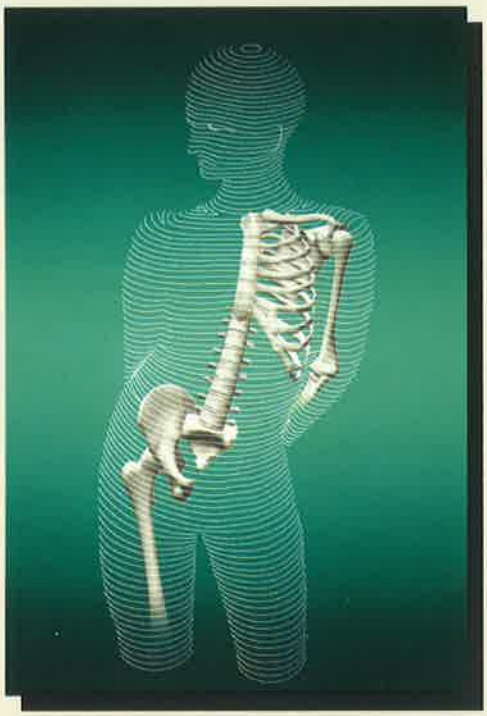

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The Role of the GP in Stroke Care

Introduction

The GP can play important roles in stroke care namely, through primary prevention, patient education for patients to present themselves early for acute stroke care, motivation and advice to patients on the need for persistence in stroke rehabilitation and prevention of a second stroke.

Primary Prevention

Perhaps it is in primary prevention that the GP can play the biggest role, It is no easy matter but worth the effort. Hypocrates observed 2000 years ago that "It is impossible to cure a severe attack of apoplexy and no easy matter to cure a mild one." The situation holds true today(1).

It is now clear that the three most important risk factors for stroke are hypertension, cigarette smoking and atrial fibrillation(2). The evidence is that stroke incidence can be reduced by some 40% after an average of two or three years of antihypertensive treatment and that this reduction appears rapidly during antihypertensive treatment.

Whilst the evidence for elevated diastolic blood pressure has been widely accepted, it is only more recently that there is certainty over the appropriate management of isolated systolic hypertension. Such hypertension increase in frequency with age and is not uncommon in the elderly. The SHEP study and the MRC Trial of Hypertension in the Elderly have shown that isolated systolic hypertension should be treated. Thiazide diuretics are the drugs of first choice in such hypertension(3).

Cigarette smoking has earned its place as a major risk factor for stroke only recently. The importance of this observation suggests the place for some skilful intervention. Similarly, the identification of patients with atrial fibrillation is important because there is evidence that these people will benefit from warfarin anticoagulation.

The role of dietary salt has also been the subject of recent studies, and meta-analysis indicate that a 50 mmol/24 hours reduction in sodium intake, which could be achieved by avoiding salty foods and by not adding salt at the table, would lead to an average of 5/3 mmHg reduction in blood pressure. This in turn could mean 26% fewer strokes and 15% fewer coronary heart disease deaths. Thus, salt restriction may be the most simple, economical and yet most effective measure available for stroke prevention (4).

Early Presentation

Results from two National Institute of Neurological Disorders and Stroke (NINDS) studies indicate that administration of alteplase (recombinant tissue plasminogen activator: rt-PA) within three hours of symptom onset to appropriately selected patients with acute ischaemic stroke improves patient outcome (5). Several factors that delay time-to-management in patients with stroke have been identified, the most important of which is probably the failure of the patients (or family member) to recognise the signs and symptoms of a stroke. It would be useful for the medical community to follow-up the outcome of such interventions in the current literature. Once it is clear that such interventions are successful in reducing morbidity and mortality, the logistics in acute stroke management may well take on a new shape. The GP certainly has a role in helping patients recognise a stroke and to emphasis the need to come in time.

Stroke Rehabilitation

Stroke rehabilitation should be extended to as many as possible who can benefit. It is a difficult process for each patient. Difficulties of relearning lost functions, despair and depression discourage many to continue. The GP has a role in advising the patient and family members of the usefulness of relearning lost functions and by reiterating that persistence has huge dividends.

Prevention of a second stroke

Unless the underlying risk factors are attended to, a second stroke may occur. There is a need, therefore, to work on the patient and family to deal with hypertension, the cessation of smoking and warfarin therapy for atrial fibrillation from rheumatic valvular disease.

Conclusion

Today, stroke stands as the third commonest cause of death in Singapore. It accounted for 11.6% of the 15586 deaths in 1996. For every death, there will be 3 or more others who are left with varying degrees of impairment, disability or handicap. Primary prevention is still the best way forward.

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Is Basic Ultrasound Relevant To Family Physicians?

Introduction

In the present day practice of Family Medicine, medical imaging has become an important adjunct to clinical examination. This is particularly true for a bedside medical imaging tool like ultrasonography. Its potential is beginning to be currently exploited by the new cadre of General Practitioners and Family Medicine Specialists who have had exposure to ultrasonography in their early formative years and are not technology shy. Some of the more senior clinicians in private practice too have begun to embrace this tool in their daily practice. It was, therefore, felt that a structured teaching programme culminating in a diploma recognizing skills acquisition in ultrasonography is timely. After in-principle approval from the Director of the School of Postgraduate Medical studies, a protem committee was assembled in June 1997 to put together just such a course that would be of major benefit to the General Practitioners and Family Medicine Specialists in Singapore. The committee includes representatives from the Department of Community, Occupational and Family Medicine, National University of Singapore, the Antenatal Diagnostic Centre of the Department of Obstetrics & Gynaecology, National University of Singapore and nominated representatives from the College of Family Physicians, Singapore.

Aims & Goals

The programme that has been agreed with the School of Postgraduate Medical Studies is targeted at health care professionals in Singapore and the Asia-Oceania region. It shall, in the first instance, be open only to General Practitioners and Family Medicine Specialists in Singapore. It will later be extended to other clinicians in private and institution practice and trained midwives. The primary objective of the course is to enable the participants to be proficient in basic ultrasonography in obstetrics and gynaecology. This will translate into better health care for the population at large; they will enjoy a higher standard of medical management at the Family Medicine echelon.

Programme Structure

The programme will be structured in modules with a large distance-learning component. There will be an appropriate blend of lectures, hands-on training, log work and formative self assessment programmes. The main teaching faculty will include staff trained in ultrasonography from the National University Hospital, the Singapore General Hospital and the KK Women's and Children's Hospital in Singapore. The assessment will be both formative and summative.

Being a hands-on subject, participants will be required to perform 400 ultrasonography scans as an examination requirement. For each participant, there will be 3 practical sessions. At each session the participant will perform up to four supervised ultrasonography scans.

Conclusion

It is important that ultrasonography be part of the armamentarium of the modern Family Physician. With a sound grounding in the use of this modality of diagnosis, the Family Physician will be able to confirm at the bedside his clinical impressions objectively. This will enable him to provide a more confident and scientific diagnosis.

Dr Alfred W T Loh
President

Regimens for Hormone Replacement Therapy

McCarthy T

1. Rationale for use of HRT.

There are 5 basic reasons for initiating treatment with 'HRT':

(1) Premature menopause: (age < 40)
(2) Symptoms associated with low oestrogens: (at any age)
(3) Therapeutic: good evidence currently for osteoporosis, coronary disease (possibly also for colo-rectal cancer, Alzheimer's Disease etc.)
(4) Preventive: women with genetic/ medical disposition to the above
(5) Informed choice: (after clinical menopause)

2. The variables for HRT regimens include:

2.1 Starting date in relation to age/ symptoms/last menses:

Patients with premature menopause clearly need treatment from the age of diagnosis until at least 40 (and probably 45) both for psychological reasons and to reduce the risks associated with premature and prolonged oestrogen loss. Therapeutic indications will usually not start before the cessation of menses since adequate circulating oestrogens will be present until that time. In at least 15% patients 'menopausal symptoms' occur before the 'last period'. This is currently known as 'the menopause transition' in the USA. Blood oestrogen levels are usually in the 'low normal' range but many patients benefit dramatically from hormone supplementation. About 15% of female bone mass is lost in the years immediately following loss of significant circulating oestrogen. Once lost this 'sex hormone dependent' bone is difficult to replace, hence the trend to start preventive treatment at the time of menopause even though the major rise in osteoporotic fractures occurs 15-20 years later (cardiovascular /coronary thrombosis 10-15 years later). An alternative is to monitor women without replacement, only prescribing HRT when evidence of disease presents.

2.2 Duration of therapy: arbitrarily divided into short term (< 1 year), prolonged (1-7 years) and 'lifetime':

If HRT is prescribed for therapeutic or preventive reasons it will be for a prolonged period starting with confirmation of the index disease. Use of HRT after the menopause has little impact on osteoporosis after the age of 75 unless it is continued > 7 years (the equivalent data on coronary artery disease are not available). If given for symptoms it is possible to stop after a few months or years and to see if symptoms return. Long term 'compliance' on HRT regimes has been consistently reported as low but it is not clear whether this is due to reduction of symptoms after a few months/ years use or to fears of possible side effects (particularly breast cancer).

2.3 Continuous or cyclical therapy

Before 1975 oestrogen was usually given in 3 weekly cycles followed by a free week, with the (unfulfilled) hope that any tendency to uterine cancer would be negated by the horrnone free period. This practice has been widely continued in the USA despite the addition of cyclical progestogens but in Europe continuous oestrogen regimes are more often prescribed. There are no data on the influence this has on benefits or risks associated with HRT but a 'carry over' effect is such that there is no recurrence of symptoms even if oestrogen is only given 3 weeks out of 4. After hysterectomy oestrogen is generally prescribed continuously on both sides of the Atlantic. Low potency oestrogens (e.g. oestriol), when given for atrophic vaginitis in older women, are often given symptomatically without opposing progestogen.

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The duration of progestogen appears to be the crucial factor in controlling endometrial hyperplasia and cancer. Originally given for 7 days each cycle the recommended exposure has been increased to 10-14 days. Even so a higher risk of endometrial cancer has been observed in some trials. If progestogen is given continuously, many women, soon after the menopause, experience disturbing spotting or irregular bleeding. Since the endometrial protection is best with continuous regimens many physicians now give cyclical progestogens in the perimenopausal period converting to 'continuous combined' regimens after 3-5 years.

2.4 Dosage of oestrogen/progestogen:

Before associations between endometrial and breast cancer were recognised, oestrogens were prescribed in high doses (up to 6mg conjugated oestrogen / day). However 0.625 mg conjugated oestrogen (or 2mg oestradiol) has been found enough to give protection against osteoporosis and heart disease while reducing symptoms to tolerable levels in most women. In general the highest circulating oestrogen levels are found with implants, lower with oral preparations and lowest with skin patches. The dosage of progestogen has been progressively reduced with realisation that duration of use is the critical factor and the least dose available to induce regular withdrawal bleeding (in cyclical regimes) or amenorrhoea (in continuous combined regimes) is usually prescribed.

2.5 Different pharmacological products and routes of administration:

A wide variety of products are available for HRT since both oestrogen and progestogens may be given by different routes. 'Pure' oestradiol may be given as subcutaneous implants, via patches or skin gels and orally in micronised form. Other oral oestrogens are either presented as esters, to protect against gastric degradation, or as conjugated oestrogens (over 60% of the oestrogen in Premarin is horse oestrogens such as equaling etc.) Protagonists of the parenteral routes claim that benefits accrue from avoiding the 'first pass' effect when oestrogens are conjugated and sulphonated on entering the liver. However it must be remembered that the data on the beneficial effects of oestrogen are based on epidemiological studies of women using predominantly oral oestrogens and that some of the direct effects of oestrogen on the liver (such as the rise in HDL levels) appear to be positive actions Micronised ('pure') progesterone is currently available in Singapore though most HRT products and regimes employ one or other of the two major progestogen groups. Progestogens of the 17-hydroxyprogesterone group (e.g. medroxyprogesterone) are more commonly used in the USA while the Europeans favour the slightly more androgenic 19-nor testosterone derivatives (e.g. norethisterone). The latter give better cycle control and bone conservation but also tend to reverse some of the oestrogen induced lipid changes.

3. Alternatives to HRT

Women are frightened by the risk of breast cancer and of 'taking hormones into the body' (the justification of the latter is hard to accept logically). Alternatives now exist for treatment of osteoporosis (bisphosphonates) and adverse lipid profiles (statins). It is perhaps ironic that the incidence of breast cancer was significantly raised in a recent large randomised trial showing the (otherwise beneficial) effects of pravastatin against placebo. Many herbs (such as extracts of Cimicifuga racemosa) are currently being presented to Singaporeans as 'safe' alternatives for menopausal symptoms. There is little scientific evidence that they have more than a placebo effect and even less that they are 'safe'. Other preparations such as 'pure progesterone' derived from Mexican yams are currently not available here though they are occasionally imported from the USA, UK or Australia by women who believe in their purported benefits and safety.

* *References for important points in this paper can be supplied if necessary.*

Questions and Answers on Dyslipidaemia and Their Management

Tan CE

Introduction

In the course of my lectures to General Practitioners, I have been asked repeatedly on numerous occasions, questions pertaining to practical management of dyslipidaemia. Hence the idea of an article to deal with such questions arose and I hope that it will clarify, for the practicing physician some of the problems related to lipid management. The treatment of hypercholesterolaemia has received much attention in recent years partly because of greater awareness in the public and also the availability of data supporting primary and secondary prevention of coronary heart disease (CHD). Information about lipid lowering available from the news media can be distorted by press sensationalism such as reports of lipid lowering resulting in increased non-medical deaths like suicides, accidents and homicides. Unfortunately such reports attract a lot of attention. Recent studies involving large number of patients such as the Scandinavian Simvastatin survival Study (4S)[1] study and West of Scotland (WOS)[2] study, have shown conclusively that lipid lowering does not result in increased non-medical deaths. It has also become increasingly clear that the reduction of serum cholesterol concentration is relevant to the prevention of CHD. Hypercholesterolaemia, though not the only cause of CHD, is certainly a major correctable cause and hence it is important to look at the issues related to the management of dyslipidaemia,

1. Does lowering cholesterol reduce total mortality?

Previous older studies, due to the lack of size, did not have enough statistical power to address this issue. Further, the drugs used in the older studies achieved only small differences in cholesterol levels, unlike trials with the statins. The WOS study showed a 32% reduction in all cardiovascular mortality compared to the group on placebo whilst the 4S demonstrated a 42% reduction in coronary deaths. Both studies also showed no statistical differences in non-cardiovascular deaths. Such recent studies make it clear that there is benefit in terms of reduction of cardiovascular mortality and has also shown conclusively that there is no increase in non-cardiovascular deaths in association with lower cholesterol levels.

2. Does lowering cholesterol reduce cardiovascular events?

Two important primary prevention trials of cholesterol lowering, the Lipid Research Clinic (LRC)[3] study and the Helsinki Heart Study[4]. established clearly that CHD morbidity could be reduced by treatment of hyperlipidaemia. The trials also indicated that to influence overall mortality as well as CHD morbidity with lipid lowering therapy, it is important to treat people at high risk. The WOS was one such study that demonstrated a 31% reduction in nonfatal myocardial infarctions. Another study, the Cholesterol and Recurrent Events (CARE)[5] study showed a 26% reduction in coronary bypass surgery and 23% reduction in coronary angioplasty in patients treated with Pravastatin as compared with those on placebo. The 4S study also demonstrated that there was reduction in coronary bypass surgery and angioplasty in the treated group.

3. How should we measure serum lipids?

The complete lipid profile comprises measurement in the fasted state (at least 12 hours), of plasma cholesterol, triglyceride and HDL cholesterol. Water and calorie free liquids are permitted. LDL is calculated from these figures using the Friedewald's formula {LDL = total cholesterol - (HDL + TG/2.2)}. The formula is invalid if triglyceride exceeds 4.6 mmol/L. Total cholesterol can be measured in the non-fasted

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state but triglyceride must be measured in the fasted state. Often in my own practice, I have encountered patients who eat extra heavy meals on the night prior to blood testing because of the need to fast. This can result in a falsely elevated triglyceride level. Hence it is important to advise the patients to take a normal meal before the fast. Cholesterol can also be measured within 24 hours of onset of chest pain in myocardial infarction. After this period, cholesterol levels decrease temporarily. Most clinical guidelines recommend that at least 2 lipid profiles (within 2 -3 weeks interval) should be taken with the further requirement that both sets of results be consistent before initiating pharmacotherapy. Further more, it is important to know the reliability of the laboratory you are using since laboratory variation is the commonest cause of discrepancy in lipid results.

4. Who should be screened for dyslipidaemia?

In the ideal situation, all adults should have their lipid screened at least once and if this is normal, it should be repeated at 5 yearly intervals. However, for population screening this may not be cost effective and in most instances, selective screening is used. Those with positive history of CHD or other atherosclerotic disease at a relatively young age (below 50 for men and below 60 for women) should be screened. Those with a family history of hyperlipidaemia, signs suggestive of hyperlipidaemia, hypertension, diabetes mellitus, obesity and/or smoking habits, should also be screened.

5. How do we decide on the choice of lipid lowering agent?

The long term safety of a medication should always be considered when initiating pharmacotherapy. The cost of the drug is a further consideration. The risk benefit ratio is most favourable when drug treatment is given to patients at high risk. Before considering drug therapy, patients should be advised on appropriate lifestyle measures such as dietary discretion, exercise and cessation of smoking.

If the lipid abnormality is predominantly hypercholesterolaemia, two main groups of drugs should be considered i.e. HMG CoA reductase inhibitor (statins) and bile acid sequestrants (resins). Nicotinic acid can effectively lower both cholesterol and triglyceride but is poorly tolerated by patients. Several statins are available in the market including Simvastatin (Zocor®), Pravastatin (Pravachol®), Atorvastin (Lipitor®) and Fluvastatin (Lescol®). Cerivastatin is currently not available in Singapore for routine use. There is little to choose between the statins if one considers equipotent doses. Hence cost is an important consideration in making a choice. However, there are more large scale studies done with Pravastatin and hence greater knowledge of its safety profile, whilst data on high dose Simvastatin (above 40mg on) is available but this is not so for other statins. Many believe that the differences in cholesterol lowering between the various statins are a result of the half life of the drugs. Hence, Atorvastatin, which has a half life of about 15 hours, has the most potent cholesterol lowering effect at a lower dose. As the efficacy of different anti - hypertensives of the same class are not evaluated based on their dosages e.g. Enalapril 5 mg versus Captopril 12.5 mg, so likewise for statins. We should rather look at availability of scientific data in large studies and based our choice on such evidence. Otherwise, there is little to choose between statins. Statins are not very effective for familial hypercholesterolaemia due to the lack of LDL receptors. There are data to suggest that Atorvastatin and high dose Simvastatin (80mg) may be effective in familial hypercholesterolaemia (FH), but such therapy should be under the care of lipidologists because of potential side effects. Resins are not well tolerated by our patients because of gastrointestinal side effects and inconvenience. Hence I rarely use it as a primary therapy but rather as an adjunct to statin treatment. Triglyceride can rise paradoxically during treatment with resins.

When the problem is predominantly hypertriglyceridaemia, then the choice of lipid lowering agent would be a fibrate. My

preference is to use the newer generation fibrates such as Fenofibrate (Lipanthyl®) and Ciprofibrate (Modalim®). These have less side effects compared with the older generation of fibrate; like Clofibrate or Gemfibrozil (Lopid®). They have also been shown to have added benefits of shifting the LDL subpopulation from the atherogenic dense LDL to the buoyant LDL particles.

In mixed hyperlipidaemia, the physician can start with either statins or fibrate. There is increasing evidence to support the use of combination statins and fibrate in mixed hyperlipidaemia, particularly in diabetics. Careful monitoring for side effects should be instituted when using such combination.

6 What kind of target levels blood lipids should be achieved?

Target levels are given by both the European Atherosclerosis Society (EAS)[6] and the National Cholesterol Education Panel (NCEP)[7]. Such guidelines of desirable levels are meant to guide our therapy and not meant as absolute targets. Other risk factors interact with lipid risks and could be synergistic in predisposing to premature atherosclerosis. Whilst focussing on reducing lipid levels, we must not forget to address other risks such as smoking, obesity, hypertension, diabetes mellitus. Treating the lipid abnormalities in isolation will not significantly reduce the coronary risks, if other risks are not lowered concomitantly.

Lipoproteins(mmol/L)	Desirable levels	
	EAS guidelines	NCEP guidelines
Total cholesterol	<5.2	<5.2
HDL cholesterol	>1.0	>0.9
Triglyceride	<2.3	<2.3
LDL cholesterol	<3.5	<3.4

We must also bear in mind that the goals for drug treatment in secondary prevention is much tighter than in primary prevention. The NCEP II guidelines mention that the LDL goal in secondary prevention should be an LDL cholesterol of 2.6 mmol/L or lower. There is now evidence to suggest that diabetics with dyslipidaemia should be treated as aggressively as in secondary prevention.

Statins can be expected to lower cholesterol by 25 to 40% and LDL cholesterol by 35 to 45% whilst increasing HDL cholesterol by 5 to 10%. It can also lower triglyceride by 10 to 20%. Fibrates can lower triglyceride by 40 to 50% and increase HDL cholesterol by 5 to 10%. It can also decrease

7 Are there any side effects and what should be monitored?

Both the statins and fibrates can result in transaminitis and raised muscle enzymes. Hence it is important to check the hepatocellular enzymes such as alanine transaminase (ALT) as well as creatine kinase (CPK). At the present stage of knowledge, drugs should be discontinued if ALT exceeds 3 times the upper limit of normal. Likewise, the drugs should be stopped when there is symptomatic myopathy (muscle pain or weakness plus increase in CPK to 10 times the upper normal limit or more). Rhabdomyolysis with acute renal failure has occurred in patients using statins together with cyclosporin, gemfibrozil, nicotinic acid or erythromycin. Other side effects of statins include mild gastrointestinal disturbances, rashes and headache. Fibrates can also cause similar side effects such as gastrointestinal disturbance, myopathy and impotence. Impaired renal function is a relative contraindication for fibrate. Hepatocellular enzymes should be monitored from 6 weeks to 3 months after initiation of drug treatment. Present knowledge suggests that there is no need to recheck these enzymes unless dosages are increased or combinations started. This is because the side effects appear to be dose related.

8 Is there a role for combination statin fibrate therapy?

Although none of the present guidelines recommend combining of statins and fibrates, I have on many occasions used such combination in my own pracice. In patients with mixed hyperlipidaemia, and particularly in diabetics, such combination have been extremely effective in achieving desirable lipid levels. We must bear in mind

that side effects can be potentiated by such combination and hepatocellular enzymes and CPK must be monitored after initiation of such combination therapy. Therapy should be discontinued when side effects appear. It would be advisable to start at lower dosages of both statins and fibrates whilst initiating combination therapy. In selected patients with resistant mixed hyperlipidaemia, there is indication for such a combination therapy.

9 When should we stop lipid lowering therapy?

There is no clear answer to this issue but in my practice, I often distinguish between inherited forms of dyslipidaemia such as familial hypercholesterolaemia and familial combined hyperlipidaemia from the "common garden variety" of polygenic hypercholesterolaemia. If it is an inherited form of dyslipidaemia, then the patients are likely to require long term medications. However, if the dyslipidaemia is due to dietary and lifestyle factors, there is reason to stop drug therapy when desirable levels are reached. In my practice, I have stopped therapy for 3 to 6 months when target lipid levels are reached. With cessation of pharmacotherapy, lipid levels may remain within desirable limits following which we can continue dietary measures. If there is a rise in lipid levels, then drug therapy should be restarted. Such measures serve two purposes. Firstly, it convinces the patient that he needs long term medications, without which his blood lipids may rise. It also discourages patients from debating with the doctors on the questions of cessation of drug therapy.

10 Is it important to treat high triglyceride levels?

Prospective studies in middle aged men have shown significant association between triglyceride and CHD[8]. There are at least 6 studies that have considered the role of triglyceride in the risk of CHD among diabetics. The conclusions from these studies appear to be conflicting. However, the Framingham study showed that triglyceride elevations are a highly significant independent risk factor for CHD in women. They also seem to be important in men with low HDL cholesterol. The Paris Prospective Study[9] showed that baseline triglyceride levels were significantly higher in men with death caused by CHD and this association persisted after adjusting for a number of other risk factors including total cholesterol, systolic blood pressure, body mass index and smoking.

High serum triglyceride is often associated with low HDL cholesterol as the formation and metabolism of HDL is closely interlinked with that of triglyceride. There are also biochemical alterations, which accompany hypertriglyceridaemia that result in the formation of small, dense LDL cholesterol. LDL cholesterol is no longer considered a single population but can be fractionated into large buoyant particles (LDL-I), intermediate particles (LDL-II) and small, dense particles (LDL-III). LDL-III particles are more atherogenic and remain in the circulation for longer periods of time and is associated with a 3 to 7 fold greater risk of premature CHD. Overall, there are sufficient evidence to implicate high serum triglyceride as a cause for CHD and hence the need to treat such lipid abnormality.

11 What is the role of red wine, garlic, fish oil and coffee?

Evidence that red wine raises HDL cholesterol has received much attention from the media and the public. The mechanism is unclear and the association at best is tenuous. Alcohol within the usually recommended limits of up to 21 units (190 g) per week in men and up to 14 units (130 g) per week in women has no untoward effect on cholesterol levels. However alcohol is best avoided whilst undergoing weight reduction. Further more for those who derive pleasure from consumption of alcohol, it is difficult to restrict the amount consumed and the amount is often underestimated, to the detriment of these patients.

Filtered coffee and instant coffee do not appear to influence cholesterol levels but coffee prepared by prolonged boiling may elevate serum cholesterol and should be avoided. So the next time your patients want a cup of brewed coffee, make sure that it is freshly brewed. Garlic has been shown by some studies to reduce the cholesterol levels. Allicin in garlic, which also produces the typical garlic smell appear to have some weak cholesterol lowering effect, similar to HMG Co-A reductase inhibitor. There is no harm should your patients decide to consume garlic tablets. My one advice is that if it does not smell, it does not work!

Fish oil in the form of Omega-3 has been shown to be useful in lowering high triglyceride levels but is not beneficial for cholesterol lowering. I have often used Omega-3 in patients with plasma triglyceride exceeding 10 mmol/L, starting at 1 g tid and eventually building up to 10 to 12 g per day. The use of fish oil in diabetics can be a problem as they can worsen glycaemic control. This is in part contributed by the calories in the fish oil. Recent data suggest that if one is careful with the total calories per day, then the consumption of fish oil does not appear to worsen glycaemic control, whilst lowering triglyceride levels.

12 What benefits do we derive from exercise?

Regular aerobic exercise is part of a healthy lifestyle. Exercise can lessen hyperlipidaemia, increase HDL cholesterol, improve glucose tolerance and insulin sensitivity and decrease obesity as well as improve the overall well-being of patients. For exercise to be of any benefit, I would usually recommend that it be undertaken' at least 3 times per week, each time lasting about half an hour. The target heart rate should be about 60 to 75% of maximum rate, (Maximum heart rate = 200 minus age). High risk patients should be supervised in the initial phase and all patients should build up their exercise regime in a gradual way.

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Should General Practitioners Practice Obstetrics ?

A Abyad

Should family physicians practice obstetrics ? The responses to this query have been varied. Reasons offered for maintaining obstetrics are that it leads to a younger family make up in a practice**(1,2)**. Family physicians are reported to provide a less interventionist and more supportive approach to deliveries (3-6). Family physicians may be the only providers available particularly in rural places. Arguments against include disturbance to the practice and after hours requirements on busy physicians and their families (1,7).

In Lebanon, amongst family medicine graduates from the Department of Family Medicine at the American University of Beirut, very few provide prenatal care for their patients. This is despite the fact that their training stresses obstetric practice and prenatal follow up.

Over the preceding decade (5,7-13), controversy over the safety of obstetric care by family physicians has led to systematic studies to appraise variances in prenatal and perinatal care provided by obstetricians and family physicians (5,7-13). Researchers have so far established only small differences in the quality of care given by the two specialties (5,7-13). Klein (14) has outlined modern research about obstetric care by family physicians by maintaining: "All these studies reinforce the fact that family practitioners should remain in obstetrics because to do so is better for their patients". The provision of maternity care by family physicians elucidates the family centred significance of the speciality, expands the area of practice by family physicians (5, 7-13), and is significant to securing satisfactory maternity care in several areas.

Training in obstetrics has been required for board certification in family practice since the American Board of Family Practice was established in 1969. The same requirements applies in Britain, the Netherlands, Canada, and other places. This is in harmony with the concept that maternal and obstetric care is part of the whole and continuous health care that distinguishes family practice.

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Many family practice residents say that insufficient training in obstetrics and life style concerns discourage obstetrics in their practices (15). Furthermore, securing obstetrical privileges is a problem in some countries (14). However obstetrical practice is important enough not to be neglected (14-16).

Over and again the debate on the question of "doing obstetrics" has centered on labour and delivery rather than prenatal care. The reasons for prenatal care are much broader than neonatal and maternal morbidity and mortality. The objectives of prenatal care for the mother include increasing maternal well-being before and after delivery; to improve and self-care; to decrease the risks to health before following pregnancies and even past the childbearing years; to decrease maternal morbidity and mortality, pregnancy loss, and needless pregnancy interventions; and to enable parenting skills.These are part of family medicine.

Prenatal care has three primary elements: risk assessment (both early and ongoing), health amelioration, and curative interventions. The risk assessment should lead to an separate plan of care for each women discovered to be at increased risk. Similarly, health improvement and education receive important emphasis as imperative parts of care for every woman.

Psychosocial problems and risks are recognised as being of similar importance to accepted medical risks and problems. They should be dealt with equal concern. Providers should encourage assessment of the family and habitat environment. They should be capable of responding to such issues as bad health behavior, occupational hazards, psychological difficulties, and prenatally identified risks for defective parenting or child abuse.

Of special interest to family physicians, is preconception care, which for most women, may be initiated following a delivery in anticipation

of the next pregnancy. This is considered a crucial and important element in maternity care. This type of care is best delivered by primary care providers as part of ongoing primary care. Such preconception care should include not only risk assessment, education, and medical interventions, but also encourage appropriate change of health behavior and decisions regarding the appropriateness and timing of pregnancies.

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Treating Ganglions in General Practice

Do you know that you need not refer all ganglions to the orthopaedic surgeon? The general practice treatment for ganglions is

- Leave it and see whether it regresses or
- needle aspiration and steroid injection. Insert 21G needle with 5ml syringe aspirate some contents and change syringes inject 0.5 ml depot steroid repeat with 0.25 ml steroid in a few weeks if necessary

From the General Practice Companion Handbook by John Murtagh.
(PS- do you know this book costs less than $10?)

Ed

Panic Disorder: Review of Recent Findings and a Report of Two Cases

Loh C Z, Mahendran R

SUMMARY

Panic disorder may present with symptoms which can be terrifying for the patient and may be associated with co-morbid conditions such as depression. A recent survey in the United States revealed that the incidence of panic disorder was actually higher than previously found. The clinical symptoms and features of panic disorder are reviewed in this article together with findings that it could become a chronic illness with significant social impairment if not detected early and treated adequately. Pharmacotherapy using benzodiazepines and the newer selective serotonin reuptake inhibitors are discussed. The two cases reported highlight the clinical presentations of this disorder, the clinical management and the response to therapy.

Key Words: Panic disorder, benzodiazepines, selective serotonin reuptake inhibitors

Introduction

The literature revealed that the term panic was derived from the name of the Greek god Pan (meaning "all"). It was thought to have arisen from the Greek's believe that Pan instilled an unreasoning terror among the Persians at the battle of Marathon leading to their defeat[1]. There are descriptions of the disorder in early medical literature and Freud reported symptoms in his patients similar to the symptoms of panic disorder. The diagnostic entity "panic disorder" however has only been in use for about the last seventeen years [1,2].

An earlier study in the United States reported the incidence of panic disorder as 1.5 % (Epidemiologic Catchment Area Study). However, the more recent National Comorbidity Study estimates the incidence as 3.5 % [3].

Being aware of the disorder, its clinical features and how the patients may present is important in general practice as most of these patients present initially at accidents and Emergency Departments and at general practice clinics. One Canadian study estimated that panic disorder patients account for 20% of emergency room visits. One-third had seen three or more healthcare professionals within a year before finally seeing a psychiatrist [4]. On average, panic disorder patients have been found to make seven times more visits to doctors than the general population[5]. Hence not only in terms of health economics but for patient care and to reduce morbidity, awareness of the condition, early diagnosis and treatment is important.

The Diagnostic and Statistical Manual of Mental Disorders DSM IV (one of the classification systems used in psychiatry) recognises that panic attacks can occur outside of panic disorder, for example, in social phobia, agoraphobia or post-traumatic stress disorder. The features of panic attack are listed in Table 1.

Table 1 Features of panic attack (from Reference 6)

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes.
1 palpitations, pounding heat or accelerated heart rate
2 sweating
3 trembling or shaking
4 sensations of shortness of breath or smothering
5 feelings of choking
6 chest pain or discomfort
7 nausea or abdominal distress
8 feeling dizzy, unsteady, lightheaded or faint
9 derealization (feelings of unreality) or depersonalization (being detached from oneself)
10 fear of losing control or going crazy
11 fear of dying

For a diagnosis of panic disorder the pains attacks must DC unexpected or uncured and there is symptomatology, for example, worry and anxiety, between attacks (see Table 2) [6].

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Table 2 Diagnosis of panic disorder (from Reference 6)

A Both (1) and (2)
(1) recurred unexpected panic attacks
(2) at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
(a) persistent concern about having additional attacks
(b) worry about the implications of the attack or its eonsequentces e.g. Losing control, having a heart attack, "going crazy"
(e) a significant change in behavior related to the attacks

B Absence of Agoraphobia

C The Panic Attacks are not due to the direct physiological effects of a substance e.g. drug abuse, (medication) or a general medial condition (e.g. hyperthyroidism)

D The Panic Attacks are not better accounted for by another mental disorder, such as Social Phobia (e.g. occurring on exposure to feared social situations), Specific Phobia (e.g. on exposure to a specific phobic situation), Obsessive-Compulsive Disorder (e.g. on exposure to dirt in someone with an obsession about contamination), Postraumatic Stress Disorder e.g. in response to stimuli associated with a severe stressor), or Separation Anxiety Disorder (e.g. in response to being away from home or close relatives).

Importantly studies have now revealed the 'chronic relapsing nature of the disorder'. Katon et al in their study found that 50% of patients continue to suffer from some form of disability[7]. Roy-Byrne and Cowley after analysing 16 studies concluded "most patients improve but few are cured"[8]. Generally outcome is poor if panic disorder occur with a co-morbid disorder like agoraphobia, major depression, personality disorder or anxiety disorder. Markowitz et al found that 50% of panic disorder patients develop 'some degree of social impairment' like avoidance behavior and 60% eventually suffer from depression[9]. Again this indicates that panic disorder needs long term, even life-long treatment.

Various medical conditions can mimic panic disorder and this could lead to a misdiagnosis. Some of these conditions are listed in Table 3[10].

Table 3 Medical Conditions that mimic panic disorder (from Reference 10)

Anemia
Angina
Arrhythmias
Chronic Obstructive pulmonary disease
Cushing's disease
Electrolyte disturbance
Epilepsy, particularly temporal lobe epilepsy
Hyperthyroidism
Hypoglycemia
Parathyroid disorder
Pheochromocytoma
Pulmonary embolus
Transient ischemic attacks

Substances like caffeine can exacerbate panic symptoms as can withdrawal from alcohol and sedative use. Hence a detailed medical and psychiatric history including medication and drug history is important followed by a physical examination.

Patient education and counselling is important. Symtoms have to be explained to reduce patient's anxiety and their frequent visits to doctors. This reassurance may have to be continued and reinforced at each visit till the panic attacks are fully controlled.

The primary goal in psychopharmacology is to block the panic attacks. This can be effectively done with high potency benzodiazepines and/or anti-depressants. Alprazolam and clonazepam have been used to treat panic disorder. The benzodiazepines block panic attacks within the first week or two of starting treatment and they rapidly decreased anticipatory anxiety. However they do not protect against depression which if present has to be treated with anti-depressants. Alprazolam is started at low doses between 0.25 and 0.5 mg three times a day tominimize sedation. However alprazolam has a short duration of action and a more frequent dosing per day may be needed. Benzodiazepines however do have the potential for abuse

especially in patients with a history of drug and alcohol problems and there may be discontinuation related difficulties. The anti-depressants that have been used as first-line in the treatment of panic disorder, especially if there is co-morbid depression, include the selective serotonin reuptake inhibitors (SSRI's). All the SSRI's are effective but they have a potential to increase anxiety during initiation of treatment and so initial doses must be low and gradually increased (example 25 to 50 mg per day for sertraline, 10 mg per day for paroxetine, 25 mg per day for fluvoxamine, 5 to 10 mg per day for fluoxetine). Side-effects sometimes associated with SSRI use include gastrointestinal tract related disturbances, jitteriness, headaches and sleep disturbances. The tricyclic anti-depressants have also been used to treat panic disorder but their side-effect profile limits tolerability especially over the long periods of treatment.

Where panic disorder is refractory or if there is co-morbid depression, a combination of a high potency benzodiazepine and an anti-depressant can be used. In addition, behavior therapy is helpful with panic disorder. Patients are taught cognitive behavioral skills to effectively handle a panic attack.

Two cases are reported here to highlight the symptom presentations and to discuss the clinical management of panic disorder.

Case Report 1

Patient A, a 32 year old man had seen various doctors for a year with complaints of episodic chest pains and shortness of breath unrelated to exertion or palpitations. History revealed that his illness began about two years ago when he heard news of an accident. He suddenly felt very anxious and had difficulty breathing. These episodes subsequently recurred and he experienced ten such attacks in two years. They had become more frequent and severe and when his anxiety rose he felt he was going to die, have a heart attack or go mad. He was increasingly fearful of leaving home, as he was afraid he would faint in public and he felt lonely and scared at home. His mood was not depressed.

Patient A was a foreigner and had no family with him here. He was frequently worried about his three children and wanted very much to return home but there were financial considerations. He also complained of 'work pressure'. There is no family history of mental illness and he described himself as a worrier and an introvert.

A diagnosis of Panic Disorder with Agoraphobia was made. Physical examination did not reveal any abnormalities and the results of blood investigations were within normal limits. He was prescribed Alprazolam starting with 0.25 mg twice a day increasing to three times a day. The panic attacks stopped in less than a month. He continued to have anticipatory anxiety which decreased by the second month and Patient A slowly reduced the dose of medication himself over the next two months. He was also given Cognitive Therapy and Supportive Therapy to deal with his worries about his children and his work pressure.

Case Report 2

Patient B, a 36 year old lady had been ill for about a year. It was precipitated by significant life events - her previous healthy father suddenly had a stroke and became disabled needing her care, a relative moved in to live with her and her unmarried sister became pregnant. She felt anxious, found it increasingly difficult dealing with these events and experienced breathlessness and severe chest pains. She was seen by her family doctor and felt better after an injection. Four months later a similar episode sent her to an Accidents and Emergency Department. She was not admitted but was later referred to a cardiologist who could not find a physical cause.

Over the next six months, she had frequent episodes of breathlessness and was rushed to hospital. She knew the symptoms and frequency of attacks were increasing. She also experienced dizziness and palpitations. The attacks were sometimes so severe she feared she would 'go mad' and felt as her brain was going to 'explode'. She also worried about having a heart attack or tumour.

Patient B had problems coping at work and where previously she was active, she found herself shunning new duties and appointments and had begun to fear she would 'collapse at work' and contemplated resigning from her teaching job.

She described herself as an extrovert but also a perfectionist. She had no biological features of depression.

Patient B was diagnosed as having a Panic Disorder with Generalized Anxiety. She was started on Alprazolam 0.25 mg twice a day increasing to three times a day. She was afraid of increasing
the dose and becoming dependent. She was given Cognitive Therapy and was taught Relaxation Exercises. After four months there were no further panic attacks but the anticipatory anxiety remained. She dealt with this by 'carrying medication with her' without actually taking it. After a year she still comes for follow-up and occasionally needs a supply of medication. she continues to receive support and counselling at each session.

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Metformin Revisited

Do you know that

- metformin reduces plasma glucose by 20-25% and non fasting plasma glucose by 30% or more;
- produces a 10% fall in LDL cholesterol and a 10-25% fall in triglycerides;
- is associated with 1-2kg weight loss over one year
- and when combined with insulin produces short term weight loss in 50% of patients.
- works by decreasing gluconeogenesis and increasing peripheral utilisation of glucose

When I start a patient on metformin, I would usually warn them first that there will be gastrointestinal upsets which include anorexia, nausea, diarrhea and vomiting. The patient would usually replied that if this is so, why should he take it. I will then reply that these side effects are particularly in the first few days of use and are self limiting. They usually occur at higher doses and at the smaller initial doses which I begin, the problem would not be significant. Besides, it induces weight loss. This would convince the patient to start especially when they are told that the drug induces weight loss. Of course you can also add that it can reduce cholesterol and triglyceride levels and it would certainly be convincing enough for the patient to take the drug.

The most serious side effect of metformin is life threatening lactic acidosis. This can be averted by avoiding its use in hepatic failure, cardiac failure and particularly renal failure. Patients at risk of nephropathy and renal failure should be monitored more closely. Another side effect which we may not be aware of is macrocytic anaemia secondary to B12 deficiency and annual estimation of serum B12 may be useful.

Ed

Comparing the Japanese and the Singapore Health Systems

Lau H C

This paper arose from a three week visit to health and elderly care institutions sponsored by Kobe City. It looks in perspective, at health care in Japan from a visitor's view in a major Japanese city and compares some aspects with our Singapore model. Some reasons behind current health care issues are discussed.

Historical-Cultural-Political-Economic Aspects of Health Care

A national health care system is linked to culture, history, politics and economy. There is a unique historical-cultural-political-economic aspect to health care in Japan as reflected in the Japanese administrative and financing system. Japan has a welfare oriented system which reduces individual responsibility. Singapore encourages personal health accountability reinforced variously by the health financing system, public health education and health legislation, eg on the prohibition of smoking in public and the ban of cigarette sale to minors coupled with high tax on cigarettes. In Singapore, out of pocket co-payment of health costs leads to reduction in the overuse of services. In Kobe City, health screening is provided free. Unlike Japan, screening in Singapore is usually not provided free although there can be free screening, eg in children and the elderly. Other types of screening are either subsidised or fully paid for.

In Singapore, a bias to the patients' desires before doctors' interest may be partly due to the fee for service system, where patients paying for doctors' services lead to a more predominant customer demand situation. On the other hand, doctors also have to be sensitive to the level general affordability and may have to calculate his charges according to the patient's ability to pay. In Singapore, the patient has the right to know without conflict of confidentiality issues, but in Japan this is not so and it is common practice to withhold clinical information from the patient showing a high degree of physician authority. The free market type of system of health care in Singapore appears to have a high degree of self regulation.

Ageing and the Health Financing System

Japan has a mature geriatric discipline by virtue of experience and number of patients. There is also more screening services for common cancers more common in the elderly. Respect for the aged in Japan is the norm. For example, this is reflected in situations where seniority decides position. In a local hospital that I visited, I learnt that promotion is not by skill or ability but rather by seniority. Perhaps the aged in Japan have earned this right through example and hard work. It could also be a Japanese traditional and cultural practice. What is not quite clear is whether the present younger generation in Japan will earn the same respect from future generations because there are generational differences in terms of economic performance and national wealth.

Health Delivery Issues

In view of the similarities in demographic transition, what would be recommended for family practice training in Singapore is probably a greater emphasis on the care of the aged. Intersectoral collaboration and integration in the health and welfare areas is useful in the care of the elderly. Japan as illustrated in Kobe city have integrated their health and welfare fields quite well because of a common funding and administrative authority being all run by local government. Many of the care facilities and the public health centres have integrated both health and welfare.

In Singapore, health care is not as restrictive. In Japan, the public health centres are more narrow in the services offered. Singapore has largely done away with stand alone and separate maternal and child clinics because the era of high birth rate

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and population control is past. We have now integrated the medical service in government clinics to family practice type clinics. General practitioners are also encouraged to have family practice type clinics and the training of the new generation of general practitioners emphasises family practice and holistic continuing care.

Managing a Health Care System in an Ageing Population

In any system, healthcare should be accessible without being wasteful. Improving care of the elderly also entails training primary care doctors in geriatric medicine and the organising of clinic services to take care of the elderly more effectively. Expensive and opulent facilities to show off our care centres must certainly be discouraged by appropriate funding caps, and judicious funding and provider policies. Centres for health care should be cost effective, practical, comfortable and friendly to the old and the handicapped. The philosophy of care and respect in Japan for the elderly is certainly desirable. The clinics that we have must be friendly to the elderly, not only in access and physical structure, but also in the provision of a rationally structured system of care which takes into account adequate consultation time for appropriate delivery of care.

A variety of financing instruments (flexibility) for healthcare financing may be desirable because different people have different needs and levels of care. Insurance is good for the most expensive care, eg Medishield which was designed for that purpose. Hospitals should provide good comfortable facilities for subsidised wards. A hospital and community care centre must be friendly and comfortable. In Kobe city, one sees the trend towards a variety of financing instruments to spread out funding and utilisation of resources. It would be wise to have a health financing system which discourages the overuse of services, over prescribing and over screening. Japan appears to have a very high cost system which also taxes the medical system tremendously. In general, the distinction in remuneration amongst doctors in Japan are narrower - the disparity in salaries of the top earners and the lowest rung of doctors in government type hospitals are not as wide as in Singapore.

Conclusion

It is difficult to rationalise the system without a political cost in Japan because this kind of system has great benefits to the average Japanese who will certainly not be anxious about the cost of health care. With the welfare system, the public do not need to complain about health care cost; it is the administrators and politicians who will worry instead about unsustainable spiralling costs. The situations in Japan, in Singapore and perhaps in the developed world indicate that health funding, policies and administration is a veritable tightrope that is precariously treaded by politicians, public pressure and other interest groups. Quite often, an underlying basis of behaviour of providers, healthcare related corporations and patients is the health financing system. The juggling act to resolve conflicts and interests may be fascinating to see or know, but for the family physician, I would quote from the WHO World Health Report 1997 "that the impact of disease on the individual is fundamental to improving health for the community at large". What is done microeconomically in our clinics, in a well-planned funding system, collectively contributes to the macroeconomics of health that will ensure a rational and cost effective health system nationally for the years to come.

Acknowledgement

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Side Effects of Commonly Used Drugs: Part II - Antihypertensives

Goh L G, Lau H C

Thiazide diuretics

The thiazide diuretics remain one of the most commonly used drugs for both initiation and maintenance of antihypertensive drug therapy. Recent revelations about the metabolic side effects (hypokalemia, increase in LDL cholesterol, increased insulin resistance leading to hyperglycaemia and hyperuricaemia) which may adversely affect cardiovascular and stroke risks have led to a reassessment of their place in therapy. It is now established that low thiazide doses (12.5-25mg/d hydrochlorothiazide) are safe. One shortcoming of thiazide is that they do not reverse LVH. When used in low doses in properly selected patients, thiazides are safe, well tolerated, inexpensive, and effective. Thiazides are particularly useful in those with sodium retention and volume expansion eg the elderly. Low to moderate dosing of 25-50 mg suffices in mild hypertension. At these doses, adverse metabolic effects are minimum. Low doses also enhance the efficacy of other first-line antihypertensive agents (e.g., ACE inhibitors, beta-blockers). Consequently, thiazides have also become an important adjunct in patients whose pressure does not respond to monotherapy.

The MRFIT study found an increased rate of cardiac sudden death in thiazide treated patients with baseline ECG abnormalities. Hence in using thiazides, selection of patients is very important. Moreover patients should be *monitored* for hypokalemia, hyperlipidaemia, and hyperglycaemia. Fortunately the degree of glucose intolerance is very mild but the problems of thiazide use has reduced its popularity as a first line antihypertensive. We should try to avoid thiazide use in patients with rhythm conduction disturbances, LVH, IHD, diabetics, hyperlipidaemics or those on digoxin.

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Beta-blockers

Most of the common side effects of beta-blockers are predictable and result from excessive or inappropriate beta receptor blockage at non-target receptor sites.

Beta-blockers can cause bronchospasm and asthma, exacerbate CCF and peripheral vasoconstriction. Fatigue and reduced tolerance to exercise is reported commonly, particularly by physically active people.

Insomnia, depression and nightmares are nervous system side effects. Beta-blockers have been associated with impotence, decreased potency and loss of libido. B-blockers not only blocks the heart but block the brain too. B-blockers may have subtle effect on the intellect. Propranolol is the major culprit but even atenolol causes a mild but consistent impairment of memory.

Other side-effects like gastrointestinal upsets are usually mild and include nausea, dyspepsia, constipation or diarrhoea. There are metabolic side effects too, viz decreased HDL-cholesterol to a mild degree, increased serum triglycerides and they may mask hypoglycaemia. Propranolol also increases insulin resistance mildly.

All these do not mean that we should drastically reduce B-blocker use. Instead we should measure benefits versus problems. B-blockers are highly effective, proven in long term prospective randomised studies to reduce strokes and cardiovascular mortality and morbidity. They decrease cardiac contractility, renin release and possibly central sympathetic output. LVH recedes. Initially peripheral resistance rises but it quickly returns to normal. Their cardioprotective effect makes them the drug of choice in hypertensives with underlying IHD. What needs to be pointed out is that in our hurried consultations not to forget that patients' complaints of lethargy, forgetfulness, dreams may be a side effect of the B-blocker we prescribe.

Selection of beta-blocker is based on price, convenience, lipid solubility and cardioselectivity. CNS penetration is greater in lipid soluble drugs

hence the likelihood of neuropsychiatric effects such as depression, lethargy, impotence and nightmares are greater in propranolol than atenolol. The elderly are especially susceptible to such side effects. Cardioselectivity is characterized by greater effect on B1-adrenoreceptors of the heart than on the B2 adrenoreceptors of the blood vessels and bronchi. Thus bronchospasm is less in cardioselective agents. However the cardioselective effect declines as dose increases.

Propranolol in comparison with Atenolol

Although propranolol is cheaper, the single dose atenolol is more convenient than the tds dosing required for propranolol. Atenolol is lipid insoluble whilst propranolol is lipid soluble. Atenolol is more cardioselective compared to propranolol.

Calcium antagonists

Nifedipine
Headache, nausea, dizziness, flushing and a sensation of heat may occur at the beginning of treatment but these are usually transient and mild. Patients should be forewarned. Starting doses should be lower in the elderly eg 5mg bd instead of 10 mg tds because the therapeutic response may be more marked in the elderly. The dosing is three times a day. If given bd, the afternoon BP may go up. For elderly patients if the afternoon pressure control is acceptable, one can use bd dosing.

Peripheral oedema is due to peripheral vasodilatation. A common mistake is to diagnose peripheral oedema as cardiac failure and treat with frusemide. It is resistant to diuretic therapy. Worsening angina or cerebral ischaemia (perhaps because of vascular steal phenomenon) may occur. In patients on beta-blockers, addition of nifedipine may produce hypotension without improving the angina; the nifedipine should then be stopped. Drug induced hepatoxicity can occur.

Verapamil
The overall tolerance to verapamil is good. GI disturbances particularly constipation, headache, dizziness and rashes may be transient. Large doses may precipitate heart failure, but bradycardia, hypotension and conduction disturbances are rare except when verapamil is given intravenously to patients receiving beta-blockers. In addition to interacting pharmacodynamically with digoxin, verapamil reduces the renal and non-renal excretion of digoxin (similarly to the interaction of digoxin and quinidine), thereby raising steady state concentration of digoxin by about 50% and increasing the likelihood of heart block

Diltiazem
Diltiazem has similar haemodynamic and electrophysiological effects to verapamil but is less potent at producing arterial vasodilatation and has greater tendency to slow the heart rate. Sinus bradycardia is seen occasionally and conduction through the AV node is slowed which suggest it should be prescribed with caution to patients who have bradycardia or sick sinus syndrome or are receiving beta-blockers or digoxin. In addition to pharmacodynamic interaction with digoxin there may also be a kinetic interaction, as seen with verapamil, which reduces digoxin elimination.

Calcium antagonists in heart failure[5]

Although most patients will tolerate first-generation calcium antagonists without significant cardiac depression, they should not be considered drugs of first choice for the treatment of angina or hypertension in patients with moderate to severe heart failure. They should preferably be avoided after acute myocardial infarction if there has been any clinical evidence of heart failure. Of the first generation drugs, verapamil is most likely to exacerbate or induce heart failure, whilst diltiazem seems to have the least potential to depress contractibility. Diltiazem or nifedipine can usually be used safely as anti-anginal agents in patients with heart failure, but nitrates should be tried first.

ACE inhibitors

Ace inhibitors block the conversion of renin-activated angiotensin I to angiotensin II. By their blocking action, ACE inhibitors reduce aldosterone levels and blunt the volume retention caused by other vasodilators.

At the recommended doses, these drugs are safe and very effective. Both captopril and enalapril are now recommended as first-line agents for

THE
COLLEGE MIRROR

Issue No.Oct - Dec 1997

FROM THE EDITOR'S DESK

Ms Yvonne Chung

It has been yet another busy and eventful quarter in the life of the College. I am happy to report that members have been involved in many activities both locally and overseas.

On the local CME scene, the College ran a successful Advance Diabetes Course for Family Physicians over three consecutive weekends in September 1997.

There's an update on further details of the proposed course leading to a Diploma in Ultrasonography (Obstetrics and Gynaecology). The College is also busy planning for another hands-on course in office orthopaedics and minor surgical techniques using life-like intelligent simulated tissue models. ("What are these ?" I hear you ask).

In the international arena, some members of the College have been involved in a joint collaboration with the Chinese Society of General Practice in Beijing, to translate and publish a WHO/WONCA report: "Making Medical Practice More Relevant to People's Needs: the Contribution of the Family Doctor". This was no mean task. Both WHO and WONCA have been kept informed of the project.

Finally, I would like to extend a personal invitation to all of you to forward articles of interest or snippets of news and information that you would like to share with other members and colleagues. It need not be earth-shattering, simply 100 words will do !

■ YC

WHAT'S BEEN HAPPENING

ADVANCE DIABETES COURSE FOR FAMILY PHYSICIANS

A training course on "**Taking Care of Your Diabetic Patient: an Advance Course for Family Physicians**" was successfully held on three consecutive Saturday afternoons on 6, 13 & 20 September 1997. This course was a joint collaboration between the College, the Ministry of Health and the Diabetic Society of Singapore. It was attended by 50 participants and was extremely well received.

The course was divided into three sessions:

Fundamentals of Care, which covered issues on what's new in diabetic care and take-away tips on the prevention of foot problems

Tools of the Trade, which covered useful advice and tips on the types of drugs used, diet, nutirician, and exercises for the diabetic patient

Living with Diabetes, which tackled the problems encountered in the daily lives of the diabetic, such as at the work place, during pregnancy and when travelling

Each session had a "Meet the Experts" slot where participants brought forward their cases for open discussion. Participants found this particularly useful as they went away with easy to remember practical tips. They were also given a copy of the "Clinical Practice Guidelines for Treatment of Diabetes Mellitus".

Our special thanks and appreciation go to the Working Committee and the Teaching Faculty for their invaluable contribution and for sharing their expertise and time. They include:

A/Prof Goh Lee Gan
A/Prof Tan Chorh Chuan
Dr Lau Hong Choon
Dr Lee Chung Horn
Dr Lim Lean Huat
Dr Sum Chee Fang
Dr Tan Chee Eng
Dr Kevin Tan
Ms Galdys Wong
N/O Lye Yee Khim
A/Prof Thai Ah Chuan
Dr Shanta Emmanuel
Dr Warren Lee
Dr Leong See Odd
Dr Soon Puay Chow
Dr John Tambyah
Dr Tan Yeang Tin
Dr Tye Lee Sze
Ms Yvonne Chung
N/O Ong See Choo

The College also thanks the pharmaceutical companies for their support in sponsoring various sessions of the course:

Bayer (Singapore) Pte Ltd
Becton Dickinson & Company
Boehringer Mannheim Singapore Pte Ltd
Eli Lilly Asia Pacific Pte Ltd
Norvo Nordisk

From the participants' feedback and as part of a follow up, the College collated and distributed an information pack containing the Ministry's Diabetic Guide to Patients and the Food Pyramid poster to all course participants on a complimentary basis.

■ YC

Moving house? Moving practice?

Dear Members

If you have already moved house/practice, or are about to do so, please forward your new contact address and tel/fax numbers to the College Secretariat so that we can update our database. (We have been receiving a lot of returned mail from members recently).

Fax your details to : Ms Kathy Chan at Fax No 222 0204

Thank you for your co-operation.

HANDING-OVER CEREMONY IN BEIJING OF THE TRANSLATION OF THE WHO/WONCA REPORT

"MAKING MEDICAL PRACTICE MORE RELEVANT TO PEOPLE'S NEEDS: THE CONTRIBUTION OF THE FAMILY DOCTOR"

As part of the Singapore College's contribution and continuing effort to support the development of academic organisations of general practitioners/family physicians, it undertook a project with the Chinese Society of General Practice/Chinese Medical Association to translate into Chinese, a WHO/WONCA (ref 1) working paper: "Making Medical Practice and Education More Relevant to People's Needs: the Contribution of the Family Doctor". This working paper resulted from the joint WHO-WONCA Conference in Ontario, Canada in 1994.

As part of the joint collaboration, the College sponsored S$10,000 which included the printing and publication of the report.

The idea for the translation project was first conceived at the 14th World WONCA Conference held in Hong Kong in 1995, when members of the Singapore delegation met with their counterparts from the Chinese Society of General Practice.

The translation was entirely carried out by members of the Singapore College and the Chinese Society. Special thanks and acknowledgement are extended to Dr Wong Song Ung and Dr Yap Gim Hong of Singapore for their unceasing effort and painstaking attention to detail, and to Professor Cao Zeyi, Dr Gu Yuan and other doctors of the Chinese Society.

Dr Alfred Loh (2nd right) with members of the Chinese society of General Practice

After much correspondence and communication across the South China Seas to verify the numerous drafts of the document, 3000 copies of the report were printed in China. The official Handing-Over Ceremony took place on 22 November 1997 in the Capital University of Medical Sciences, Beijing. This memorable occasion was attended by Dr Alfred Loh, President, and Dr Arthur Tan, Honorary Treasurer of the Singapore College, Professor Dai Yuhua, the newly elected President and other dignitaries of the Chinese Society of General Practice, members of the Chinese Medical Association and members of the Capital University of Medical Sciences. An exchange of commemorative plaques was made and press coverage was given to the occasion.

We are pleased that the translated reports have been distributed to the Heads and Assistant Heads of the Medical Faculties and Teaching Departments of various Universities throughout China.

We believe that the results of this collaborative project is just one small step in the right direction to establish, develop and enhance the role and practice of family medicine in China. In the true WONCA spirit, the College of Family Physicians Singapore undertook this project with the aim of improving the quality of primary health care through the fostering and maintaining of high standards in general practice/family medicine.

Ref 1: WHO World Health Organization WONCA World Organization of Family Doctors

CORRIGENDUM

THE 1997 MMED (FAMILY MEDICINE) EXAMINATIONS

Apologies to **Dr Wong See Hong**, whose name was omitted from the list of successful candidates for the 1997 MMed (Family Medicine) Examinations published in the previous issue of The College Mirror.

A WARM WELCOME TO OUR NEW MEMBERS

The following doctors were accepted as **Associate Members** of the College during the period October–December 1997

Dr Thoh Tiam Kiat
Dr Tan Lip Pin
Dr Colin Tey
Dr Muhamed Usaf Ansari

MEMBERSHIP TO THE COLLEGE OF FAMILY PHYSICIANS SINGAPORE

We invite you to join the academic body of your discipline of Family Medicine.

Membership to the College has been steadily increasing over the past few years. We would like to invite you to support the College and apply for membership. The benefits derived from being a member are mainly concerned with the upgrading and updating of knowledge in our field of medical practice. They are chanelled mainly through the Continuing Medical Education (CME) courses, lectures and seminars.

Your support to the College is invited so that we may continue to grow as a corporate body, and that new talent may be injected into the College to bolster more activities for our members.

How do I apply ?

Complete the attached application form and send it to:

The Honorary Secretary
College of Family Physicians Singapore
College of Medicine Building
16 College Road, #01-02,
Singapore 169854.

As a Consitutional requirement, each application must be signed by a Proposer (who is already a Fellow, Diplomate or an Ordinary Member of the College) and a Seconder (any Member of the College).

What type of membership ?

Associate Membership is for doctors holding a registrable qualification but with less than 5 years of family practice.

Ordinary Membership is for doctors holding a registrable qualification for 7 years or more and with at least 5 years of family practice experience.

(Please note that those who are eligible for Ordinary Membership may not apply for Associate Membership)

What are the benefits ?

- Automatic registration for the SMC-CME programme at no extra cost. Non-members have to pay an annual registration fee. This means you will be accredited with CME points for each CME event that you attend providing you sign the attendance register (which are submitted to the College by the organisers afterwards).
- A complimentary monthly CME calendar of events at the beginning of each month.
- Members will enjoy discounted registration fees (over non-members) for seminars, courses, conferences and other events organized by the College.
- You will receive a complimentary copy of the quarterly "The Singapore Family Physician" journal and The College Mirror newsletter.
- Free use of the College's library facilities; the College subscribes to a wide range of medical journals, books, visual and audio tapes.

What are the Annual Subscription Fees ?

S$50	One-time entrance fee
S$75	Associate Membership
S$150	Ordinary Membership
S$50	Overseas Membership (for non residents of Singapore)

SIGN UP AND JOIN NOW !

COLLEGE OF FAMILY PHYSICIANS SINGAPORE

APPLICATION FOR ORDINARY/ASSOCIATE/OVERSEAS* MEMBERSHIP

(Please Print or Type)

**** Delete where inappropriate***

PERSONAL PARTICULARS

Name in Full ..... Sex .....

Marital Status ..... No of children .....

Date of Birth ..... Nationality .....

NRIC No/Passport No .....

Name of Spouse ..... Occupation .....

Practice Address .....

.....

.....

Telephone No ..... Fax ..... Pager .....

Home Address .....

.....

.....

Telephone No .....

MEDICAL EDUCATION

- Medical School .....

Year of graduation ..... Degree .....

Other qualifications and diplomas

(i) .....

(ii) .....

(iii) .....

POSTGRADUTE EXPERIENCE AND TRAINING:

Position Held	Hospital Institution	Country City	From (Month/year)	To (Month/Year)
Housemanship				
Medical Officer				
Other Appointments				

Are you now engaged in active family practice? Yes/No*

Family Practice -

Assistant/Trainee	*Year*
Partner	*Year*
Principal	*Year*

Published Papers

.....

.....

.....

MEMBERSHIP OF ANY OTHER MEDICAL SOCIETIES

(i) .....

(ii) .....

(iii) .....

DECLARATION

I hereby make application for membership in the College of Family Physicians Singapore.

I will undertake and continue approved postgraduate studies while I remain in active family practice.

I am enclosing my fees for a 12 month period in the class of **Ordinary/Associate/Overseas** * membership and *S$50/- Entrance Fee (Entrance Fee is a one-time payment).*

I understand that the money will be refunded if my application is not approved.

In submitting this application, I hereby agree to abide by the regulations of the College of Family Physicians Singapore.

Date: ..... Signature of Applicant .....

[Sponsors must be a Fellow, Diplomate or Ordinary members of the college]

NAME OF PROPOSER : .....

Address .....

Signature of Proposer .....

NAME OF SECONDER : .....

Address .....

Signature of Seconder .....

To be completed by Proposer

The applicant, Dr _____ is personally known to me for _____ years, and to be the best of my knowledge he/she* is of good character and a person of integrity.

Signed ..... Date .....

Name of Doctor .....

Designation .....

Address .....

Eligibility for

Ordinary Membership - 7 years since graduation, 5 years in family practice. Subscription S$150 per financial year.

Associate Membership - Family Practitioner with less than 5 years in family practice. Subscription S$75 per financial year

Overseas Membership - A non resident of Singapore. Subscription S$50 per financial year

Please note that those who are eligible for Ordinary Membership may not apply for Associate Membership.

FOR OFFICIAL USE

Recommended for *Ordinary/Associate Overseas** Membership

Date .....

.....
Censor-in-Chief

Applications should be sent to: THE HONORARY SECRETARY
COLLEGE OF FAMILY PHYSICIANS SINGAPORE
COLLEGE OF MEDICINE BUILDING
16 COLLEGE ROAD #O1-02, SINGAPORE 169854

COLLEGE GIFTS AND ACCESSORIES

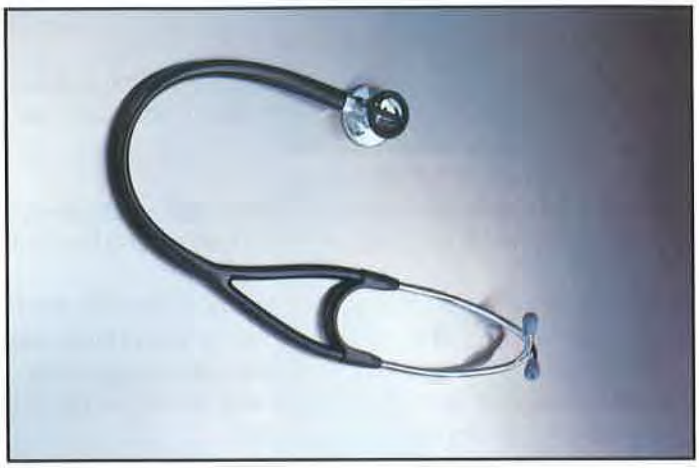
ESPECIALLY FOR YOU !

Stereophonic Stethoscopes

Open up to a whole new world of stereophonic auscultation.

These stereophonic stethoscopes were first launched in Singapore at the College's 6th Scientific Conference in May 1997 and are available at S$285.

The discrete two-channel design – it's left and right ear tubes are independently connected to right and left semi-circular microphones in the chest piece- allows the stethoscope to differentiate between the right and left ausculatory sounds. This is something not achieved by traditional monoaural stethoscopes.



Stereophonic Stethoscope

College briefcases

College Conference briefcases are available at a very affordable price of only S$25 each (similar ones are retailing at S$40 but without the embossed College logo of course).

College Silk Ties and Scarves

The College ties are all are made of 100% pure silk and come in 3 colours: claret red, dark green and navy blue at only S$25 each.

The 100% silk scarves are beautifully designed with multi-coloured orchids, the national flower of Singapore, at only S$30 each.

You are most welcome to come to the College and have a look at any of the above items. They make idea gifts to yourselves or friends and colleagues.

College briefcases

College Silk Ties and Scarf

WHAT'S COMING YOUR WAY . . .

KEEPING YOU UPDATED ON EXCITING PROGRAMMES . . .

More on Ultrasound

Since we reported on the proposed course leading to a Diploma in Ultrasonography (O&G) in the previous issue of the The College Mirror, the Ultrasound Protem Committee has had numerous meetings to finalise the course details and to iron out the procedural formalities.

The Diploma course will be a joint programme between the School of Postgraduate Medical Studies, NUS, the O&G Department of the National University Hospital and the College.

Fully understanding the demanding and busy lifestyle of a Family Physician, the programme has been designed with an element of flexibilty and will be offered on a part-time basis, but must be completed within a maximum period of 24 months. It will be structured in modules with a large distance learning component. There will be an appropriate blend of lectures, hands-on training, log work and formative and summative assessments. To optimize trainer-trainee ratio, the first intake will be limited to 24 trainees.

The Ultrasound Course proposal has been presented and agreed in principle by the Director of the School of Postgraduate Studies.

We will keep you posted on further details of the launch date and fees in due course.

Minor Surgery course

The College is preparing for another hands-on course on office orthopaedics and minor surgical techniques. For some of our members who attended the workshops during the College's Scientific Conference in May 1997, you would have had a taste of the type of training that we have in store for you using the life-like intelligent synthetic tissue models. These models are exact anatomical replicas and are constructed with an accurate representation of underlying bony structures, musculature, tendons, soft tissue and allows for palpation of the relevant body parts.

These tissue models (which, increasingly, we have been calling 'body parts' for short) were specially purchased from the UK. They include the following:

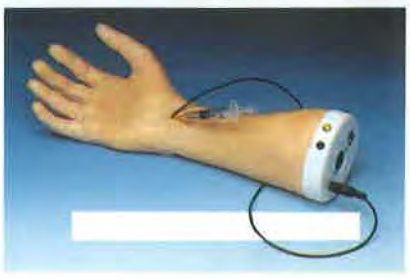
Shoulder – for the practice of injection techniques:

- Shoulder joint capsule
  anterior approach
  posterior approach
- Subacromial space
  Lateral approach
- Bicipital tendon
- Acromio – clavicular joint

Dr Allfred Loh demonstrating on theShoulder Injectable Model

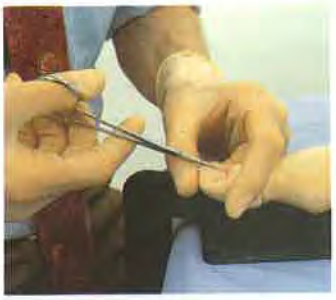
Wrist and Hand –for the practice of injection techniques:

- Carpal Tunnel Syndrome
- Trigger Finger
- De Quervain's tenosynovitis
- 1st carpo-metacarpal joint (thumb)



Breast for Diagnosis – for the teaching of self-diagnosis to patients and procedures for clinicians

- contains a simulated carcinoma
- fibroadenoma
- benign cyst



Ingrowing toe nail - for the practice of the following procedures

- wedge excision of the nail
- total ablation of the nail
- ring block with local anaesthetic

Knee - for the practice of injections and aspiration of an effusion of the knee

Elbow – for the practice of injections

- Tennis elbow
- Golfer's elbow

Sebaceous Cysts and Lipomas – allows the practice of

- removal in one piece
- removal of sutures and resuturing

The College has long recognised the need for more skills upgrading and practical hands-on courses for its members. We certainly hope that the investment in these training materials will be put to full and good use in the near future. We will keep you informed of further details – watch this space !

■ YC

ANNOUNCEMENTS

BOOKS FOR SALE

"Caring for the Elderly – A Guide for Family Physicians"

This is a most useful handbook for Family Physicians/GPs published by the Ministry of Health. It contains the most up to date information on the provision of medical care for the elderly.

This book is authored by a number of distinguished doctors involved in caring for the elderly, and is available from the College at **S$10** per book (self collection). *Please **add** S$3.00 for despatch and domestic postage.* Cheques should be made payable to "College of Family Physicians Singapore".

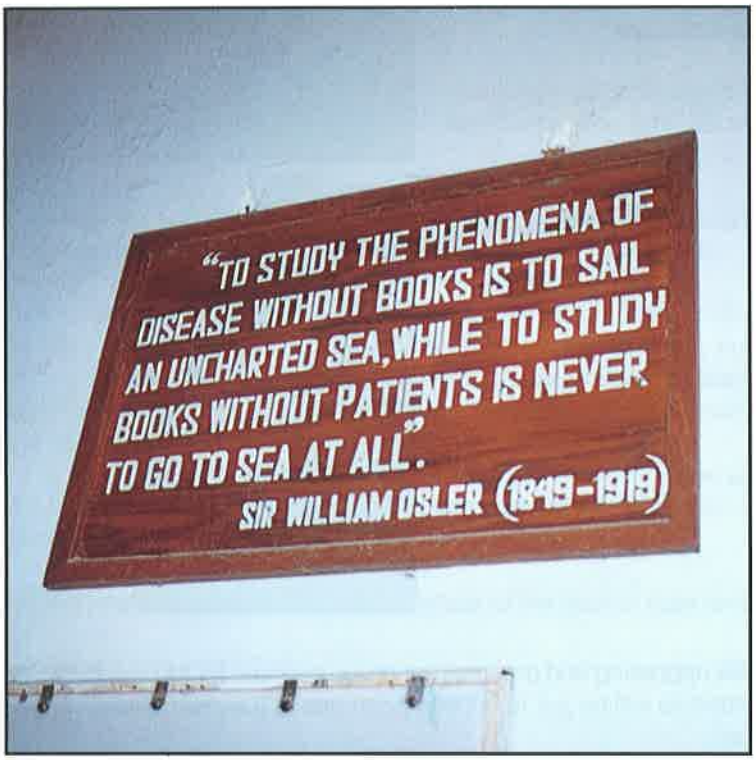
A BIG and gentle reminder . . . .

A large number of our members have still to pay their membership fees despite reminders being sent out. We would be grateful if outstanding payments could be made as soon as possible by cheque, payable to College of Family Physicians Singapore.

YOUR CO-OPERATION WILL BE MUCH APPRECIATED

To all of our members who have submitted their annual subscriptions –THANK YOU.

POINTS TO SHARE



Quote of the Issue

Who's this ?

We invite your comments, suggestions or anything of interest that you would like to share with other members and Family Physicians. Please send your articles by fax at 2220204 or by email at rccfps@pacific.net.sg

Or simply mail it to:

The Editor
The College Mirror
College of Family Physicians Singapore
College of Medicine Building
16 College Road #01-02
Singapore 169854,

WE WELCOME YOUR CONTRIBUTIONS!

treatment of hypertension, being well tolerated and free of the fatigue and lethargy so common to many other antihypertensive medications. In diabetic patients, ACE inhibitors help to reduce proteinuria and preserve renal function, presumably through dilation of efferent arterioles and reduction of intraglomerular pressure. Cardiac output improves in patients with impaired left ventricular systolic function.

Captopril
Dry cough is the most annoying vide effect occurring in about 10% of patients. It is mostly nocturnal and described as an irritation in the throat. Half of those with cough find it troublesome enough to stop the drug.

ACE inhibitors block the production of aldosterone. This can lead to dangerous degrees of hyperkalemia when used in conjunction with potassium supplementation or in potassium sparing diuretics.

Loss of taste is seen exclusively with captopril and is also related to dose. Probably 0.5% of patients who have normal renal function and receive the lower recommended doses suffer from loss of taste. The sense of taste may take several weeks to return.

Alpha blockers

Prazosin
These act peripherally at vascular postsynaptic alpha adenergic receptors causing arteriolar and venous dilatation. With prazosin, profound first dose hypotension occurs 1- 3 hours after the initial dose and can lead to syncope. This is especially so in elderly patients and those taking anti-diuretics and can be avoided by starting with low dose at bedtime and instructing the patient to lay supine for at least 3 hours Postural lightheadedness is a problem affecting about one fifth of patients and more likely as dose is increased to 1 mg per day.

Prazosin is coming into vogue because of its beneficial effects on benign prostatic hyperplasia. This effect is, however, short term. It relaxes detrusor and prostatic smooth muscle, thereby relieving some of the dynamic component of obstruction. Other beneficial effects include the fact that they mildly raise HDL cholesterol and reduce LDL cholesterol both on the order 3-5%. In addition they *reverse ventricular hypertrophy.*

The Elderly

Antihypertensive drug therapy should be carried out more cautiously in the elderly because older patients may be more sensitive to volume depletion and sympathetic inhibition than younger patients. Older individuals may have impaired cardiovascular reflexes that make them more susceptible to hypotension. For this reason blood pressure should be measured in the standing as well as the seated positions and antihypertensive therapy should be initiated with smaller doses. Where large randomised control trials are concerned, only B-blockers and diuretics have been used and these have shown a reduction in mortality and morbidity.

Sexual dysfunction

Sexual dysfunction has been reported with almost every antihypertensive drug, probably a consequence of the reduction of blood flow through the genital vessels already sclerotic from the ravages of smoking, hypercholesterolemia and diabetes. *However there are differences between drugs.* ACE inhibitors and calcium antagonists appear not to cause impotence. As impotence often has a psychogenic component, it can do no harm to the patient that nifedipine will bring blood to the penis on the basis of a few case reports of nifedipine induced priapism.

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Stroke Prevention

Lee S H

Summary

Primary prevention is the most cost-effective way to reduce stroke mortality and morbidity. After a TIA or stroke, the risk of a stroke is 10% in the first year, and is highest in the first month. Therefore, early treatment is important. Aspirin is the most widely used antithrombotic agent for non-cardioembolic stroke prevention. Cardioembolic stroke should be anticoagulated. Carotid endarterectomy is highly beneficial for patients with TIA and non-disabling stroke associated with high grade extracranial internal carotid artery stenosis. However, the beneficial effect of carotid endarterectomy for asymptomatic internal carotid artery stenosis is controversial.

Keywords: prevention, cerebrovascular disease, stroke, aspirin, warfarin, carotid endarterectomy, atrial fibrillation

Introduction

After a stroke, the risk of recurrence is 10% in the first year; thereafter, 5% yearly. The risk of a recurrent stroke can be reduced by 50% with appropriate therapies which have good risk-benefit ratio. As the risk of stroke is highest during the first month after a stroke or TIA, patients should be evaluated and started on preventive therapy as soon as possible.

PRIMARY STROKE PREVENTION

Correction of risk factors

On a global level, correction of risk factors is the most cost-effective way to reduce stroke mortality and morbidity. Primary preventive trials of blood pressure reduction have shown that lowering of blood pressure in hypertensive patients reduces the risk of first stroke within a few years of starting treatment. The risk of ischemic stroke revert to normal about 2 to 5 years after stopping cigarette smoking. Meta-analysis of randomized, controlled trials suggests that in hyperlipidemic patients who have not previously had stroke, HMGCOA reductase inhibitors ('statins') reduce the incidence of stroke.

Medical treatment

Risk of stroke in the elderly is 1% annually. However, atrial fibrillation is more common in this age group and when present their risk of stroke is 5% yearly. Low-dose anticoagulation with warfarin reduces the relative risk of first stroke in patients with non-valvular atrial fibrillation (NVAF) by 68%. The risk of major systemic bleeding is low if the INR range is between 2 to 3. Aspirin is also probably effective for primary stroke prevention in NVAF.

In order to improve the risk-benefit ratio, analysis of pooled data were done to identify high risk patients where anticoagulation is mandatory (Figure 1). It showed that NVAF patients ≤ 75 years old with risk factors of previous embolism, hypertension, recent heart failure, and diabetes mellitus have a high risk of stroke and warfarin (INR 2-3) is recommended NVAF patients ≤ 75 years old without any of the above risk factors have a very low risk of stroke and aspirin 300 mg/d is adequate but they must be observed carefully for development of the risk factors for thromboembolism. For patients > 75 years old, bleeding complications are higher, and the recommendation is either very low-dose warfarin (INR 2) or aspirin 300 mg/d.

Age	Risk factors	Antithrombotic agent
≤ 75 yr	(high risk) hypertension recent heart failure diabetes mellitus prior TIA or stroke	warfarin (INR 2 - 3)
≤ 75 yr	(low risk) none of the above	aspirin 300 mg/d
> 75 yr	(high risk)	warfarin (INR 2) or aspirin 300 mg/d

Figure 1. Selection of antithrombotic therapy for primary prevention of ischemic stroke in non-valvular atrial fibrillation.

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Surgical treatment

For patients with asymptomatic extracranial internal carotid artery stenosis (≥ 60% diameter stenosis), endarterectomy has been shown to reduce the risk of ischemic stroke from 10% to 5% at 5 years, provided that the perioperative risk, inclusive of angiogram, is less than 3%. This is a very criteria as the operative risk of the average stringent neurosurgeon is about 5%. Endarterectomy for asymptomatic carotid stenosis is also not appealing to many neurologists because the magnitude of benefit is small, having to operate on close to 100 cases to prevent one stroke per year. Moreover, major stroke and death were not prevented, and women did not benefit from the procedure. However, selectively, the risk-benefit ratio may be improved by operating on male patients with greater than 80% diameter stenosis who have higher risk for stroke.

SECONDARY STROKE PREVENTION

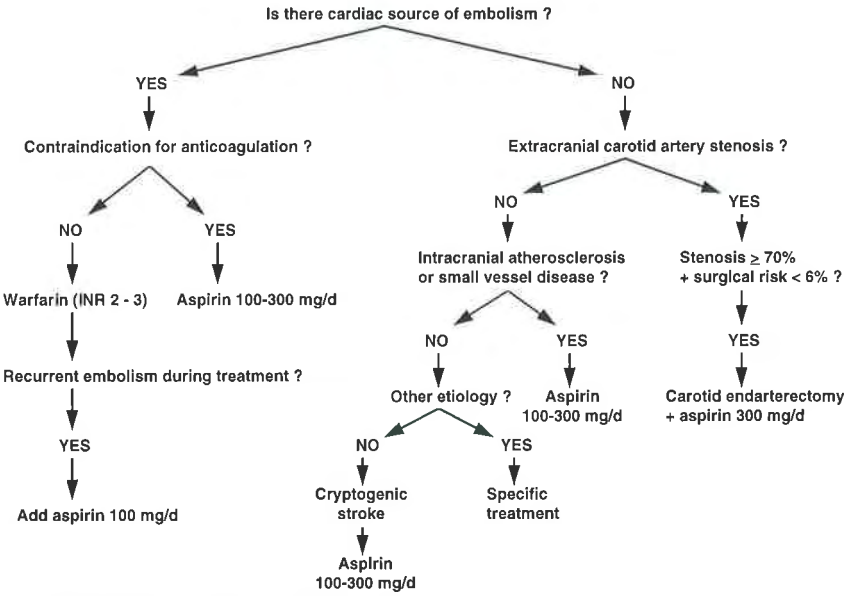

Figure 2. Algorithm for secondary prevention of TIA and minor stroke

Approach to classification

Accurate classification of ischemic strokes into etiologic subgroups is important for selecting the optimum preventive therapy (Figure 2). More than 90% of ischemic stroke are due to atherosclerosis or cardiogenic emboli. Among ischemic strokes, it is important to distinguish lacunar infarcts from cardiac embolism and from atherosclerosis of major carotid and cerebral arteries. Accurate history and careful examination, together with CT brain, duplex Doppler carotid ultrasound, ECG, and CXR form the basis of classification.

Cardioembolic stroke: Cardioembolic stroke is suspected if CT brain shows a superficial wedge-shape infarct, clinical examination of the heart reveals ischemic or valvular heart disease, or when ECG/CXR is abnormal. Two-dimensional echocardiography may be required for confirmation of cardiac source of embolism.

Carotid stenosis: Carotid ultrasound of the extracranial carotid arteries is routine for all stroke patients as 8% of all local patients with acute ischemic stroke have significant internal carotid artery stenosis.

Lacunar stroke: Patients with classical lacunar infarct present with one of the following clinical patterns: pure motor stroke, pure sensory stroke, ataxic hemiparesis, clumsy-hand dysarthria, and sensorimotor stroke. In addition, CT may show a small subcortical infarct or is normal, and there should be absence of significant carotid artery stenosis and cardiac source of embolism. Lacunar infarct is usually associated with chronic hypertension. The prognosis is good and extensive investigation is not warranted.

Cryptogenic stroke: Patients who do not have the usual atherosclerotic risk factors such as advanced age, hypertension, smoking, diabetes mellitus, hypercholesterolemia and do not have the usual cardiac source of embolism, should be thoroughly evaluated for procoagulant and

immune dysfunction. The following screening tests are recommended: Protein S and C, antithrombin III, ANA, anticardiolipin antibody, lupus anticoagulant, PT/PTT, VDRL, and ESR. Transesophageal echocardiography or 2-D echocardiography with bubble contrast study may be necessary to exclude patent foramen ovale. When indicated, cerebral angiogram is performed to exclude dissection and vasculitis. If the cause is still unknown despite extensive investigations, patients are classified as having cryptogenic stroke or stroke of unknown etiology.

Secondary prevention for non-cardioembolic stroke

Aspirin is the most widely used antithrombotic agent in the world for stroke prevention. The Food and Drug Administration of USA recommends aspirin as the first-line drug for patients with threatened ischemic stroke. So far, no single antiplatelet agent has been shown to be clearly better than aspirin, and there is nothing as cheap or less toxic. It is equally efficacious in men and women, in young and old, in diabetics and nondiabetics, and in patients with or without hypertension. The earlier trials which showed that aspirin was ineffective in women suffered from type II statistical error as women generally do better than men after a cerebrovascular event. Subsequent trials invólving large sample sizes all demonstrated that the efficacy is similar for both sexes.

The commonest dose of aspirin is 300 mg daily. The dose is reduced to 150 mg or 100 mg daily if there is gastric discomfort. For those using less than 150 mg of aspirin daily, they should start with a dose of 300 mg, as this can achieve almost instant inhibition of platelet aggregation, followed by 75-100 mg daily. The recent Chinese Acute Stroke Trial showed that Aspirin 160 mg daily started within 48 hours of stroke onset is associated with a small but significant reduction in risks of recurrent stroke and death. The optimal dose of aspirin is undetermined but it is certain that higher doses are associated with greater risk of gastric side-effects. Although data concerning the efficacy of aspirin after 3 years is lacking, lifelong therapy is recommended as long as the risks for cerebrovascular disease persist.

Recently, the European Stroke Prevention Study 2 (ESPS2), shows that combination of aspirin 25 mg twice daily and dipyridamole SR 200 mg twice daily confers additive effect by reducing the risk of stroke by 37% when compared with placebo ($p < 0.001$). Combination therapy was also better than either agent alone. Further trials are needed for validation.

At present, there is no conclusive proof that ticlopidine is better than aspirin and the FDA recommends ticlopidine for patients with threatened stroke who are unable to tolerate aspirin. Many physicians also prescribe ticlopidine to patients who have failed aspirin. The proven dose of ticlopidine is 250 mg BD; the beneficial effects of 250 mg once daily is unproven. It is important that total white count be checked every 2 weeks for the first 3 months of ticlopidine therapy because of the 2.4% risk of neutropenia. Subgroup analyses showing that ticlopidine is better or worse than aspirin suffer from type I statistical error. Clopidogrel, a synthetic analogue of ticlopidine, was recently tested for secondary stroke prevention but it was not significantly better than aspirin. However, the frequency of neutropenia is lower with copidogrel use than with ticlopidine use.

Secondary prevention for cardioembolic stroke

Patients with ischemic stroke associated with potential cardiac source of embolism such as mitral stenosis, prosthetic heart valves, cardiomyopathy, recent myocardial infarction, atrial fibrillation, segmental akinesia, global dyskinesia, and mural thrombus should be anticoagulated, provided there are no contraindications. The recommended intensity of anticoagulation is INR 2 to 3. Patients with metallic prosthetic heart valve generally require higher intensity of anticoagulation. For patients with prosthetic heart valve who continue to have systemic embolism despite anticoagulation therapy, addition of aspirin 100 mg/d has been shown to further reduce the risk of ischemic stroke.

Secondary prevention for stroke associated with carotid stenosis

Carotid endarterectomy is highly beneficial for patients with TIA and non-disabling stroke associated with significant stenosis of the

extracranial internal carotid artery (> 70% diameter stenosis). It reduces the absolute risk of stroke by 17% and relative risk by 65%, at 2 years. For the procedure to be beneficial, the perioperative risk must be less than 6%. Patients should be continued on aspirin 300 mg/d after endarterectomy for maximum protection.

Conclusion

For primary prevention, high-risk patients with non-valvular atrial fibrillation should be anticoagulated, whereas for low-risk patients aspirin is adequate. Endarterectomy for asymptomatic internal carotid artery stenosis may be recommended under special circumstances for men with very severe stenosis who have high risk for stroke when surgery is performed by surgeons with very low surgical mortality and morbidity records. Control of hypertension, treatment of hypercholesterolemia and cessation of smoking will further minimize the risk of ischemic stroke in primary prevention.

For secondary prevention, patients with non-cardioembolic TIA or ischemic stroke should be prescribed aspirin. For patients who are unable to tolerate aspirin, ticlopidine is a good alternative. Those with potential cardiac source of embolism requires anticoagulation. Patients with TIA and non-disabling stroke, associated with severe extracranial internal carotid artery stenosis should undergo carotid endarterectomy followed by aspirin for prevention of further stroke.

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Outpatient Evaluation and Treatment Options for Acute Stroke

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Summary

Stroke is a major cause of mortality and morbidity in Singapore. The approach to a patient presenting with acute stroke would include making an accurate diagnosis of stroke, determining the stroke risk factors, localising the lesion, and establishing the mechanism of the stroke; this is achieved by a proper history taking, clinical examination and appropriate investigations. The acute stroke patient may best be managed in hospital. Hypoglycemia may mimic a stroke and should be excluded by capillary sugar test. Avoid aggressive treatment of hypertension in the acute phase. Careful follow-up post-stroke enhances the outcome of the patient after a stroke.

Keywords: cerebrovascular disease, cerebral ischemia, cerebral hemorrhage, risk factors

Introduction

Stroke is a major cause of morbidity and mortality in Singapore. It is the third leading cause of death, accounting for 10 to 12% of all deaths, and a crude death rate of 50 to 60 / 100 000[1]. The number of admissions to Singapore hospitals for stroke has been rising, and reached 6084 in 1994[2]. About 28% of stroke patients consult a family physician before coming to hospital[3]; after discharge from hospital, most stroke patients are followed-up by their family physicians. Some stroke patients may even opt not to go to hospital, but instead remain under the management of the family physician. Thus the family physician plays a pivotal role in the immediate and subsequent management of the stroke patient.

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Approach

The following questions may be asked to assist in the management of the patient suspected to have had a stroke:

1. Is it a stroke?
2. Why is there a stroke?
3. Where is the anatomical location of the stroke?
4. Is the stroke ischemic or hemorrhagic?
5. What is the mechanism of the stroke?
6. What treatments are appropriate?

Terminology

Stroke may be diagnosed when there are rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of a vascular origin[4].

Transient ischemic attack(TIA) refer to those events that resemble a stroke, but the signs and symptoms subside completely within 24 hours.

Reversible ischemic neurological deficit(RIND) or prolonged reversible ischemic neurological deficit(PRIND) refer to those events that resemble a stroke, but subside completely within 1 to 3 weeks.

Cerebrovascular accident(CVA) or stroke refer to those events that subside after this time.

Most TIAs resolve within 6 hours. The terms RIND and PRIND are less used nowadays. Thus events lasting less than 24 hours are considered TIAs, those lasting more than 24 hours are considered strokes.

Clinical Evaluation

Common symptoms of stroke include unilateral weakness and/or numbness of the face, upper limb and lower limb, dysarthria, dysphasia, confusion, loss of vision in one hemifield, diplopia, ataxia, dizziness associated with other neurologic symptoms, the worst headache in one's life, and reduced consciousness.

History: The patient's age, sex, race and handedness should be recorded. History taking includes the nature of the symptoms, time of onset, activity preceding onset, progress of symptoms since onset, and development of additional symptoms.

Clinical examination includes blood pressure, pulse rate and rhythm, respiratory rate; general medical examination including the cardiovascular system and for carotid bruits. The neurological examination includes evaluating the motor, sensory and coordination systems; cortical signs such as dysphasia, anopia, neglect, apraxia; and brainstem signs such as lower motor cranial nerve deficits and crossed sensory loss.

Lacunar syndrome The lacunar syndrome[5] is a distinct clinical syndrome of any of the following: pure motor stroke (unilateral weakness of face, upper limb, lower limb), pure sensory stroke (unilateral numbness of face, upper limb, lower limb), sensorimotor stroke (unilateral numbness and weakness of face, upper limb, lower limb), and ataxic-hemiparesis/dysarthria-clumsy-hand syndrome (unilateral ataxia out of proportion of weakness, severe dysarthria and upper limb ataxia). Cortical and brainstem signs are notably absent. Consciousness is preserved. It occurs in approximately 40% of strokes locally[6]. The lesion lies in the contralateral internal capsule, corona radiata, or paramedian pons. The prognosis for recovery and stroke recurrence is generally better than for the other stroke subtypes[5].

Risk Factors

There are a number of well-known risk factors for stroke[6,7]:

1. *advancing age*. Stroke risk rises with age. The mean age of stroke patients in a local study was 65.9 years, range 23 to 96.5 yr
2. *hypertension* raises stroke risk by 4 to 8 times. It was found in 67.8% of local patients
3. *smoking* raises stroke risk by 2 to 4 times. It was found in 22.3% of local patients
4. *diabetes mellitus* raises stroke risk by 1.5 to 3 times. It was found in 39.7% of local patients
5. *hyperlipidemia* raises stroke risk by 2 to 3 times. Approximately 6.3% of local stroke patients have a history of hyperlipidemia
6. *atrial fibrillation* raises stroke risk by approximately 5 times and was found in 7.4% of non-lacunar infarcts locally. There was a history of *heart disease* in 12.8%
7. *previous strokes/TIAs*. These patients have a 5 to 10% chance annually of stroke recurrence, and was found in 22.3% of local stroke patients

Other risk factors include excessive alcohol intake and severe carotid stenosis.

Differential Diagnosis

Important mimics of the stroke syndrome include brain tumour (primary and metastatic), brain abcess, subdural hematoma, post-seizure, multiple sclerosis, metabolic derangements (hypo- and hyper-glycemia, dehydration, hypo- and hyper-natremia, liver failure, renal failure), and complicated migraine. Laboratory investigations may be required to make the distinction. Accurate diagnosis should precede treatment.

Progression of symptoms, prognosis

Acute stroke is an unstable state, particularly in the first week. While many patients remain well, about 20% may progress and worsen in the hours to days following a stroke. Thus, acute stroke patients may be best managed in a hospital setting The risk of stroke recurrance ranges from 5 to 10% per year. About 10 to 30% of stroke patients recover fully. The remainder recover partially or not at all. Most of the recovery occurs in the first 3 to 6 months, with minor improvement over the succeeding 1 to 2 years.

Stroke Subtypes

Stroke may either be due to arterial rupture(26%) or arterial occlusion(74%)[6].

Intraparenchymal hemorrhage is usually related to hypertension, especially if it is in the putamen, thalamus, pons or cerebellum. Less common causes include arteriovenous malformations (AVMs), moya-moya disease, amyloid angiopathy(especially in the elderly), and excessive anticoagulation. *Subarachnoid hemorrhage* (SAH) is usually due to a rupture of an intracranial aneurysm.

Infarction may be due to occlusion of a small artery, usually causing a *lacunar* infarct (and a lacunar syndrome, as described earlier), or of a large artery, causing cortical or brainstem signs. Vascular occlusion is most commonly due to in-situ *atherothrombosis,* but may also be due to embolism from a cardiac source (cardioembolism), embolism from a more

proximal arterial stenosis in the carotids or aortic arch *(artery-to-artery embolism)*, or from *hemodynamic* consequences of a proximal severe stenosis or occlusion.

It is difficult to confidently differentiate hemorhagic stroke from ischemic stroke purely on clinical grounds. A Brain Scan is the most reliable method of doing so. Scans can also rule out some of the other differential diagnoses. A Computed Tomography(CT) scan is a good screening test. Magnetic Resonance Imaging(MRI) may be required for CT-negative patients, or in patients suspected to have had a brainstem stroke.

Laboratory Investigations

Investigations are performed to detect the underlying cause of the stroke, and to exclude other causes.

A *capillary sugar* is a quick bedside test that should be done in all patients who appear to have had a stroke. Hypoglycemia is a great mimic of stroke, and is easily corrected. Blood *biochemistry* would detect other metabolic abnormalities.

Full blood counts may detect polycythemia (high hemoglobin) or thrombocytosis (high platelet counts) that predispose to thrombosis. Thrombocytopenia (low platelet counts) or prolonged *PT/PTTa* may lead to hemorrhagic stroke.

Blood sugar and HbAlC screen for hyperglycemia and diabetes mellitus; stroke patients with severe hyperglycemia may have a poorer outcome. *Lipid profiles* screen for hyperlipidemia.

Chest X-rays assess the cardiac size. The *electrocardiogram*(ECG) is particularly helpful in detecting atrial fibrillation and previous myocardial infarction, which are among the important causes of cardioembolism. *Cardiac echocardiography,* transthoracic and transesophageal, is a more accurate way of detecting potential causes of cardioembolism. Anticoagulation may be preferred in this group to reduce stroke recurrance.

Carotid and vertebral color-coded Duplex ultrasonography and transcranial Doppler allow a non-invasive assessment of the carotid and vertebral arteries in the neck, and the status of the intracranial circulation. Carotid endarterectomy may be preferred in those with 70 to 99% internal carotid artery stenosis ipsilateral to a TIA or minor ischemic stroke as a treatment to reduce stroke recurrance.

Young patients with ischemic stroke can be screened for deficiencies of Protein C, Protein S, and Antithrombin III, and for antiphospholipid antibodies (VDRL, lupus anticoagulant, anticardiolipin antibodies), as these are recognised *prothrombotic states*.

Arteriography is reserved for those with subarachnoid hemorrhage or those suspected to have AVMs. It is also performed to confirm the ultrasound findings of carotid stenosis prior to surgery.

Strategies for Acute Stroke Treatment

Treatment strategies currently employed or under clinical trials include(8):

1. *Reperfusion of occluded arteries.* Acute thrombectomy or embolectomy have not been found to be beneficial. Thrombolysis appears very promising, but needs to be given very soon after onset of stroke, and runs the risk of serious hemorrhage. It is not suitable for administration in the outpatient setting by family physicians.

2. *Neuroprotection of ischemic tissue.* This is the current thrust of industry-funded clinical research in stroke. There are no proven neuroprotectants at the moment, but some are already showing promise. If found useful and safe, they can conceivably be administered by the family physician in the clinic while awaiting the ambulance to take the patient to the hospital.

3. *Prevention of progression/recurrance of stroke.* This involves the use of antiplatelets or anticoagulants, and surgery in selected cases. This is discussed in more detail in a subsequent chapter.

4. *Prevention of complications.* This is discussed below.

5. *Risk factor detection and treatment.* This may reduce the risk of stroke recurrance. The appropriate tests have been discussed earlier.

6. *Rehabilitation/Stroke Education/Stroke Support.*
This is an extremely important part of stroke treatment. Rehabilitation helps the patient regain independence in his daily activities. There are a number of inpatient and outpatient rehabilitation centres available in Singapore. Some patients develop post-stroke pain. This is discussed in more detail in a subsequent chapter. *The Singapore National Stroke Association* is a national level stroke support group for stroke patients and carers (Tel 3596020).

Complications of Stroke

Mortality and morbidity in the acute phase of stroke is usually related to the large size or critical anatomical location of the stroke. The outcome after this acute phase is dependant upon the complications. Measures should be taken to reduce the risk of these complications, and to detect and treat them early.

1. *Stroke recurrence.* The risk of stroke recurrence is 5 to 10% annually. Treatment options are discussed in a subsequent chapter.

2. *Infections.* These include pneumonia, particularly aspiration pneumonia in those who are drowsy or who are unable to swallow safely. Preventive measures include avoiding oral feeding in the drowsy patient who is awaiting an ambulance. Nasogastric tube feeding may be used in those with poor swallowing. The patient should be fed propped up, and remain propped for 45 minutes post-feeding. Percutaneous gastroenterostomy (PEG) feeding is another option for those who will require prolonged nasogastric feeding. Urine infections are also common, especially in those with indwelling catheters. The risk may be reduced with proper genital hygiene and catheter care.

3. *Dehydration/starvation.* Patients who are unable to take orally may inadvertantly be starved. There are a number of powder and ready-made formula preparations in the market. A dietitian will be able to advise on suitable preparations. Sufficient calories and water must be given. Overfeeding may lead to excessive weight gain.

4. *Constipation/urinary retention.* This is a problem in those who are unable to visit the toilet regularly. The use of laxatives and bulk formers would help reduce the incidence of constipation and consequent urinary retention from impacted stools. *Urinary and fecal incontinence* may also occur in those who have major stroke with drowsiness or cognitive impairment. Conscious patients who are unable to get to the toilet should be encouraged to call when the need to pass urine or open their bowels arises.

5. *Deep venous thrombosis.* This is believed to be rare in Singapore. It tends to occur when the leg is severely weak. Preventive measures include the use of antiembolic stockings or subcutaneous heparin.

6. *Pressure sores.* This is a problem in those who are kept in a single position for extended periods. Regular turning and proper positioning may reduce the frequency of this complication.

7. *Depression.* Physicians and caregivers should be aware of this potential complication Family support is vital to every stroke patient.

What to do for the Acute Stroke Patient

The family physician meeting the acute stroke patient should adopt the approach described in the beginning of this paper. The following measures may be taken while awaiting the arrival of an ambulance[9]:

1 position the patient comfortably. He may be propped up if drowsy to reduce the risk of aspiration.
2 oxygen may be helpful if available.
3 avoid aggressively treating high blood pressure(BP). The BP is often elevated in the acute phase; this may be related to the stress of the illness or from the stroke itself. There is some loss of cerebral autoregulation in acute stroke. Lowering the BP may result in recurrent stroke due to hypotension and

cerebral hypoperfusion. The BP usually comes down spontaneously and stabilises within a few weeks.

4. check the capillary blood sugar. Hypoglycemia is an easily treated condition.
5. avoid oral intake. This is in case the patient deteriorates or needs emergency surgery. If possible set up an intravenous line: this would allow hydration and will provide a life-line in case of a collapse. Avoid glucose-containing or hypotonic solutions.
6. send to hospital as soon as possible.

What to do for the follow-up Stroke Patient

Many stroke patients return to the family physician for follow-up. The following measures may be helpful:

1. obtain as much information about the stroke as possible. The hospital may need to be contacted.
2. encourage regular follow-up with you.
3. encourage strict compliance with medication, unless otherwise advised by you or the hospital doctors.
4. monitor for complications of stroke.
5. monitor for complications of medications, especially bleeding among those on antiplatelets or anticoagulants.
6. reinforce the importance of early recognition of symptoms of recurrent stroke, and the need for early assessment and treatment if they occur.
7. send for rehabilitation, and encourage continuation of exercises.

Conclusion

Stroke is a major health problem in Singapore. Appropriate care from the family physician will no doubt go a long way in reducing the impact of this terrible disease.

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Neuroimaging in Stroke

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Abstract

Management of the stroke patient requires imaging of the patient's brain. The Computed Tomography (CT) scan done in the acute setting tells us instantly whether the stroke is due to a brain haemorrhage or infarction, a piece of information that is vitally important in deciding the line of treatment for the patient. Follow up scanning of the stroke patient is helpful in assessing the evolution of the disease as well as detect complications which may require immediate treatment. Cerebral angiography provides the finest detail in assessing the cerebral arteries and veins while Magnetic Resonance (MR) techniques shed much light on the stroke process. With future advances in imaging techniques, further enhancement of stroke management is expected.

Introduction

Since the introduction of the Computed Tomogram (CT) by Godfrey Hounsfield in 1973[1] technological advances in brain imaging have revolutionised the management of stroke patients. The availability of accurate brain scans with great sensitivity and specificity in evaluating the morphological changes in stroke patients enables physicians to achieve a level of precision in diagnosis previously unattainable.

There are four basic goals in the diagnostic approach to a stroke patient. These are (1) to identify the cause and mechanism of stroke, (2) to localise the lesion in the brain, (3) to quantify the severity of brain damage, and (4) to identify conditions that may pose a risk of further stroke[2].

The purpose of brain imaging is not just to answer these vital questions but also to detect other conditions such as tumours or infection that may masquerade as stroke.

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Computed Tomogram

The Computed Tomogram (CT) scan uses a fine collimated beam of X rays to produce images of the brain differentiating tissues according to their density values. The present generation of CT scanners is able to produce very detailed and accurate axial images of the brain within minutes. Coronal images can be acquired if needed. Since its introduction, the CT scan has quickly become an indispensable tool in the assessment of the stroke patient.

In the acute setting, clinical findings alone cannot reliably distinguish between haemorrhagic and ischaemic strokes. To answer this important question, the CT scan is needed because of its exquisite ability to detect haemorrhage.

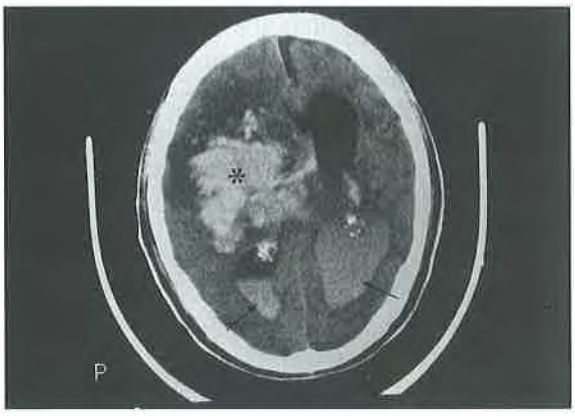


Fig. 1 Axial CT scan showing a large haematoma seen as a space occupying lesion(asterix) located in the right basal ganglia of higher density compared to normal brain causing severe mass effect on the adjacent brain parenchyma. The haemorrhage has extended to theventricles(arrows) causing hydrocephalus.

On the CT scan, intracerebral haemorrhage is instantly recognised as an area of increased density in the affected region on the scan relative to the brain parenchyma(Fig. 1). Density of tissue is measured by Hounsfield units. Normal grey matter ranges from 37 to 41 Hounsfield units and normal white matter is from 30 to 34 Hounsfield units' whereas fresh blood is about 50 to 60 Hounsfield units. The size, location, extent and mass effect of the haematoma can thus be easily identified. Related complications such as hydrocephalus can occur when there is interruption of the drainage of the cerebra spinal

fluid(CSF) or when there is direct extension of the haemorrhage into the ventricles. Mass effect causing shift of the midline structures and brain herniation are visible on the scan and correspond to a more severe clinical picture. There are also features on the scan which can help to differentiate haemorrhage due to causes such as tumour, arteriovenous malformation and aneurysms from that of spontaneous haematomata.

After a few days, the density of the haemorrhage starts to decrease slowly as the reparative mechanisms take effect to clear the clot. Over the next one to two months, the region of haemorrhage is gradually transformed to a hypotenuse slit with a density close to that of CSF. After this time, the residual area of scarring would be indistinguishable from that of an old ischaemic infarct.

Ischaemic stroke is caused by blockage of intracranial arteries by thrombus, atherosclerosis or embolus resulting in cerebral infarction. The majority of strokes is caused by embolic disease. These can arise from arterial stenoses, atheromatous plaques with or without ulceration and cardiac sources. Strokes can also occur with reduction of blood flow, often producing infarcts in the watershed regions which are supplied by the most distal portions of the intracerebral vasculature.

The CT scan is a useful and efficient tool in the assessment of ischaemic stroke. The location and extent on the infarct can be documented. Even if the scan is done in the hyperacute phase when the morphological changes in the infarct may not be apparent, it helps by excluding other causes of stroke such as haemorrhage or tumours.

Small infarcts of less than 1.5 cm in size are usually caused by occlusion of a small end artery. Striato capsular infarcts are larger in size and are located in the basal ganglia and internal capsule region. These result from occlusion of a larger vessel or a group of arteries. Infarcts in the basal ganglia are common and often indicate the presence of diffuse cerebral ischaemia[4]. Occlusion of a large cerebral artery will bring about a large infarct in the part of the brain supplied by that artery. For example, sudden cessation of blood flow in the posterior cerebral artery leads to an infarct in the occipital lobe with a well defined border outlining the vascular territory of the artery (Fig. 2).

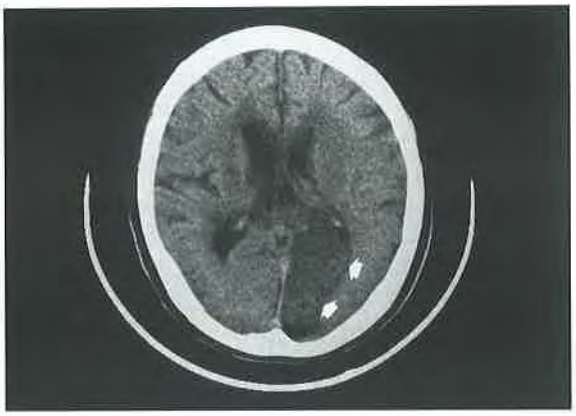


Fig. 2 Axial CT scan showing an infarct which appears as an area of lower density(white arrows) compared to adjacent brain involving the left occipital lobe. This corresponds to the territory supplied by the left posterior cerebral artery and would be indicative of an acute obstruction of the main artery.

Watershed infarcts occur when there is reduction in cerebral blood flow so much so that the regions of the brain fed by the most distal parts of the vasculature (watershed zone) become starved of arterial blood. Major watershed zones are those between the anterior and middle cerebral and the middle and posterior cerebral arteries. Another type of watershed (internal watershed zone) is that located in the corona radiata and centrum semiovale between the medullary arteries arising from the superficial pial plexus and deep penetrating vessels arising from the basal cerebral arteries[3].

Venous infarcts has a different mechanism of onset compared to arterial strokes. Instead of the target organ suffering from lack of blood supply as in arterial stroke, venous strokes are due to venous thrombosis causing obstruction to normal cerebral venous drainage. This results in venous congestion, oedema and even haemorrhage. On the CT scan, venous infarcts often appear as areas of oedema with or without scattered foci of haemorrhage. After intravenous contrast, a filling defect may be seen in the sagittal sinus(empty delta sign) in patients with sagittal sinus thrombosis.

Subarachnoid haemorrhage is visible on the CT scan as increased opacification of the subarachnoid spaces since the low density CSF is replaced by high density blood (Fig. 3). This occurrence, especially in the absence of a history of trauma warrants an angiogram to evaluate the cerebral

vasculature in search for a ruptured aneurysm or arterio venous malformation.

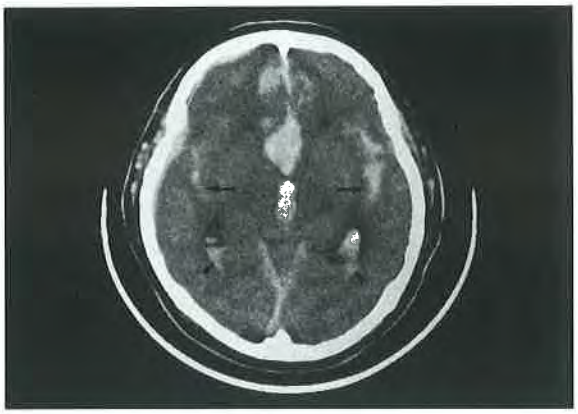


Fig. 3 Axial CT scan depicting subarachnoid haemorrhage. The Sylvian fissure are filled with high density blood(arrows) instead of low density CSF. Blood is also seen in the lateral ventricles(arrowheads).

Extra cerebral but intracranial haemorrhage in the extradural or subdural spaces can occasionally present with the same symptoms as stroke. On the CT scan, extra cerebral haemorrhage appears as a lentiform area of increased density producing compression on the underlying brain Subdural haematomata, on the other hand, are crescenteric in shape (Fig. 4). In some patients, especially in those of the geriatric age group, a chronic subdural haematoma can present with clinical findings indistinguishable from stroke.

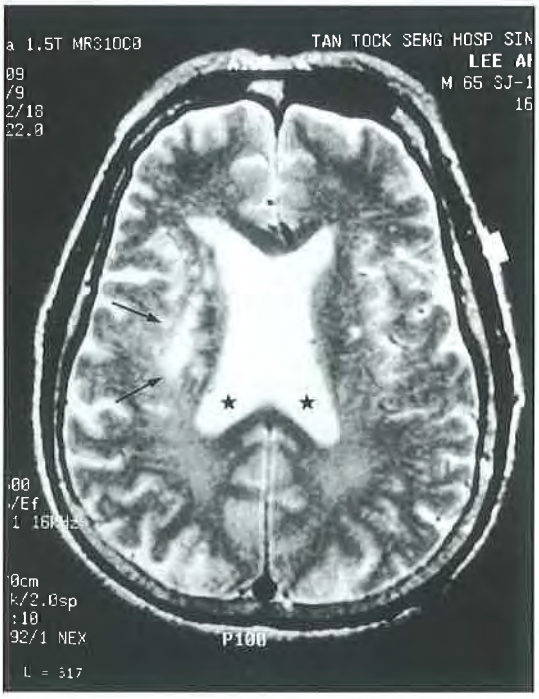


Fig. 4 In a T2 weighted axial MRI image, the skull vault(white arrow) is black and the CSF in the ventricles is white(stars). The infarct in the right corona radiata appears as a bright lesion (black arrows)

Magnetic Resonance Imaging (MRI)

Although CT has proven to be an efficient way of brain imaging in the stroke patient, MRI is growing in importance as a complementary imaging modality. This is due large to the exquisite detail obtainable with the present MR machines which are capable of producing images in a matter of minutes or even seconds.

Whereas the contrast in a CT image is based only on tissue density as the one and only parameter to produce contrast in the CT image, MRI uses three parameters, namely, T1, T2 and proton density of different tissues to generate three separate sequences. This helps in further categorising components of brain parenchyma and thereby improving diagnostic accuracy. MR also has the added advantage of imaging in the coronal and sagittal planes in addition to the axial images without the need to reposition the patient.

T2 weighted sequences are very sensitive to the water content in brain tissues and are useful in detecting regions of infarcted brain which become oedematous in the early stages of stroke (Fig. 4). It can detect an infarct earlier than the CT scan. T1 weighted sequences are helpful in studying the morphological changes in the brain during the evolution of a stroke and the presence of haemorrhagic transformation in an infarct. Intra and extra cerebral haematomata of different ages are also easily recognisable (Fig. 5).

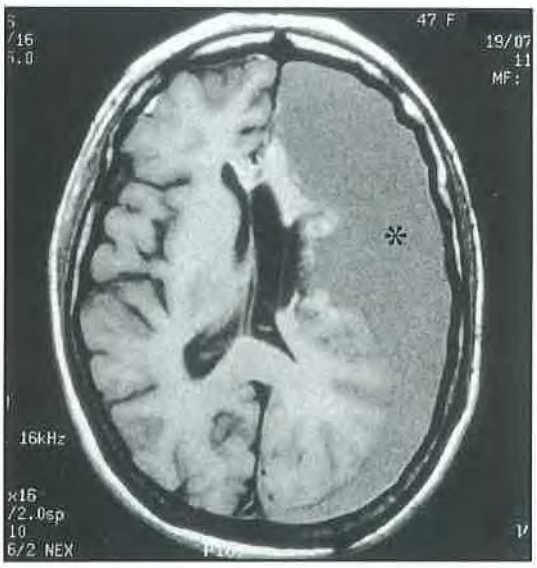
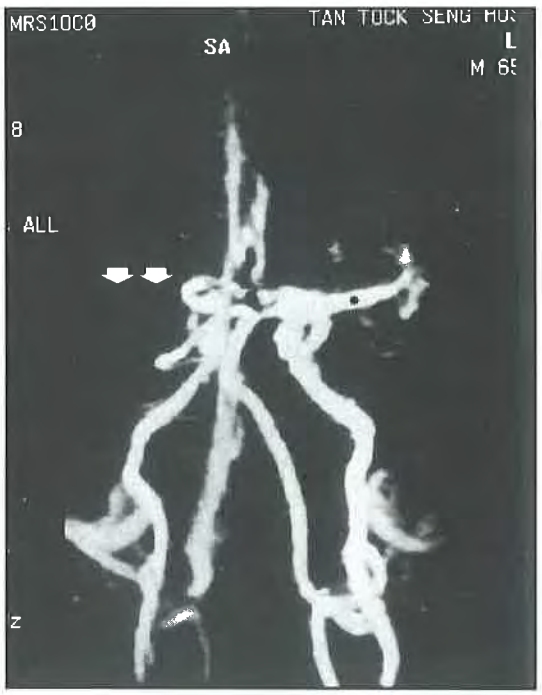


Fig. 5 In this T1 weighted axial MRI image, a large left sided sub dural haematoma(asterix) is noted to cause severe compression of the adjacent brain

Modern MR scanners are also capable of generating images of the cerebral vasculature (MR angiography). This can be particularly helpful especially if the stroke is due to a large vessel occlusion (Fig. 6). Although it is still unable to match the resolution of catheter angiography, it is useful in assessing the major intracranial vessels. Improved radio frequency coils and sophisticated software have enabled the generation of MR images quickly and accurately. Currently, the more advanced clinical MR systems are able to carry out functional examinations such as diffusion and perfusion imaging, spectroscopy and task activation studies.



Diffusion weighted MR images uses the different diffusion coefficients of abnormal tissue to produce an image. This method can detect an ischaemic infarct much earlier than the routine MR sequences. Different infarcts can also be graded as new or old according to their appearance on these images

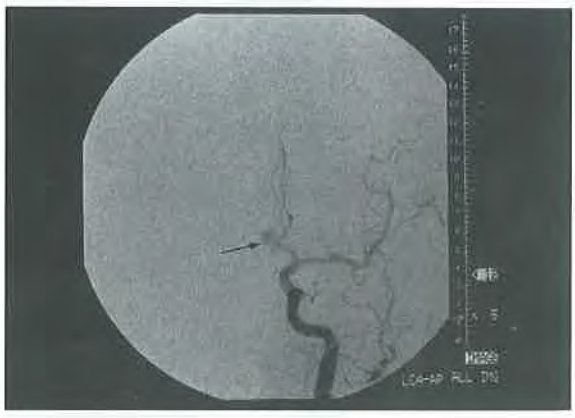
Perfusion weighted MR maps the subtle changes in a region of the brain as a bolus of MR contrast passes through it. Valuable information on brain perfusion can be obtained with this technique, enabling radiologist to acquire data on the cerebral blood flow and volume.

Proton MR spectroscopy used to be only available in experimental high field strength machines but it can now be performed in current MR scanners with the necessary hardware and software to support this application[5]. Such a study produces a graph depicting the concentrations of various metabolites in various parts of the brain. Since different disease processes such as infarcts and tumours produce different metabolites, invaluable data can be obtained, enhancing the diagnosis of brain lesions.

Angiography

Cerebral angiography is by and large the gold standard in the assessment of the vascular architecture of the brain. It is able to map the cerebral vasculature with high resolution. The procedure is carried out in the radiology department. A catheter is introduced via the femoral artery into the carotid and vertebral arteries. Contrast is then injected and a digital subtraction angiogram is then acquired to visualise the intracranial as well as extracranial circulation clearly.

Presently, the role of angiography is in the diagnosis of aneurysms (Fig. 7) and arteriovenous malformations in patients with intracranial haemorrhage, assessment of the nature and severity of arterial stenoses and the presence of vasculitis in patients with ischaemic stroke. All these can be achieved with a degree of accuracy unmatched by current ultrasound, MR or CT angiographic techniques.



The ability of angiography in assessing the degree of stenosis in the carotid bifurcation is important in deciding whether the patient should be treated by carotid endarterectormy or medication alone. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) has shown that carotid endarterectomy is highly beneficial to

patients with recent hemispheric transient ischemic attacks or nondisabling strokes and ipsilateral high-grade stenosis (70 to 99 percent) of the internal carotid artery [6,7]. Similar benefits were found in asymptomatic patients in the ACAS (Asymptomatic Carotid Atherosclerosis Study)[8].

Ultrasound

Duplex ultrasound employs both the imaging capability and Doppler principle to produce information of the blood flow in the carotid bifurcation of patients with symptoms of cerebrovascular disease.

Flow velocities in the carotids are accelerated in the presence of luminal stenosis. By analysing the systolic and diastolic flow velocities as well as the spectral broadening values, the sonographer is able to categorise the degree of stenosis into different ranges of percentages, namely, less than 40%, 40 - 59%, 60 - 79%, 80 - 99% and 100%.

Patients with severe stenoses are then referred for angiography for accurate calculation of the degree of stenosis as called for by the NASECT guidelines[9]. As the Doppler signal may not be detected in very severe stenoses with only a trickle amount of flow, such vessels may be misdiagnosed as occlusion and should also be studied by angiography.

Nevertheless, ultrasound serves a useful role as a non invasive method of screening for such patients prior to definitive angiography.

Conclusion

Brain imaging has come a long way over the past two or three decades. In most centres, the ubiquitous CT scanner is the first line imaging option for stroke patients. MRI, angiography and ultrasound complement the role of CT and provide additional anatomical and functional data which is necessary for the proper management of the patient.

With the aid of information gathered from these imaging studies, the severity, extent, progression and prognosis of each individual patient can be accurately documented in the early phase. On follow up, CT and MR scans are also useful in spotting any new changes that may have occurred or even detecting a separate pathology. These techniques can also be utilised in the prophylaxis of stroke. Brain perfusion can be studied by imaging studies in order to distinguish a group of patients at high risk of development of stroke. Aggressive revascularisation therapy can then be instituted for such patients.

Further improvements in software and radio frequency coils have enabled MR functional imaging such as diffusion and perfusion sequences which are proving to become important tools in the understanding of stroke. With further progress in technology, more refinements in brain imaging is to be expected. In the final analysis, both anatomical and functional neuroimaging will continue to play a greater role in the evaluation of the stroke patient.

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Rehabilitation of the Post Stroke Patient

Tow A M, Kong K H

Introduction

Each year, an estimated 5000 Singaporeans suffer a stroke. While the initial event is often perceived by the patient and family as a tragedy, the outcome is by no means uniform in all patients. In fact, the functional prognosis of stroke patients can roughly be divided into 3 groups i) those with minimal or no deficits and disabilities, ii) those with moderate residual deficits and disabilities and iii) those with severe residual deficits. Most of the patients in the first category are able to return to their former lifestyle and vocation and do not require rehabilitation. It is the second and third groups of patients, however, rehabilitation can play a very important role in management. The goals of rehabilitation, both as inpatient and outpatient, are the development of a person to the fullest physical, psychological, social, vocational, avocational and educational potential consistent with his/ her anatomical impairment and environmental constraints.[1]

This concept of rehabilitation should carry over in the outpatient evaluation and management of the post stroke patient. In addition to evaluating the patient's medical, condition, problems should also be assessed in relation to how they impact upon the patient's function and management strategies should aim at improving his/her quality of life. Some of the day to day problems encountered in an outpatient setting include: i) shoulder pain, ii) spasticity, iii) urinary incontinence, iv) post stroke depression and v) psychosocial problems.

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Shoulder Pain

Shoulder pain is common following the onset of hemiplegia, especially within the first year following the stroke[2-]. Common causes are mainly musculoskeletal in origin and include subacromial impingement with rotator cuff tendonitis, glenohumeral subluxation, bicipital tendonitis, adhesive capsulitis and myofascial pain. In addition, neuropathic causes. For example reflex sympathetic dystrophy and post stroke central pain, may be encountered.

Subacromial impingement with rotator cuff tendonitis is probably the commonest cause of shoulder pain post stroke. Clinically, the patient may manifest with pain at the lateral aspect of the shoulder, especially on lying on the affected side, or abducting to about 60-120 degrees. Impingement sign may also be positive. The diagnosis can be further confirmed if the pain improves with injection of about 3 mls of 1% lignocaine into the subacromial space. If a trial of analgesics does not improve the pain, subacromial injection of 10mg (1ml) of triamcinolone with 3mls of 1% lignocaine will usually relieve the pain for a longer period.

Shoulder subluxation from weakness of the rotator cuff and deltoid muscles occurs in about 3050% of post stroke patients, but not all patients develop shoulder pain from this. Diagnosis is mainly clinical: a palpable gap will be felt between the acromion and humeral head. Management of the subluxed shoulder consists of proper positioning of the hemiplegic arm so as to prevent further complications caused by the altered biomechanics. Wheelchair lapboards and forearm troughs may be useful in the seated position. The use of shoulder slings remains controversial[3] as they may not mechanically reposition the humeral head into the glenoid fossa and may encourage excessive flexor synergy and the development of contractures by maintaining the arm in a flexed position. In an ambulating patient with a flaccid arm, however, a sling appears to be useful.

The development of adhesive capsulitis or frozen shoulder may be accelerated in post stroke patients due to immobility, spasticity and altered biomechanics. Typical features include restricted shoulder range of motion in all directions especially external rotation. The mainstay of treatment is that of exercises to increase range of motion. Injection of the glenohumeral joint with a mixture of steroid and lignocaine may help

relieve pain, and in so doing, facilitate performance of exercises.

Reflex sympathetic dystrophy is a clinical condition characterized by distal limb pain, edema, and vasomotor instability. Metacarpo-phalangeal joint tenderness and hyperalgesia has been found to be characteristic of the condition in hemiplegic patients.[4] It is believed to be a sympathetically mediated entity, and occurs usually between 14 months post stroke. A short course of steroids, prednisolone 10 mg three times a day, for 2 weeks has been found to be useful in relieving the pain. Analgesics and non-steroidal antiinflammatory medications may help. Unresponsive cases may respond to sympathetic blockade and alpha blockers.

Lastly, central post stroke pain, although rare (occurring in less than 2% of cases), can be extremely distressing to patients. It often manifests as burning and unpleasant pain sensation and is generally associated with some sensory anomaly on the affected side. The condition is generally intractable to therapeutic interventions. Tricyclic antidepressant medications have been shown to have a beneficial effect in central post stroke pain states[5]. Anticonvulsants, for example carbamazepine, and recently, the selective serotonin reuptake inhibitors have also shown some promise.

Spasticity

Immediately following a stroke, there is initial flaccidity, followed by a gradual increase in tone over days to weeks. This may be accompanied by other manifestations of the upper motor neuron syndrome, for example, clonus, spasms and synergy patterns (for example flexor synergy in the upper limb manifesting as flexed, adducted and internally rotated shoulder with flexed elbow, wrist and fingers)[3]. In the assessment of the post stroke patient, the manifestations of spsaticity should be examined in conjunction with its influence on the patient's function. For example, an increase in extensor tone in the lower extremities may aid walking and standing in spite of decreased muscle power. On the other hand, excessive plantar flexion tone accompanied by ankle clonus on standing may impede gait. Excessively increased finger flexor tone may also cause difficulty for caregivers in maintaining hygiene of the hands and fingers. There may also be pain caused by excessive spasticity in the muscles. In these instances, there is indication to treat excessive spasticity. Our experience so far is that medications, for example baclofen, diazepam and dantrolene, are not effective for severe localized spasticity. In addition, side effects may occur, for example sedation (baclofen, diazepam), and hepatotoxicity (dantrolene). We have found that local treatment of spasticity with motor point and nerve blocks is more effective for localized problems.(6) Agents used include 50% alcohol, phenol and botulinum toxin. The effects usually last about 6-12 weeks and side effects are minimal: localized hematoma in about 1-2% of cases.

Urinary Incontinence

Urinary incontinence is a distressing problem for post stroke patients, often contributing to decrease in morale, motivation and self respect. The etiology could be due to neurologic, urologic, psychologic or mobility problems. Detrussor instability from cortical disinhibition of micturition, or post stroke areflexic bladder especially in brainstem strokes, may occur. Concomitant urologic problems commonly include benign prostatic hypertrophy in men and stress incontinence in women. Often, psychologic factors like post stroke confusion, depression and amotivation contribute. As much as possible, etiologic factors should be delineated. In addition to careful history taking and physical examination, the post void residual urine has been found to be a useful guide. Post void urine volumes of less than 100mls generally indicate an inability to contain urine, of which detrussor hyperreflexia, stress incontinence and functional incontinence due to psychologic factors or lack of mobility could be contributory. On the other hand, post void urine volumes of more than 100-150 mls generally indicate a problem of either bladder outlet obstruction (for example benign prostatic hypertrophy or urethral stricture), or a poorly contractile bladder for which fecal impaction and concomitant medications such as anticholinergics, should first be ruled out. Urodynamic examination will help confirm the diagnosis. Smooth muscle relaxants like flavoxate at a starting dose of 100mg three times a day, or anticholinergics, for e.g. oxybutynin at 5mg three times a day, may help

detrussor instability, in addition to fluid restriction, urge suppression and habit training. Patients with poorly contractile bladders may respond to bethanechol at a starting dose of 10mg three times a day to aid detrussor contractility.[7] If unsuccessful, intermittent catheterisation can be taught to the caregiver and done 4-6 hourly. Timely referral to a urologist may help solve concomitant urologic problems

Post Stroke Depresssion

This problem occurs in about 30% of patients and often contributes to their lack of functional improvement and decreased participation in therapy. In addition to manifesting commonly encountered depressive symptoms such as lack of appetite, reduced mood, inability to sleep and feelings of worthlessness, post stroke patients may also present with an indifferent, apathetic mental state associated with inappropriate cheerfulness [8], and apparent deterioration from a previously stable neurological deficit. In addition, communication impairment may impede a full psychiatric history and a flattened affect from frontal lesions may mask underlying depression. For these reasons, the threshold for starting antidepressants should be lowered. Tricyclic antidepressants have been the mainstay of treatment; however, sedation and anticholinergic side effects are common. Recently, the selective serotonin reuptake inhibitors have gained favour. Fluvoxamine and recently, paroxetine, has been shown to have a neutral effect on psychomotor performance. Starting doses should be small, for example, fluvoxamine at 25-SOmg a day, and gradually increased. Alleviating depression is definitely rewarding and will often go a long way in increasing quality of life and functional independence in post stroke patients.

Psychosocial Issues

A stroke in a family member inevitably affects the well being of the entire family unit. Carergivers of stroke patients have been found to suffer greater rates of depression and deterioration in their own health, especially when the patient has behavioural problems or when family support from other members is lacking[9]. In addition, the post stroke patient's quality of life and socialization in terms of hobbies, pastimes and work markedly decrease. Community resources should be utilised to aid full reintegration of the patient and to reduce carergiver stress. Counselling and family education given early following a stroke often helps in terms of stroke knowledge and problem solving. In the long term, emotional and social support of stroke patients and their caregiver can be provided for in support groups, for example, the Singapore National Stroke Association. In addition, day care centres are available to provide exercise and socialisation. centres for respite care, for example Ang Mo Kio Community Hospital, are available for carergivers to need respite from caregiving for about 3-4 weeks. Family counselling centres and vocational centres are available to help improve family dynamics and aid in vocational placement.

Conclusion

In the long term outpatient follow up of the stroke patient, increasing function and quality of life is the key to good patient management. Early identification and management of potential problems, as well as tapping on community resources, will go a long way in alleviating the distress of post stroke patients and their families.

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Estrogen and Progestin Compared With Simvastatin For Hypercholesterolemia In Postmenopausal Women

Source: NEJM 1997;337:595-601

Postmenopausal oestrogen therapy has favourable effects on serum lipoproteins in women. In a randomized crossover trial, Giselle et al in Melbourne Australia, studied 58 postmenopausal women who were put on simvastatin 10mg daily for eight weeks, and postmenopausal hormone therapy (conjugated equine oestrogens up to 1.25mg daily, with medroxyprogesterone acetate 5mg daily) for eight weeks, with a washout period of eight weeks between the two treatment phases. Fasting blood samples were taken at weeks 4, 8, 16, 20, 24 to measure lipids and lipoproteins and to monitor liver function and creatine kinase levels.

Results: Both hormone therapy and simvastatin caused significant reductions in total cholesterol (14 vs 26 percent) and LDL cholesterol (24 vs 36 percent), but simvastatin was more effective than hormone therapy ($p < 0.001$). Both treatments caused a significant increase in HDL cholesterol (7 percent) with no significant difference between the two. Hormone therapy increased triglyceride levels (by 29 percent), while simvastatin reduced them (by 14 percent). Hormone therapy significantly reduce Lp(a) lipoprotein (by 27 percent), while simvastatin had no significant effect.

Conclusion: In postmenopausal women with hypercholesterolemia, hormone therapy may be an effective alternative to treatment with simvastatin, especially in women with normal triglyceride levels.

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Review by Phang J

See The Marvellous Waterfalls On Stamps

Tan N C

Since time immemorial, Man has been awed by the celestial beauty of the waterfalls. I am no exception. I marvel at the sight of the incessant torrent, like an aquatic ballet of dancing water with its own symphony. I like to be embraced by its misty spray, enchanted by its accompanying rainbow and refreshed by its cool water. In fact, all my senses rejoice in its presence. Each waterfall is unique but its character can be temperamental. One moment it may be a plume of water, next it may become a cauldron of seething water. Such manifestation is fascinating in the eyes of the beholder.

Busy doctors like us may find it difficult to enjoy such pleasure. One option is to admire the waterfalls from a collection of stamps and philatelic material. You can appreciate it in solitude or generously allow others to share your joy by displaying it in stamp exhibitions.

A story is a prerequisite in such a display. With some earnest research and a little imagination, an entertaining story can be vividly illustrated with stamps and philatelic items which include pictorial postmarks and postal stationery. This is the essence of thematic philately.

My collection begins with an introduction to the myriad forms of waterfalls, from gentle cascades to powerful cataracts. Next, I touch on the legendary formation and geological background of waterfalls. Two Singapore stamps depicting the world's highest man-made waterfall in Jurong Bird Park are included in this section. Waterfalls were hindrance to exploration in the last century. How Man ingeniously overcome this natural obstacle was shown in the following chapter.

Other chapters deal with the waterfall's varied roles in the human society, such as geographical landmarks, source of hydroelectric power, popular tourist attractions and even national emblems. Waterfall is the perfect destination for a relaxing picnic, camping, cool immersion, fishing and of course, romantic rendezvous. It is also a source of inspiration for artists, writers and composers. The numerous paintings, music, songs and literature dedicated to waterfalls serve as a good testimony.

The last chapter depicts the waterfall as the lifeline of flora and fauna, being a source of fresh water. Nonetheless, many waterfalls are facing the threats of pollution and destruction from infrastructure development. Conservative measures such as the organisation of educational campaigns and the establishment of national parks are needed to protect these waterfalls. Unless these measures are taken up seriously, Man will lose one of his wonderful natural heritage. This massage can be effectively conveyed to all corners of the world by stamps. Indeed, a picture of the marvellous waterfall on a tiny stamp is worth more than a thousand words!

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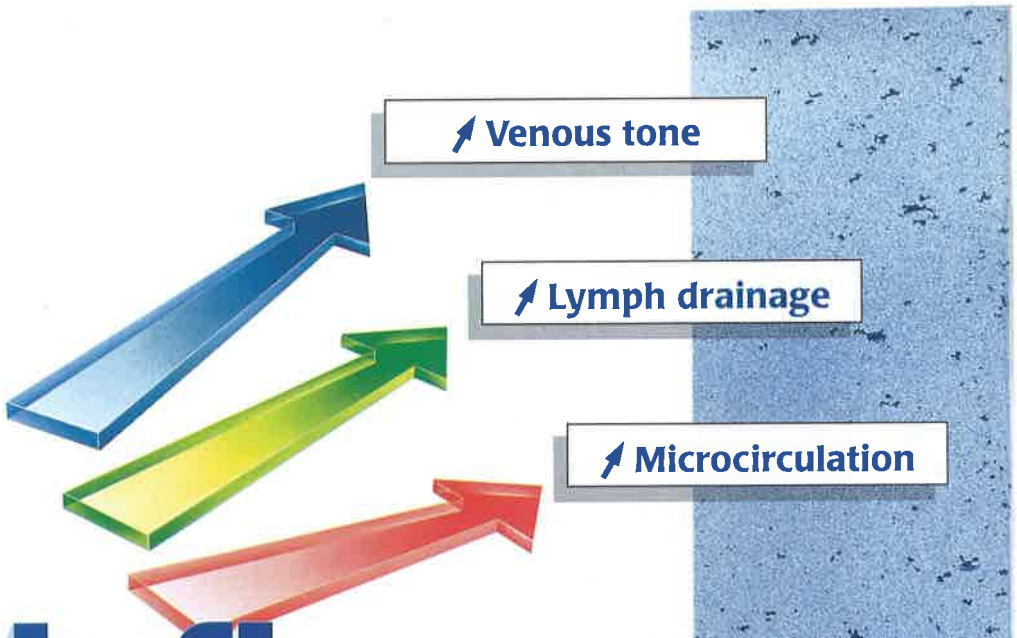

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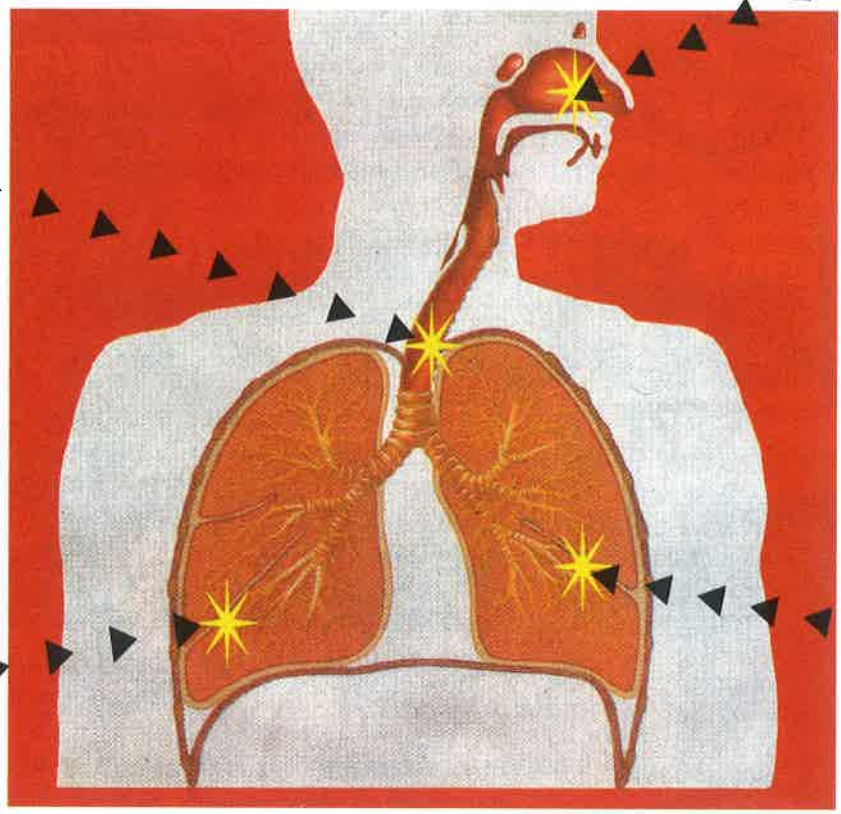
Power activity within macrophages

"High and persistent concentration within macrophages ensures destruction of intracellular strains thereby avoiding relapses"[7]

Power against a wide spectrum of respiratory pathogens[1]

"97% efficacy as first-line of attack on community-acquired pneumonia[2]"



Power in high tissue penetration

"Excellent tissue diffusion levels above MICs of most pathogens[1]

Power as a 16-C macrolide

Rovamycine has a remarkable intracellular half-life (72 hours)[3] and its biological half-life is longer than erythromycin (14-C) amd clarithromycin (14-C)[1,4] It also has better GI safety[3] compared to most 14-C macrolides and is free of drug interactions[6]

ROVAMYCINE

spiramycin

References: 1. Kernbaum S. Spiramycin therapeutic use in man. Semaine des Hopitaux, 1982, 58 (5) 289-297. **2.** L. Jeannin, J. Vergeret, K. Caillaud, R. Poirier, A. Vandevenne, J.B. Vercken. Community-acquired pneumonia in healthy adults: 188 patients treated with spiramycin in private practice. Rev. Pneumol. Clin., 1992, 48, 263-268. **3.** J. J. Pocidalo, an interview with; Macrolides in the treatment of community-acquired pneumonia. Infectiologie: Theorie et pratique therapeutiques, Issue 112, excerpted from issue no 38. November-December 1992. **4.** Neuman M. Vade-Mecum des antibiotiques Ed Maloine., 1990. **5.** Bertrand J. C et all: Infection broncho-pulmonaire: a efficacite egale, la rovamycine par voie veineuse est mieux tolere que l'erythromycine. Pana. du med supp. No 2796 (1988). **6.** Perit P, Massei T, Mini E, Novelli A. Pharmacokinetic drug interactions of macrolides. Clin. parmacokinet. 23 (2): 106-131, 1992. **7.** Boussougant Y, Weber Ph: Macrolides et germes intracellulaires-infectiologie 6:32-36 (1985).

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1. Anderson J T et al: Can Finasteride reverse the progress of BPH? A two year placebo-controlled study. Urology 46(5),1995

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