Epistaxis vs. Nose Bleed:The Importance of Teaching Students to Communicate Effectively

Heather Church, Editor

Over the years, people have said to me too often: 'Yes, but if you had to decide between a doctor with effective communication skills and one with medical competence, which would you choose?' Given all that we know, my resolute response has become: 'We shouldn't have to choose anymore.' "
Dr. Suzanne Kurtz, Canadian Journal of Neurological Sciences, 2002

Only 30 years ago, some medical schools required students to take acting classes. Instead of learning ways to establish an effective doctor/patient dialogue, student doctors were shown how to “fake” it. Acting classes implied that doctors did not need strong communication skills, but instead were expected to excel in feigned emotive reactions.

Time has shown that effective communication skills are essential in medicine. As medical students, we are taught that over 80% of diagnoses can be made on history alone. Obtaining a patient’s history is the driving force behind creating an effective doctor/patient dialogue. The importance of simply asking the right questions, and then to listen, cannot be understated.

Additionally, effective communication can serve both practical and idealistic purposes. Good "bed-side manner" can have a positive impact on the healing process of a patient. A doctor who communicates well with patients will foster trust, promote compliance with treatment, and can be considered a unique form of placebo. Doctors are not separate from the healing process; they are as important as the medicine.

Practical reasons for doctors to communicate effectively include saving time and decreasing the possibility of litigation. A doctor, who spends a few extra moments to make certain all of a patient’s questions are answered, will ultimately find that she is spending less time on future encounters. Moreover, doctors who are medically sound but fail to create a good rapport, are more likely to be sued compared to doctors who are fallible, yet forthcoming, and create a mutually trusting relationship with the patient.

For example, a study published in the Journal of the American Medical Association (JAMA) in December 1999 shows just how much work is required. More than 1,000 patient/physician discussions were analysed, involving more than 3,500 clinical decisions. Only 9% met the study's criteria for informed patient decision-making. JAMA also published that year an AMA Council on Scientific Affairs' report detailing the widespread problem of patients' medical illiteracy. More than 40% of patients did not comprehend an instruction to take a medication on an empty stomach. Common sense and professional medical studies tell us that patients cannot make informed treatment choices when medical terminology has not been broken down into simple terms, and when they are not briefed on the various treatment options.

Having seen the need for effective communication, the medical profession must emphasize effective doctor/patient communication skills. Medical schools that base admission on exam results, without an interview, perpetuate the notion that good communication has no value. Only a smattering of medical schools have adopted coursework focusing on communication skills. For those students where no institutionalised emphasis on communication skills is in place, much of the learning rests on instructor personalities.

With incredible technological advancements being made every day, and the practice of medicine becoming increasingly global, medical schools cannot simply throw up their hands and leave it to a student’s personality to determine whether they will learn how to effectively communicate. The need for strong communication skills is overwhelming, and we know that good communication strategies can be taught. Won’t the medical profession be better off if the line of communication between a doctor and a patient is crystal clear?

Physical Activity Levels in Irish School Children

Laurie Carrier, Lara Herbert, Hilary Allen, William McChesney, Catherine O'Connor, Anna O'Kane

Abstract

Objectives: This study aimed to assess the number of hours of physical activity engaged in by Irish school children per week, and compare them with the American Heart Association's recommendations. Both hours of physical activity per week and hours of television viewed per week were compared with sex, age and school location. Methods and Patients: Questionnaires were distributed to 9 co-educational schools (3 rural, 3 inner-city, 3 suburban). Irish school children (173 males and 116 females) between the ages of 10 and 12 years and 15 and 17 years participated. Results: Results showed that 81% percent of boys and 75% of girls met the criteria set by the American Heart Association regarding physical activity. Urban girls reported more physical activity than rural girls. Younger boys reported more physical activity than older boys while younger girls reported more physical activity than older girls. Finally, older girls also reported significantly less physical activity than older boys. The Irish school children surveyed watch an average of 15.5 hours of television per week. Boys attending urban schools reported watching less television than boys attending rural schools. Younger boys reported watching more television than older boys and suburban boys reported less television watching than boys in inner city schools. Conclusion: Older girls and rural school children appear to be particularly vulnerable to the development of sedentary rather than active lifestyles. This may provide two target groups for interventions to increase activity.

Introduction

Many modifiable risk factors for cardiovascular disease have been identified in childhood. These include physical inactivity, obesity and hypertension. Identifying children and adolescents at risk is the first step in modifying or preventing these risk factors. Encouraging increased physical activity is one way to assist young people in achieving a balance between energy intake and expenditure, and establishing healthy behaviour that will continue into adulthood. In addition to a positive contribution to weight control, physical activity helps young people to build and maintain healthy

bones and muscles, and contributes to psychological well being.[1] Public Health guidelines promote physical activity and steady-state aerobic exercise, which enhance cardiorespiratory

fitness and have an impact on body composition.[2] Body composition in childhood has been shown to have an impact on several aspects of adult health, including the risk of heart disease,

diabetes mellitus and hypertension.[3] Behavioural modifications, including increasing the amount of daily physical activity, have been shown to be beneficial in improving these cardiovascular

outcomes.[4] This is especially important since scientific reports and epidemiological studies have

shown that atherosclerosis begins in childhood.[5] Therefore, the earlier that preventative measures are initiated, the better the results that are achieved.

The American Heart Association (AHA) recommends that all children aged 5 years and older should participate in at least 30 minutes of enjoyable, moderate-intensity activities every day. They should also perform at least 30 minutes of vigorous physical activities at least 3-4 days each week to achieve a good level of cardiorespiratory fitness. They also suggest that children should increase their physical activity by reducing non-school sedentary time (e.g. watching television,

playing video games).[6]

This study aims to assess the hours of physical activity engaged in per week by a sample group of Irish school children, and to compare these with the recommendations of the AHA. Both the number of hours spent at physical activity and time spent watching television per week will be compared by sex, age and school location.

Materials and Methods

Questionnaires assessing the hours of physical activity per week as well as the hours spent engaging in non-physical activities (e.g. television watching, playing video and computer games, socialising with friends) were sent to nine co-educational schools. There were three schools in inner city Dublin, three schools in suburban Dublin and three rural schools. The questionnaires were distributed to children between the ages of 10 to 12 years old and also between the ages of 15 to 17 years old. There were 289 completed surveys returned (173 males and 116 females). The questionnaires were distributed to and collected from the children by their teachers. The children were encouraged to fill them in honestly and individually. The completed questionnaires were compared to assess how physical activity and the number of television hours per week

varied with age, sex and school location. The data was analysed using Microsoft Excel® and by performing unpaired T-tests.

Results

Analysis of the data revealed one clear trend. Boys report more hours of activity than girls, both in physical activity and television watching. This is independent of age and school location.

Activity Levels

Eighty-one percent of boys and 75% of girls met the criteria set by the AHA of at least 5 hours of exercise per week. There were several significant findings regarding activity levels. Urban girls engage in more physical activity than rural girls ($p<0.00003$) (Figure 1). Younger boys engage in more physical activity than older boys ($p<0.05$), while younger girls engage in more physical activity than older girls ($p<0.0001$). Finally, older girls also engage in significantly less physical activity than older boys ($p<0.0005$) (Figure 2).

Figure 1. Comparison of Activity Levels with Age in Irish School Children.

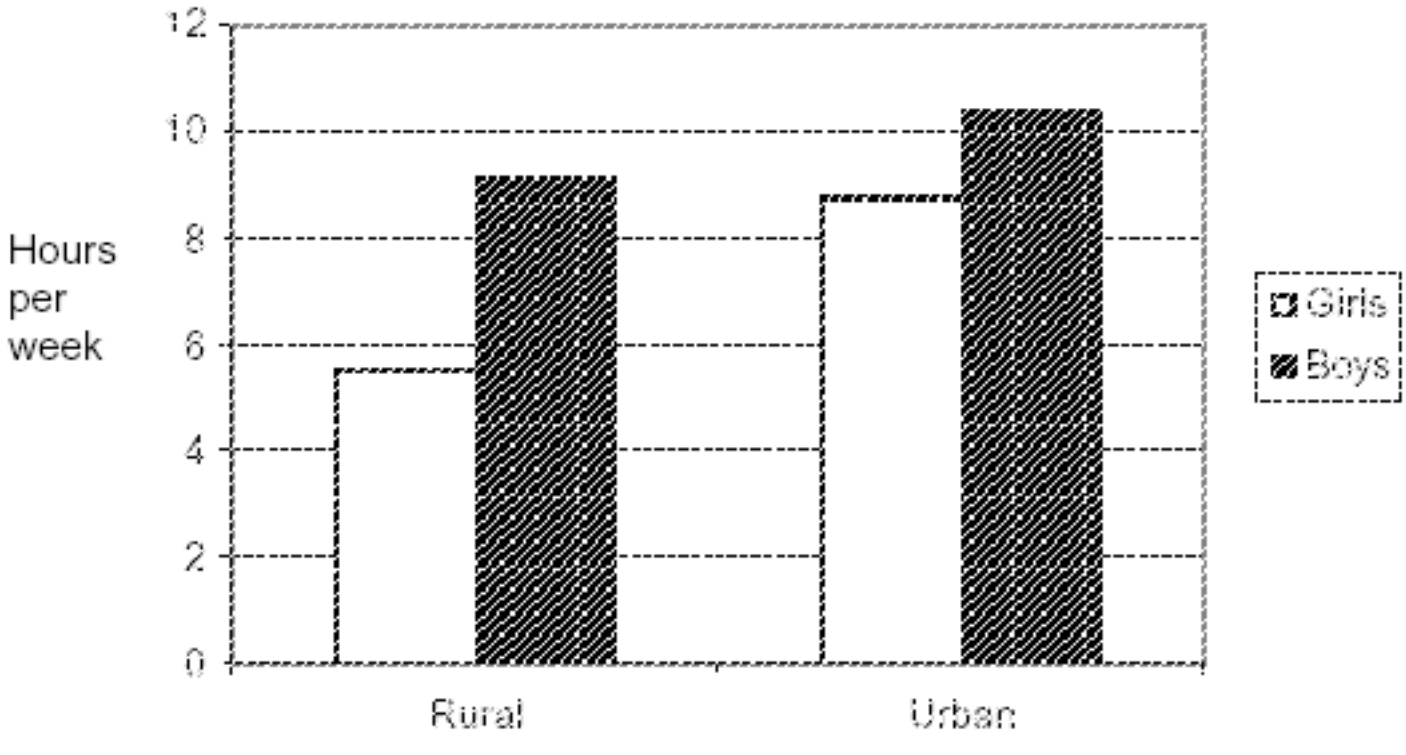
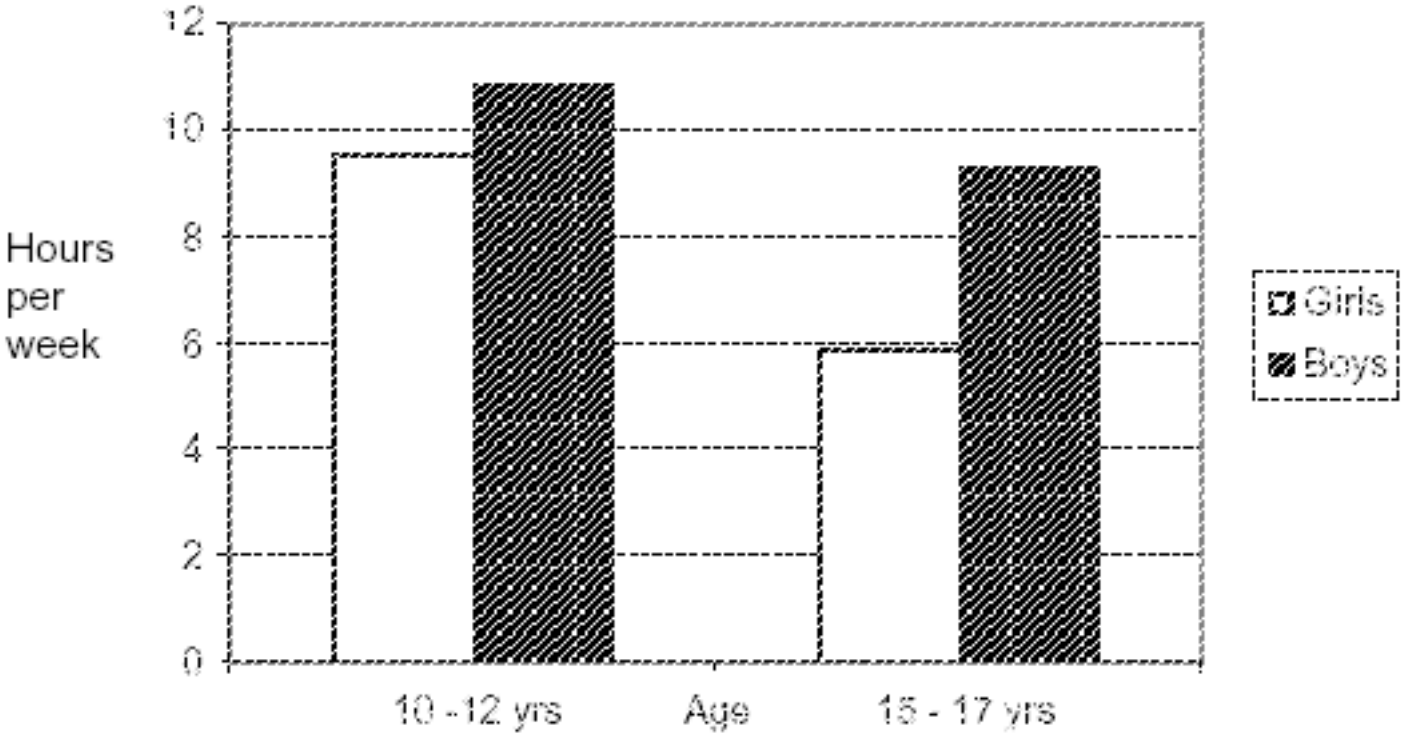


Figure 2. Comparison of Activity Levels with Age in Irish School Children



Television Watching

Hours spent watching television, playing video games and using computers were collated and analysed. Irish school children watch an average of 15.5 hours of television per week. It was reported that urban boys watch significantly less television than rural boys ($p<0.01$) (Figure 3). The younger boys watch more television than older boys ($p<0.03$), and suburban boys watch less television than inner city boys ($p<0.02$) (Figure 4).

Figure 3. Comparison of Television Hours between Rural vs. Urban School Children

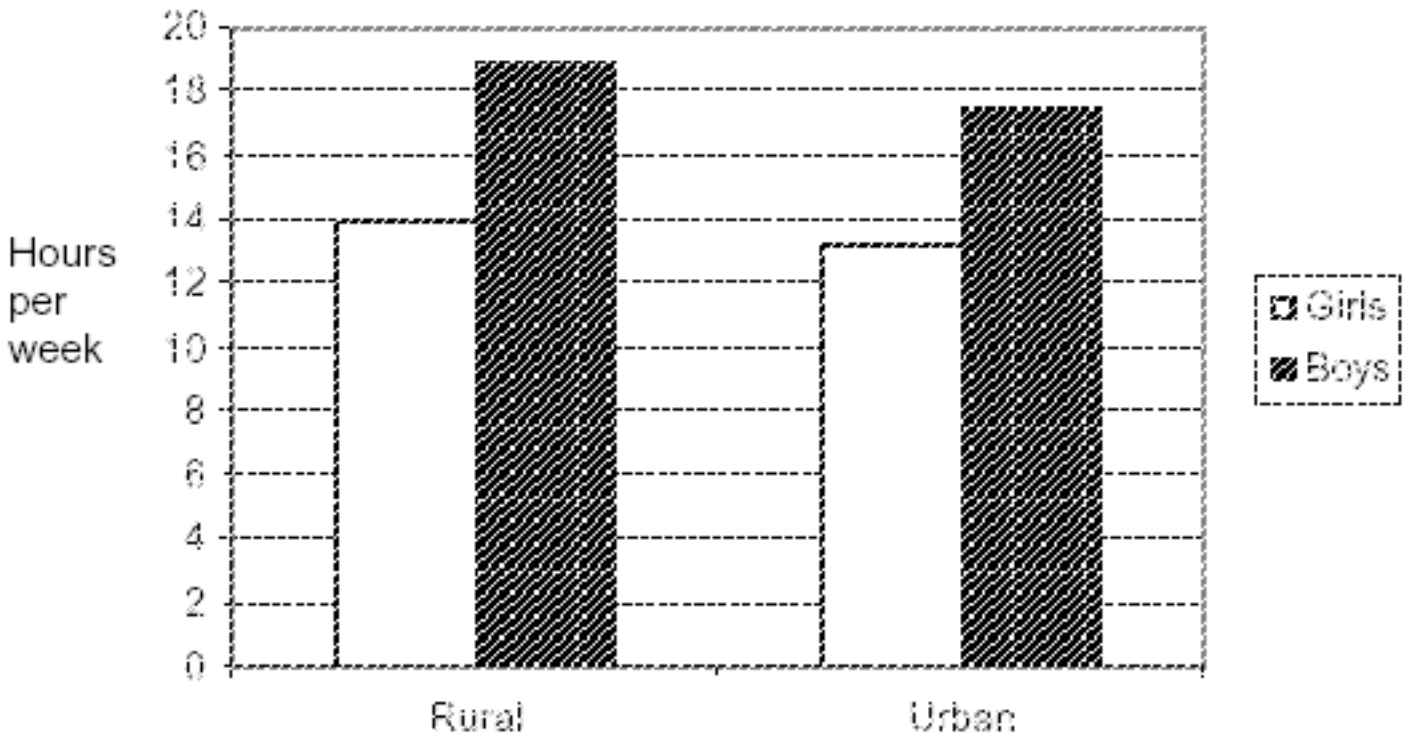
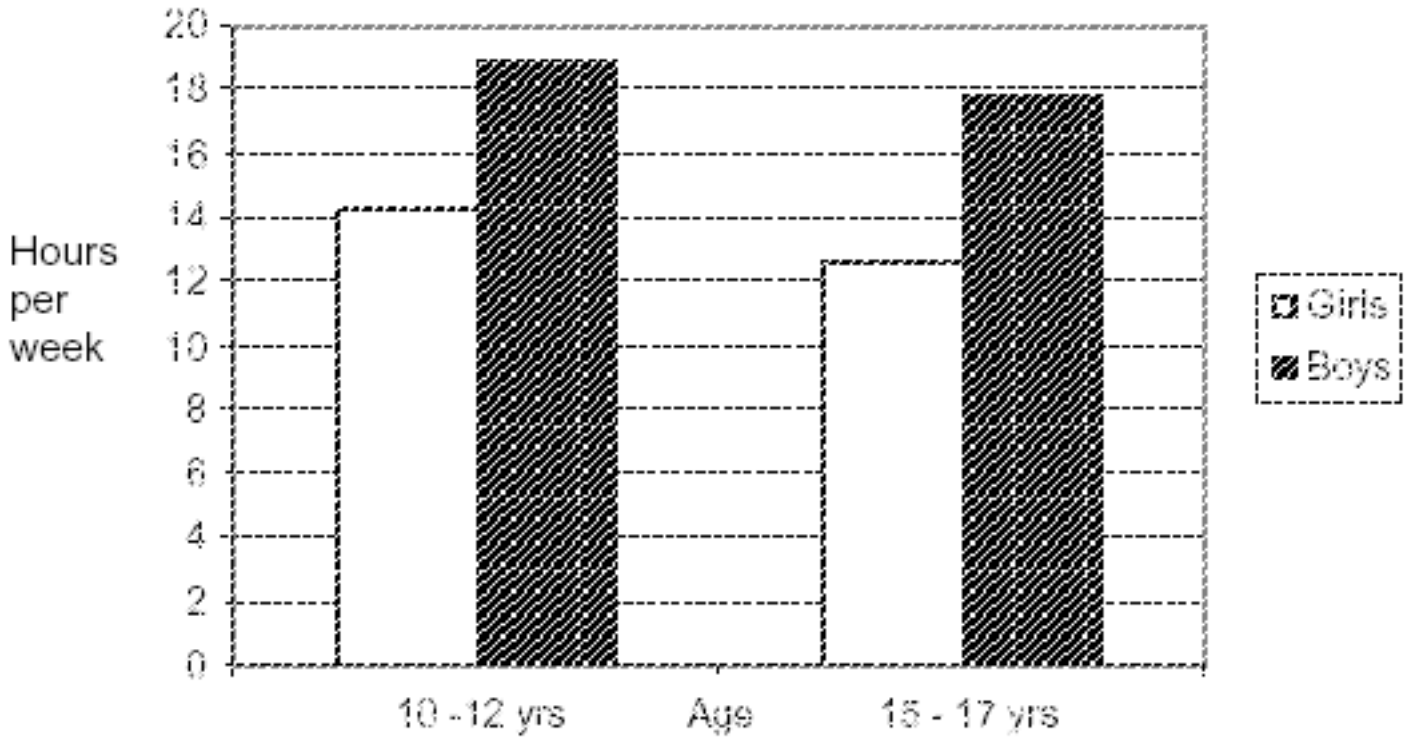


Figure 4. Comparison of Television Hours with Age in Irish School Children



Discussion

Our results target particular groups in which development of interventions to increase physical activity may be beneficial. We found that physical activity was more prevalent in urban than in rural areas. This is consistent with an analysis of the 2002 Behavioural Risk Factor Surveillance

System.[7] Possible reasons for our results may be that rural school children living on farms do not regard farm labour as exercise, or perhaps our results reflect a lack of recreational facilities in the rural areas surveyed.

Our results regarding gender and age differences are consistent with previous studies in several

respects.[8] One such consistency was that girls were less physically active and watched less television than boys. We cannot assume on this basis that physical activity is the direct converse of inactivity. There was also a decrease in physical activity with age, especially in females. Possible explanations for our findings include that boys tend to overestimate the number of hours spent at activity and in sedentary pursuits, and females are being modest. Self-esteem may interfere with opportunities for physical activity as girls age. Girls may be spending more time doing homework or sedentary school and social activities than boys.

Conclusion

Physical activity can make a major contribution to general health, energy and an overall sense of well-being. Although a large percentage of adolescents met the criteria of the AHA, the decline in physical activity with increasing age suggests that many young people are not maintaining exercise patterns that will predispose to healthy adulthood. Older females as well as rural school children are more vulnerable to developing sedentary rather than active lifestyles. While we should encourage all Irish school children to engage in physical activity, these particular groups should be primary targets in tailoring school and community interventions to promote an increase in activity among young people.

Acknowledgments

We would like to thank:

Dept. of Paediatrics, AMNCH Tallaght, Dublin

Patrician College Ballyfin, Co. Laois

The King's Hospital, Palmerstown, Dublin Kildare

Primary School, Rathmines, Dublin Scoil Mhuire,

Parnell Sq., Dublin 1

Colaiste Scoil Mhuire, Mountjoy Sq., Dublin 1

Abbeyleix National School, Co. Laois Camross

National School, Co. Laois

St. Theresa's Primary School, Dublin 1

St. Conleths College, Donnybrook, Dublin 4

REFERENCES

1. Troiano RP. Physical Inactivity among Young People. NEMJ 2002; 347(10): 706-707.

2. Winett RA, Carpinelli RN. Potential health-related benefits of resistance training. Prev Med 2001; 33(5):503-13.

3. Cambell K. Interventions for preventing obesity in children. The Cochrane Library 2002; Issue 1.

4. Graves KD, Miller PM. Behavioural medicine in the prevention and treatment of cardiovascular disease. Behav Modif 2003; 27(1): 3-25.

5. Strong JP, Malcom GT, et al. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. JAMA 1999; 281(8): 727-35.

6. American Heart Association® 2002.

7. Parks SE, Housemann RA et al. Differential correlates of physical activity in urban and rural adults of various socio-economic backgrounds in the United States. J Epidemiol Community Health 2003; 57(1): 29-35.

8. Kim SY, Glynn NW. Decline in physical activity in black girls and white girls during adolesence. NEMJ 2002; (347)10: 709-715.

Multiple Sclerosis: A Review of Disease Modifying Therapies

Sinead Doyle

INTRODUCTION

Multiple Sclerosis (MS) is an acquired primary demyelinating disease of the CNS, in which myelin is the target of an autoimmune inflammatory process. It is the commonest cause of non-traumatic, chronic neurological disability in young adults, with at least 50,000 cases in the UK and more than 1 million cases worldwide. The female to male ratio is 2:1 and the clinical manifestations usually appear between 20 and 40 years of age. The disease has a varied worldwide distribution, the prevalence being directly proportional to the distance from the equator. At latitudes of 50 to 60 degrees north, roughly from Southern England to Iceland, the prevalence is 50-120 per 100,000 people; at latitudes of less than 30 degrees north the prevalence is less than 10 per 100,000.

Multiple Sclerosis is rare at the equator.[1] Hence, it is clear that MS is place-related.

Epidemiological evidence has suggested that two factors are involved in causing MS: a genetically determined susceptibility and exposure to an environmental agent. Genetic studies have shown that there is not one single gene for MS. Instead multiple genes are thought to be

involved.[2] First degree relatives of a patient have an increased risk of developing MS, though there is no clear –cut pattern of inheritance. While there is a high degree of concordance of MS in identical twins, this never exceeds about 40 per cent, hence suggesting that non-genetic factors are also important. Prevalence studies for migrants from high to low risk areas, show that the age of adolescence is critical for risk retention: those migrating beyond the age of 15 are thought to retain the MS risk of their birthplace, whilst those migrating before the age of 15 acquire the lower

risk of their new homeland.[3] It has also been discovered that clustering of MS occurs in different countries throughout the world. Such clustering, in addition to the migrant data and the geographical distribution of MS, serve to define MS as an acquired, exogenous, environmental disease.

AETIOLOGY

It is widely assumed that the environmental agent that is responsible is infective, and is most likely to be of viral origin. Numerous viruses have been implicated, but the evidence has so far been inconclusive and only a minority of scientists believe that a single, unique virus is involved. It is not yet understood how the environmental agent and the predisposing genetic factors interact in order to establish disease.

CLINICAL COURSE AND SYMPTOMS

Multiple Sclerosis has two clinical hallmarks; the first is the temporal profile of symptoms and neurological deficits occurring in multiple episodes, designated as a relapse, followed by the disappearance of symptoms and/or the restoration of function, known as a remission. Disease progression may substitute or be associated with relapses and remissions, thus resulting in the different subtypes of disease. Such subtypes include relapsing-remitting (RR), relapsing progressive (RP), secondary progressive (SP), and primary progressive (PP). The second hallmark is the anatomical dissemination of lesions within the CNS. 70% of MS patients experience the prototypical relapsing-remitting pattern, and roughly 50% of these will have converted to a secondary progressive form of MS within 10 years. 15% of patients exhibit the

relapsing progressive pattern and 15% the primary progressive variety.[4] MS can also be classified according to clinical severity. Benign MS is defined as disease which allows patients to retain fully functional neurological systems 15yrs after its onset. Malignant MS is characterised by a rapid progressive course leading to significant neurological disability or death soon after the onset of disease. 20-40% of patients have benign MS. MS is generally not a fatal disease. The average

survival is 30 yrs from onset and 25 yrs from diagnosis.[5] The majority of deaths are due to complications that occur secondary to the MS, for e.g. pneumonia, pulmonary embolus and

aspiration.[6]

Multiple Sclerosis is a complex clinical disorder with highly variable signs and symptoms arising from CNS demyelination and the consequent disturbance of conduction in axons. Despite the fact that any part of the CNS can suffer from demyelination, the majority of patients usually have a limited number of initial symptoms (see Table 1). Negative signs or symptoms for e.g. loss of vision, loss of strength or sensation, are the usual presenting symptoms. At some stage throughout the disease-course, virtually all MS patients will have increased reflexes, spasticity, sensory loss and visual impairment. Bladder, bowel and sexual dysfunction are also common.

Table 1. Multiple Sclerosis: symptoms commonly found at presentation and throughout the course

of the disease.[7]

Deficit	At Presentation	Throughout course of disease
Visual/Occulomotor	49[a]	100
Paresis	43	88
Paraesthesias	41	87
Incoordination	23	82
Genito-urinary/Bowel	10	63
Cerebral	4	39

[a] Expressed as a percentage.
Note: some patients had >1 symptom hence the total is >100%

PATHOPHYSIOLOGY

The widespread belief, although yet unproved, is that MS is an organ-specific autoimmune disease, orchestrated by auto-reactive T Lymphocytes. It is thought that the auto-reactive cells are activated systemically, with their subsequent passage through the blood-brain-barrier. This ultimately leads to multi-focal areas of peri-vascular cuffing of lymphocytes and the destruction of myelin within the CNS. It is suspected that the T cell-mediated autoimmune mechanism, and the resulting demyelination, might be triggered by earlier viral infection and/or other factors in those that have a genetic predisposition to the development of MS. This concept of MS as being an autoimmune disease stemmed, in part, from studies which reported the occurrence of Experimental Allergic Encephalomyelitis (EAE) in animals that had been inoculated with neural

tissue and also from the discovery of an increased immunoglobulin level in patients with MS.[8]

DIAGNOSIS

The diagnosis of MS involves the identification of the dissemination of lesions in time and space. The former relates to the clinical history of the patient and the latter will only be evident after further investigations have been carried out. MRI of the brain and spinal cord, where available, is

the first line of investigation. Brain MRI demonstrates multi-focal white matter abnormalities in

greater than 95% of patients with clinically definite MS.[9] The typical findings are of multiple white matter lesions, principally in the peri-ventricular region, brainstem and cervical cord. With diagnostic Magnetic Resonance Images and a compatible clinical picture, examination of the CSF is often unnecessary. The CSF picture in MS is typified by a raised mononuclear cell count and the presence of oligoclonal IgG bands. Evoked potentials might also be assessed in the diagnosis of MS. Delay in the visual-evoked response (VER) follows optic neuropathy. Brainstem and somatosensory evoked potentials also become delayed when these pathways have been damaged.

TREATMENT OF ACUTE RELAPSE

The treatment of relapse encompasses those which might occur in patients with relapsing-remitting or secondary progressive disease. Corticosteroids are most commonly used for this indication. Several studies have demonstrated the superiority of steroids over placebo in shortening recovery from relapses. In one of the first controlled trials of ACTH for the treatment of relapses, there was found to be a significant improvement in 11 of 22 patients in the treated group

by the end of the 3-week trial period, compared to 4 of 18 in the control group.[10] A similar result

was reported from a subsequent study of 197 MS patients.[11] In the mid-1980s intravenous methylprednisolone (IVMP) was shown to be as effective as ACTH in the treatment of relapses and subsequently replaced ACTH for this indication. One trial that compared the efficacy of ACTH

and IVMP, reported no difference in outcome between the two treatment groups.[12] However, fewer adverse effects were observed with IV methylprednisolone. Despite a lack of evidence of its superiority, an intravenous, rather than an oral course of methylprednisolone is often prescribed for treating acute relapses in MS. In an attempt to discover if any such superiority exists, Barnes et al (1997) carried out a study of 80 patients, who received either IVMP (1g for 5 days) or oral

MP (48mg for 7 days, 24mg for 7 days or 12mg for 7 days).[13] None of the outcome measures exhibited any significant benefit of either regimen over the other at any time interval. Despite these significant findings, and the fact that oral MP is cheaper to prescribe and more convenient to administer, the majority of neurologists still use IVMP as the steroid of choice, the most common regimen used being 1g daily for 3 days or 0.5g daily for 5 days.

It has been suggested that steroids might also have a role in the treatment of chronic progressive MS. In 1998, the results from a Phase 2 dose comparison trial of cyclical pulses of IV methylprednisolone in secondary progressive MS, demonstrated a modest treatment effect in

favour of the high-dose treatment option.[14]

Hence, corticosteroids are effective in hastening recovery from clinical relapse. They do not, however, benefit eventual outcome, either in terms of degree of disability or subsequent disease activity.

DISEASE MODIFYING AGENTS

The management of MS not only involves the treatment of symptoms, acute relapses, and rehabilitation, but also aims to reduce the frequency and severity of such relapses and to prevent or postpone the onset of the progressive phase of the disease. Over the last decade, disease modifying drugs for MS have finally emerged, which are believed to be partially effective in altering the natural history of the disease. Such disease modifying therapies include interferon b (IFN-b), glatiramer acetate, immunoglobulins and azathioprine.

Currently, two forms of recombinant IFN- b, IFN-b-1a and IFN- b-1b have been approved by US and European regulatory authorities for the treatment of relapsing-remitting MS. IFN- b is the

most commonly used disease modifying agent in relapsing-remitting MS. IFN-b 1a (Avonex, Rebif), is a glycosylated, recombinant product from mammalian cells, which is identical to the human protein. IFN- b-1b (Betaferon, Betaseron), is a non-glycosylated recombinant product from bacterial cells, which differs from the human protein by one serine residue. IFN-b has a wide range of effects that are both immunomodulatory and antiviral. IFN- b-1b has been shown to reduce the annual exacerbation rate in relapsing-remitting MS, by approximately one-third

(p=0.001).[15] The same multicentre, randomized, double-blind, placebo-controlled trial of IFN-b-1b, also looked at the proportion of patients who were exacerbation free. During the 1st 2 years-16% in the placebo group, as opposed to 31% in the high-dose treated group (p=0.007). Also, the time to the first relapse was doubled (p=0.015) in the treatment group. This study also showed a

significant treatment-related difference in serial MRI activity.[16] Those in the placebo group showed a 17.1% increase in mean lesion area over 3 yrs Vs a 6.2% decrease in the high-dosage interferon group (p=0.002). A subgroup of 52 patients underwent serial MRI examinations every 6 wks for 2 years- a 75% reduction in the rate of new lesion formation was reported in the high-dose treatment group compared to placebo. The number of new lesions observed on the proton density scan is very important, because the number of lesions that are evident at the onset of clinical symptoms and the rate of formation of lesions at 5 yrs, will predict the clinical severity of MS at 5

and 10 year follow up.[17]

IFN-b-1b has also been shown to be effective in treating secondary progressive disease.[18] The results of a randomised, double- blind, placebo- controlled trial of IFN-b-1b for the treatment of secondary progressive MS were published in 1998. The study involved 718 patients, who were given either subcutaneous injections of 8 Miu IFN-b-1b every other day (n=360), or placebo
(n=358). The trial showed a highly significant difference in the time to confirmed progression of disability in favour of IFN-b-1b (p=0.0008).

IFN-b-1a has also been shown to have a positive treatment effect in relapsing-remitting MS. It has been shown to reduce exacerbation frequency, the accumulation of permanent physical disability and disease activity as estimated by gadolinium-enhanced lesions on brain Magnetic Resonance

Images. [19]

Hence, both IFN-b-1b and IFN-b-1a are believed to be effective disease modifying agents for the management of relapsing-remitting MS, whilst IFN-b-1b has also been proven to have an additional role in the treatment of secondary progressive disease. Side effects of the treatments are similar and include injection site reactions and flu-like symptoms or fever. Neutralising antibodies to IFN-b-1b are also detected in some patients. Patients would probably find IFN-b-1a to be a more attractive therapy than IFN-b-1b. INF-b-1a is administered by intramuscular (IM) injection once a week instead of by subcutaneous injection every other day. Also, painful injection-site reactions occur less frequently with IFN-b-1a, and there are also concerns regarding the possible loss of efficacy in those who form neutralising antibodies to IFN-b-1b.

Glatiramer Acetate (Copaxone, Copolymer 1), is another disease modifying agent that is used in the management of MS. It is a synthetic copolymer, whose structure is similar to that of myelin basic protein, one of the major constituents of myelin and the presumed autoantigen in MS. Work began to create such a copolymer after it was discovered that EAE (the animal model for MS), could be induced by immunisation using myelin basic protein. Hence, it was then theorised that a polypeptide similar in structure to myelin basic protein, might induce immune tolerance for myelin basic protein. The results of a pivotal Phase 3 multi-centre clinical trial of copolymer 1 in patients with relapsing-remitting MS, were reported in July 1995. In this trial 251 patients with ambulatory relapsing-remitting MS were randomly assigned 20mg of daily subcutaneous copolymer 1 or placebo for 2 years. The primary outcome measure was difference in MS relapse rate. The mean number of relapses was reduced 27% by glatiramer (1.19 +/- 0.13 glatiramer Vs 1.68 +/- 0.13 placebo, (p=0.007)). Significantly more patients receiving copolymer 1 were improved and more

receiving placebo worsened (p=0.037). Such change in performance were measured by a change of one step (>0.5 points) in the Kurtzke Expanded Disability Status Scale (EDSS). Glatiramer Acetate was found to be well tolerated, the most common adverse effect being an injection-site

reaction.[20] A self-limiting systemic reaction was observed in 15.2% of actively treated and 3.2% of placebo treated patients. Glatiramer Acetate is also believed to significantly reduce MRI-measured disease activity and burden, the effect on the rate of accumulation of gadolinium-

enhanced lesions being evident as early as 2 months following initiation of treatment.[21] Glatiramer Acetate has been found to be well tolerated an is thought to have less side effects compared to IFN-b. However, it must be administered daily by injection and hence might be more cumbersome than IFN-b-1b (subcutaneous injection every other day) or IFN-b-1a (weekly injection). It has also been suggested that because of the differences in the presumed mechanism of action of IFN-b and glatiramer acetate, the combination of them might well have additive effects. Although in-vitro data supports this, data developed in mice has suggested that a

combination of them is ineffective in blocking the induction of EAE.[22,23] The early MRI signature of glatiramer's effect on the disease process also differs substantially from that reported for the beta interferons. Hence, the data suggests that glatiramer acetate can be expected to reduce the relapse rate by 1/3 over the first 2 yrs and that the protection from relapses may steadily increase thereafter. Despite such data and the fact that the indications for the use of glatiramer acetate are comparable to those for IFN-b, most clinicians consider it a second line treatment for relapsing-remitting MS.

Azathioprine has been used in the treatment of MS since the 1960s, although the degree of clinical benefit has been difficult to establish. Azathioprine is a purine analogue, designed as a "pro-drug" of the cytotoxic agent 6-mercaptopurine (6-MP). Although it has many effects, the exact mechanism of its immunomodulatory effect is not known. Although glatiramer acetate and IFN-beta have convincingly shown to be effective in the long-term management of MS, they also have limitations, for e.g. their high cost, inconvenience (parenteral administration) and modest effect on disease course. Such limitations have prompted many experts to urge the reconsideration of the use of azathioprine and other immunosuppressants in the management of MS. The relative probability of remaining exacerbation-free for 3 yrs while taking azathioprine,

compared to placebo is 1.97.[24] This benefit from azathioprine compares favourably with the

reduction in exacerbation rate reported with IFN-b-1b in relapsing-remitting MS.[15] However, azathioprine is similar to IFN-b-1b, in that it offers only a modest degree of protection against the progression of disability. This benefit only becomes evident after 2-3 years. Although the results of the azathioprine trials are less robust than those of the newer agents, one advantage of its use is the long-term experience of azathioprine and hence the extensive knowledge of its side-effect profile. Even though toxicity with azathioprine is quite common, cessation of therapy is necessary in less than 10% of MS patients. The incidence of malignancy associated with treatment is uncommon and treatment is usually stopped as a result of drug-related fever, rash or gastrointestinal intolerance. The fact that azathioprine is cheap, readily available and effective in reducing relapses has helped to establish it as one of the most commonly used immunosuppressants in MS. At present, however, the evidence for its effectiveness is somewhat weak, though it may well be as good as the newer treatments. Such lack of evidence, coupled with the possibility of such severe side-effects and the lack of convincing data for immunosuppressants from MRI (as opposed to IFN-b and glatiramer acetate), has probably contributed to their rather modest acceptance. These days, azathioprine is usually only administered to patients with moderately aggressive disease, for whom the newer disease modifying agents cannot be prescribed.

To date, 3 prospective, randomised, double-blind, placebo-controlled studies have shown a beneficial effect of Intravenous Immunoglobulin (IVIG) on disease activity and accumulation of

deficits in patients with relapsing-remitting MS.[25,26] These results , though modest, are

comparable to those that have been reported for other treatments, such as IFN beta and

glatiramer acetate.[15,16,19,20] However, the amount of supportive evidence for IVIG still lags far behind that for IFN-b. Also, the mechanism of action of IVIG in the treatment of MS is largely unknown; they are thought to act most probably through immunomodulation, and perhaps even by promoting remyelination. IVIG generally has few side effects, transient rash or fatigue, headache and low-grade fever being the most common, all of which resolve within hours. A possible long-lasting side effect of IVIG therapy is severe eczema, which resolves after discontinuation of the therapy. A huge advantage of IVIG, is that it only needs to be administered once a month, in comparison to IFN-b (every other day or once a week) and glatiramer acetate (once a day). Local painful reactions at the injection site can become a problem with the usage of IFN-b and glatiramer acetate. In such cases, IVIG could be considered as a further treatment option. Despite the uncertainties surrounding its efficacy and mechanism of action, the scientific evidence that is available for the use of IVIG in relapsing-remitting MS appears to be consistent enough to allow it to be used in a number of settings (see Table 2).

Table 2. The use of IVIG in the treatment of patients with relapsing-remitting disease: points to be considered.

Concerns about its use	Factors supporting its use
1. Relatively unknown mechanism of action	1. Found to be well tolerated
2. Dose-response relationship unclear	2. Administered once a month
3. Proven Efficacy in small populations only	3. Very few contraindications to its use
4. No available MRI data parallel to larger clinical trials	
5. Not widely available and significant cost	

Mitoxantrone (Novantrone), is a cytotoxic anthracenedione that is thought to have both immunosuppressive and immunomodulatory activity. Because of such activity, mitoxantrone has been studied in animal models of MS, as well as in phase 2 and phase 3 clinical trials for the treatment of relapsing-remitting and secondary progressive MS. Mitoxantrone has been found to reduce the annual relapse rate ($p<0.001$), and to improve or stabilise relapsing-remitting and/or secondary progressive MS patients, as assessed by a number of clinical scores (EDSS,

Ambulation Index, and Standard Neurological Status).[27,28] Evidence has also been found that

mitoxantrone profoundly reduces the number of gadolinium-enhancing lesions on MRI.[29] Overall, mitoxantrone is thought to be well tolerated. Common side-effects include predictable and reversible leucopenia, mild alopecia, nausea and menstrual disorders. There is also a risk of mitoxantrone-related cardiotoxicity, which is characterised by a decrease in the left ventricular ejection fraction (LVEF), and congestive heart failure. The risk of cardiac damage increases as the total dose increases. Despite its positive clinical impact on MS patients, there is clearly an unknown potential for long-term toxicity, particularly cardiotoxicity. At the moment, it is mandatory to perform cardiac monitoring (ECG and ECHO) before, during and after stopping treatment. Hence, there are undoubtedly a lot of important questions to be answered before considering the use of mitoxantrone in preference to IFN beta or glatiramer acetate for the routine treatment of relapsing-remitting and secondary progressive MS.

CONCLUSION

Hence, there is clearly no shortage of novel compounds undergoing clinical trial for the treatment of MS. Treatment strategies currently under investigation include the induction of immune tolerance, the use of cytokines, anti-cytokines, anti-adhesion molecules and metalloproteinase inhibitors, the administration of monoclonal antibodies, agents promoting remyelination and even

bone marrow transplantation.[30]

The identification of effective technologies to treat MS has undoubtedly just begun. The introduction of IFN-b and glatiramer acetate as drugs effective in modifying the natural course of MS, has vastly improved the management of this highly debilitating disease. Such drugs have given immense hope to all those suffering from MS, and have provided the tools to further unravel the mechanisms of this condition. The development of such disease modifying agents has ensured that, although still incurable, Multiple Sclerosis is, at present, no longer untreatable.

REFERENCES

1. Raine CS, McFarland HF, Tourtellotte WW. Multiple Sclerosis: Clinical and Pathogenetic basis. Chapman and Hall.1997
2. Oksenberg JR, Hauser SL. New insights into the immunogenetics of multiple sclerosis. Curr Opin Neurol 1997; 10:181-185.
3. Alter M, Leibowitz U, and Speer J. Risk of multiple sclerosis related to age at immigration to Israel. Arch. Neurol 1996; 15:234-7
4. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: A geographically-based study 1. Clinical course and disability. Brain 1989; 112:133-46.
5. Bronnum-Hansen H, Koch-Henriksen N and Hyllested K. Survival of patients with multiple sclerosis in Denmark: a nationwide, long-term epidemiologic survey. Neurology 1994; 44:1901-7.
6. Sadovnick AD, Eisen K, Ebers GC, et al. Cause of death in patients attending multiple sclerosis clinics. Neurology 1991; 41:1193-6.
7. Poser S, Wikstrom J and Bauer HJ. Clinical data and the identification of special forms of multiple sclerosis in 1271 cases studied with a standardized documentation system. J. Neurol. Sci 1979; 40:159-68.
8. Rivers TM and Schwentker FF. Encephalomyelitis accompanied by myelin destruction experimentally produced in monkeys. J. Exp. Med 1935; 61: 689-702.
9. Ormerod IEC, Miller DH, McDonald WI, et al. The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a qualitative study. Brain 1987; 110:1579-616.
10. Miller H, Newell DJ, and Ridley A. Multiple Sclerosis: treatment of acute exacerbations with corticotrophin (ACTH). Lancet 1961; 2:1120-22.

11. Rose AS, Kuzma JW, Kurtzkes JF et al. Co-operative study in the evaluation of therapy in multiple sclerosis: ACTH versus placebo: final report. Neurology 1970; 20:1-59.
12. Thompson AJ, Kennard C, Swash M, et al. Relative efficacy of IV methylprednisolone and ACTH in the treatment of acute relapses in multiple sclerosis. Neurology 1989; 39:969-71.
13. Barnes D, Hughes RAC, Morris RW, et al. Randomised trial of oral and intravenous methyprednisolone in acute relapses of multiple sclerosis. Lancet 1997; 349:902-6.
14. Goodkin DE, Kinkel RP, Weinstock-Guttman B, et al. A phase 2 study of IV methylprednisolone in secondary progressive multiple sclerosis. Neurology 1998; 51:239-45.
15. IFN beta Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis, 1. Clinical results of a multi-centre, randomised, double-blind, placebo-controlled trial. Neurology 1993; 43:655-61.
16. Paty DW, Li DKB, UBC MS/MRI Study Group and the IFN beta multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. MRI analysis results of a multi-centre, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43:662-7.
17. O'Riordan JI, Thompson AJ, Kingsley DPE et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain 1998; 121:495-503.

18. European Study Group on Interferon beta-1b in secondary progressive MS: placebo-controlled, multi-centre, randomised trial of interferon beta-1b in the treatment of secondary progressive multiple sclerosis. Lancet 1998; 352:1491-7.
19. Jacobs LD, Cookfair, DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing-remitting multiple sclerosis. Ann. Neurol. 1996; 39:285-94.
20. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer-1 reduces relapse rate and improves disability in relapsing-remitting MS: results of a phase 3 multi-centre, double-blind, placebo-controlled trial. Neurology 1995; 45:1268-76.
21. Comi G, Filippi M, Wolinsky JS. European/Canadian glatiramer acetate study group: multi-centre, double-blind, randomised, placebo-controlled study of the effects of glatiramer acetate on MRI-measured activity and burden in patients with relapsing-remitting multiple sclerosis. Ann. Neurol. 2001; 49:290-7.
22. Milo R, Panitch H. Additive effects of copolymer-1 and interferon beta-1b on the immune response to myelin basic protein. J. Neuroimmunol 1995; 61(2):185-93.
23. Brod SA, Lindsey JW and Wolinsky JS. Combined therapy with glatiramer acetate and a type 1 interferon (IFN alpha) does not improve experimental allergic encephalomyelitis. Ann. Neurol 2000; 47:127-31.
24. Yudkin PL, Ellison GW, Ghezzi A, et al. Overview of azathioprine treatment in multiple sclerosis. Lancet 1991; 338:1051-1055.
25. Fazekas F, Deisenhammer F, Strasser-Fuchs S, et al. Treatment effects of monthly intravenous immunoglobulin on patients with relapsing-remitting multiple sclerosis: further analysis of the Austrian Immunoglobulin in MS study. Multiple Sclerosis 1997; 3:37-42.
26. Edan G, Miller D, Clanet M, et al. Therapeutic effect of mitoxantrone combined with methyprednisolone in multiple sclerosis: a randomised, multi-centre study of active disease using MRI and clinical criteria. J. Neurol, Neurosurg, Psychiatr 1997; 62:112-18.
27. Millefiorini F, Gasperini C, Pozzilli C, et al. Randomised, placebo-controlled trial of mitoxantrone in relapsing-remitting MS: 24 month clinical and MRI outcome. J. Neurol 1997; 244:153-9.
28. Hartung HP, Gonsette RE and the MIMS study group. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, randomised, observer-blind European phase 3 multi-centre study. Clinical data. Multiple Sclerosis 1998; 4:325.
29. Sorensen PS, Wanscher B, Jensen CV, et al. IV immunoglobulin G reduces MRI activity in relapsing-remitting MS. Neurology 1998; 50:1273-81.
30. Hohlfeld R. Biotechnological agents for the immunotherapy of multiple sclerosis. Principles, problems and perspectives. Brain 1997; 120: 865-916.

Resistance of Microbial Cells to Antimicrobial Agents by Efflux

Jennifer Hogan

INTRODUCTION

Efflux mechanisms provide microbes with a means of reducing the antibiotic concentration at the target site. As the topic of antimicrobial resistance is expanding in many directions, this review is divided into sections. Efficacy of antimicrobials depends on their ability to reach their target. Factors that influence the accumulation of drugs within the microbial cell can have a big effect on antimicrobial resistance. Efflux mechanisms in microbes have become a huge problem for scientists and clinicians as many of our antimicrobials are becoming useless as a result of these resistance systems.

Many microbes have both intrinsic and acquired resistance to antimicrobials because of their efflux pumps. Acquired resistance comes from the acquisition of plasmids from other microbes or through mutations

whereas intrinsic resistance occurs independently of these.[1] Acquired efflux pumps called multi-drug resistant (mdr) pumps have been found in bacteria. These are very worrying as the genes for these often encode

resistance to a variety of drugs, biocides and other chemicals.[2] They have been found on plasmids (as well as some bacteria having them intrinsically) and these have led to widespread transfer of the mdr phenotype

between bacteria.[3] A number of studies have demonstrated that resistance to almost any antibiotic can be achieved through the activity of these mdr pumps.[4] Acquired resistance highlights that the bacteria can pass these resistance mechanisms from one to another very rapidly.[3,5] Alternative treatments to antimicrobials will have to be evaluated if we are to continue curing people of serious microbial infections.

Intrinsic resistance implies that the efflux pumps have another function in the cell and that the pumps

coincidentally cause the efflux of antimicrobials.[6] The efflux systems have been found in all bacteria, and because of this, it is thought that they may have a "housekeeping role" within the cell.[1,7] Bacteria often encounter substances that are toxic to them. Many of these may be lipophilic and able to penetrate the cell relatively easily. Therefore, in order to survive, the microbe must eliminate these toxic substances. Having a pump that can eject the substance would be a very efficient way for the bacteria to survive.[8]

In studying the efflux pumps of Escherichia coli and Neisseria gonorrhoeae, two systems have been found (the AcrAB system of Escherichia coli and the MtrCDE system of Neisseria gonorrhoeae) that have the natural function of excreting toxic substances from the cell as well as the proposed acquired function of the efflux of antimicrobials. The Escherichia coli AcrAB system pumps various bile acids out of the bacterium. These transporters have been seen to be dispensable in some instances, but this may be because most microbes

have multiple efflux systems each with overlapping functions.[1] Other efflux systems may be able to compensate for the loss of another.

INTRODUCING THE EFFLUX PUMPS

There are 5 classes of efflux pumps: Major Facilitator Superfamily (MFS), ATP-Binding Cassette transporter family (ABC), Resistance-Nodulation-Division family (RND), Small Multidrug Resistance family (SMR), and

Multi-Drug and Toxic Compound family (MATE).[7,9]

Figure 1. The proton-driven drug pumps in Gram-negative bacteria

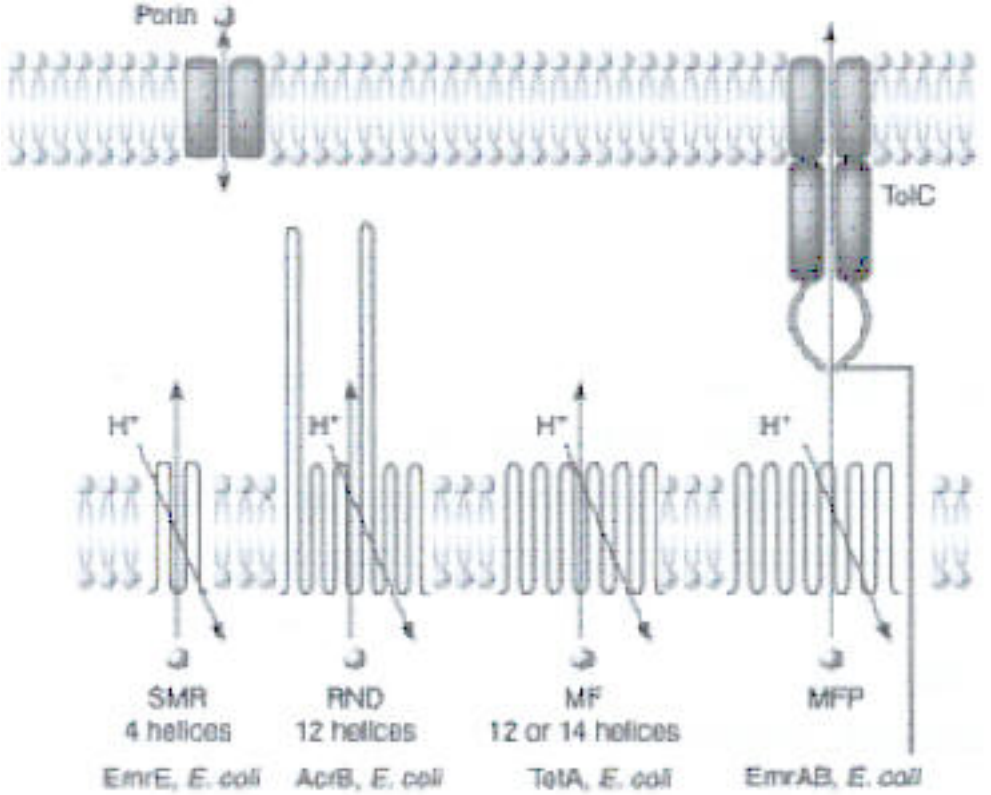


Figure taken from Borges-Walmsley et al.[9]

Most function as drug/proton antiporters although the ABC class uses ATP (adenosine triphosphate) to drive the removal of cationic and lipophilic antimicrobials.[9,10,15] At the moment, no direct knowledge is available about the mechanism of coupling drug transport with the inward transport of protons or with ATP hydrolysis.[11]

The RND family is the most relevant with respect to antimicrobial resistance, so this is the type that will be focused on to illustrate the mechanism of efflux in microbes. RND transporters have been found in all major kingdoms but only have a role in resistance in gram negative bacteria. The RND transporters work with a periplasmic Membrane Fusion Protein (MFP) and an Outer Membrane Factor (OMF) to cause efflux across both the inner and outer membranes (no accumulation occurs in the periplasm).[9,12,13] These transporters are usually chromosomally encoded and they are involved in multidrug resistance, heavy metal ion export, transport of oligosaccharides and extrusion of hydrophobic solvents. It is thought that the RND component of this transporter system is the part that confers substrate specificity, but the cause of this specificity is still unknown.[14,15] RND transporters have a wider range of substrates compared to SMRs or MFSs and RND transporters can expel drugs that are targeted to both the cytoplasm and the periplasm.[11] Studies of the transporter suggest that the only requirement for the drug to be a substrate of these efflux pumps is the presence of a hydrophobic domain capable of insertion into the phospholipid bilayer but they don not tell us how the pump discriminates between its substrates and natural components of the cell membrane. From studies on the BmrR transporter of Bacillus subtilis, it is thought that the hydrophobicity, shape and size of the molecules are important in binding to the transporter.[7,13]

Membrane fusion proteins also form part of this transporter system. Two hydrophobic domains have been identified near the N- and C- termini of the MFPs which are proposed to interact with the inner and outer membrane components of the complex and to transfer the substrate across the periplasm. The MFP's probably function in the tri-partite complex by preventing substrate release into the periplasm. There are two general models of MFP action. Either oligomerisation with the OM component occurs to form a closed channel through the periplasm or the MFP brings the inner and outer membranes together in close apposition.[2,9,13] There is more support for this latter model, as the AcrA protein which is a MFP was shown to promote the close association of the two membranes and to possibly promote a hemi fusion event under conditions similar to those found in the periplasmic space. MFP's seem to be very specific for their own transport efflux systems as even highly homologous MFP's such as MexA and MexC (periplasmic components from Pseudomonas aeruginosa) cannot be interchanged in the tripartite complex.[8,13] This suggests the presence of specific interactions between the MFP and the inner membrane transporter.

In contrast, the formation of the tripartite complex and more specifically the involvement of the outer membrane component, appears to be transient and to be formed only in the presence of the protein substrate. The MFP component is thought to have a role in recruiting the outer membrane component although it is not known how the specificities of the bi- and tripartite complexes are determined.[1]

The outer membrane components are interchangeable between different multidrug efflux systems and a single OMF can function with different pumps.[12] The most widely studied OMF is TolC. It is a porin like protein.[9] It is essential for the activity of the drug transporter AcrB in prokaryotes and protein transporters HlyB and CvaB in eukaryotes.[3] This protein can also work with McaD and MexY from Pseudomonas aeruginosa if these components are expressed in Escherichia Coli.[13] This demonstrates the diversity of this protein.

RND transporter systems are not always tripartite. In some cases, all three components of the efflux pump are coded for in the same gene cluster, e.g. MexAB-OprM from Pseudomonas aeruginosa and MtrCDE from Neisseria gonorrhoeae.[14] Some pumps, however, lack the gene for the outer membrane component in the gene cluster, e.g. MexXY from Pseudomonas aeruginosa and AcrAB from Escherichia coli. There is evidence that AcrAB recruits TolC as the outer membrane component and MexXY appears to share the outer membrane component with MexAB because both of these systems require the presence of a functional OprM channel.[3,14]

SYNERGISTICALLY WORKING WITH THE OUTER MEMBRANE?

The efflux pumps work with exceptional efficiency in gram-negative bacteria. This is thought to be due in part to their synergistic action with the outer membrane. In gram-positive bacteria, the efflux pumps move the substrate across just one membrane. This is rather inefficient, as they have to compete with the rapid spontaneous influx of the lipophilic inhibitor molecule back into the cytoplasm. A high rate of efflux is therefore required to produce significant levels of resistance. The efflux pumps in the gram-negative bacteria traverse both the inner and outer membranes. As the outer membrane is composed largely of LPS, it has different permeability properties to the membrane of gram-positive bacteria. It does allow the penetration of lipophilic molecules but at a rate 50-100 times slower than the phospholipid bilayer.[11,13] The decrease in penetration of lipophilic molecules is responsible for the intrinsic resistance of gram negatives to certain antibiotics (e.g. glycopeptides). Hydrophilic molecules enter the gram-negative cells through porins in the membrane but in the presence of antibiotics or when efflux mechanisms are induced, a decrease in the number of porins in the membrane is also seen. This leads to decreased penetration of the hydrophilic molecules.

The synergistic action between the pumps and the outer membrane is seen in mdr or multiple antibiotic resistant (mar) mutants in Escherichia coli where a simultaneous decrease in porin production and an increase in efflux activity is observed.1 This synergy explains how gram-negative bacteria become hypersusceptible to antimicrobials with the inactivation of the efflux pumps or with permeabilisation of the outer membrane.[13]

The outer membrane itself does not provide resistance to antibiotics as it only has decreased permeability. It is dependent on the other resistance mechanisms such as efflux but these mechanisms have enhanced effectiveness in the presence of the outer membrane. The synergy between the efflux pumps and the outer membrane probably explains the variable effectiveness of related multidrug efflux systems in providing resistance in organisms with differences in intrinsic outer membrane permeability properties.[1,16]

ARE BIOCIDES CONTRIBUTING TO RESISTANCE?

Antibiotics are used predominantly for the treatment of bacterial infections in humans and animals, whereas biocides are employed for their antiseptic, disinfectant and/or preservative properties (Table 1).[17] Efflux pumps can remove therapeutic levels of antibiotics and low but probably not "in use" concentrations of biocides.[18,19] Many mdr systems can also accommodate biocides such that these strains are both antibiotic and biocide resistant·[20] There is a conflict over whether the biocides are contributing to the increasing resistance to antibiotics by activating or increasing the activity of the efflux pumps.[1,21]

Table 1. Biocides to which bacterial resistance may be a problem (taken from A.D. Russell.)[17]

Biocide group	Example(s)	Bacterial resistance
QACs	Cetrimide, Benzalkonium chloride, cetylpyridinium chloride	*Ps. aeruginosa, Proteus* spp., *Providencia* spp., *Staph. aureus* (containing *qac* genes)
Bisbiguanides	Chlorhexidine	
Diamidines	Propamidine, dibromopropamidine	*Staph. aureus* (containing *qac* genes)
Bisphenol (phenylether)	Triclosan	*E. coli* (?), *Staph. aureus* (?), *Ps. aeruginosa*, *Myco. tuberculosis* (?)
Acridines	Acriflavine, proflavine	*Staph. aureus* (containing *qac* genes)

Antibiotics rely on selective toxicity and usually only have one target in a cell whereas a biocide may have many targets. Therefore, resistance development to biocides is highly unlikely because of the multiple targets that the active agent has. However, there has been speculation that the use of a sub-lethal concentration of biocides against microbes might lead to the selection of bacteria that have better efflux or resistance

mechanisms.[22]

Cationic agents (quaternary ammonium compounds, chlorhexidine) and triclosan have been implicated as

possible causes for the selection and persistence of bacterial strains with low level antibiotic resistance.[17,18] It has also been claimed that the emergence of qacA and qacB determinants in clinical isolates of

Staphylococcus aureus mirrors the introduction and usage of cationic biocides.[7,17] If biocides and antibiotics are both pumped out by the same efflux system, then resistance to the antibiotic might develop because of upregulation due to the presence of the biocide. Recent evidence has emerged that sub-lethal concentrations of the antibacterial and antifungal agent triclosan can select for resistant mutants in Escherichia coli. It has been suggested that the triclosan may select for mutants in a target that is shared by diazoborine compounds

and the anti-tuberculosis drug, isoniazid.[17,22]

Sub-lethal treatment with chemical antimicrobial agents has also been shown to induce the expression of multidrug efflux pumps and efflux mutants. The increased or changed efflux pattern does not protect the microbe against "in-use" concentrations of biocides, but is sufficient to confer protection against therapeutic doses of many antibiotics. It has been speculated, therefore, that biocide misuse may have an insidious effect and that it may be contributing to the evolution and persistence of drug resistance within microbial

communities.[22]

The mar operon in Escherichia coli and homologues in other bacteria have been seen to be involved in both

biocide and antibiotic resistance.[17] Mutations in MarR (which regulates expression of MarA) protein of the mar operon upregulates AcrAB and TolC to produce resistance to antibiotics, organic solvents, pine oils, bile salts, antiseptics and disinfectants such as triclosan, quaternary ammonium compounds and chlorhexine (Figure

2).[4,22] The subsequent overexpression in MarA was seen to activate multidrug efflux pumps which were able

to cause the efflux of pine oil as well as antibiotics such as the tetracyclines.[4] Overexpression of the MarA protein gave a 3-4 fold increase in resistance to triclosan (an increase of the same magnitude as that seen for antibiotics). Other evidence reported that Escherichia coli mutants selected for resistance to pine oil overexpressed the marA gene and showed low level resistance to ampicillin, tetracycline, chloramphenicol and nalidixic acid. However, tetracycline-selected mar mutants, which also overexpressed marA (and also showed resistance to pine oil), had much higher resistance to the antibiotics than the pine oil mutants. This would suggest that exposure to antibiotics in this instance was much more important for causing antibiotic resistance than exposure to a biocide. Although some of the evidence suggests that exposure to triclosan may be leading to increased antibiotic resistance, this has not yet been proven in a clinical setting. Likewise, the finding that exposure to triclosar of a triclosan-sensitive Pseudomonas aeruginosa mutant switched on an efflux pump and rendered the cells highly resistant to ciprofloxacin has not as yet been translated to a clinical

situation. [4,17]

Figure 2. Efflux mechanism of Escherichia Coli causing resistance to multiple compounds.

The Mar A protein causes activation of the AcrAB/TolC complex which causes the efflux of many compounds.

Figure taken from S.B. Levy. [4]

There is some evidence that the introduction of biocides into clinical practice might have had an impact on antibiotic resistance. Probably far more significant, however, is the selective pressure exerted by the antibiotics themselves in the treatment of human and animal infections as a result of their incorporation into

animal feedstuff.[19] The issues over biocides and increased resistance is far from being resolved. Also often neglected is that hyper-expressed mutants of efflux pumps are resistant to antibiotics in laboratory cultures, but they pump out key metabolites and therefore, may be relatively non-competitive in mixed microbial communities. This would especially be the case when the antimicrobial selection pressure is removed or

transient.[22]

OVERCOMING THE EFFLUX PUMP RESISTANCE MECHANISMS

As resistance is developing rapidly to antibiotics, biocides and other compounds, there is a need to overcome this resistance in order to effectively combat serious infections. Some approaches are being developed, although most of the research is still in the early stages. Failure encountered with antibiotics designed specifically to resist inactivating enzymes (e.g. beta-lactamases) has shown that chemical improvements are likely to be overcome very quickly by bacteria. Specific and potent inhibitors of antibiotic transporters appear to be the therapeutic approach of most promise. Ligand-based approaches have been tried, but as the transporters displayed non-specificity, this has not successful. There has been some success with target-based approaches. With this method there is more flexibility, as effective inhibitors do not necessarily have to

be directed against the binding site of the natural substrate.[19,23] The first inhibitors of the broadly specific multi-drug efflux system of Pseudomonas aeruginosa (an RND transporter system) have recently been reported and they are effective at both overcoming existing resistance to a certain of antibiotics (i.e. the fluoroquinolones) and also at preventing the emergence of the resistance in the first place. These inhibitors are also likely to be effective at compromising intrinsic and acquired biocide resistance in this organism as

well as antibiotic and biocide resistance in organisms expressing homologous multi-drug efflux systems.[20]

Inhibitors of the NorA multi-drug transporter of Staphylococcus aureus have also been reported and they are effective at enhancing fluoroquinolone susceptibility and preventing the emergence of fluoroquinolone

resistance.[7,24,25] Examples of NorA inhibitors are reserpine and omeprazole (These drugs are already used clinically for the treatment of hypertension and peptic ulcer disease. They inhibit pumps at their site of action in humans). These drugs lack antimicrobial action but are thought to potentiate the antimicrobials. It is thought that these inhibitors may slow down the development of resistance or prolong the life of current quinolones

like the beta-lactam inhibitors did for the beta-lactam antimicrobials. [20,25]

One problem, however, with inhibitors of efflux pumps is that these pumps could be proteins with important physiological functions; use of these inhibitors might have toxic effects in the host. Therefore, inhibitors against antibiotic extruding pumps operating only in prokaryotes may offer significantly greater chances at

therapeutic success.[23] The other interesting group of drugs being studied for potential anti-efflux activity are

the SSRI's (selective serotonin re-uptake inhibitors used in the treatment of depression).[26] They also act as

efflux inhibitors in man and have been shown to help overcome resistance in some bacteria.[25] Little is known on their mode of action in the microbes. They may be acting as efflux inhibitors, which would explain their synergy with tetracyclines and fluoroquinolones in Clostridium urealyticum. However, they also appear to have some anti-microbial activity themselves and may be acting on basic metabolic processes in the microbe. Their

target has not yet been identified.[26] Prudent use of antimicrobials (especially those that leave residue) should also be employed in order to try to curb resistance and preserve the efficacy of these compounds for when

they are needed in life threatening situations.[4,5,19]

CONCLUSION

The purpose of this review was to examine the impact of efflux mechanisms on antimicrobial resistance in

microbial cells. Efflux pumps contributing to resistance in microbes are widespread and are creating major problems with regard to the efficacy of antimicrobials. Efflux pumps are rapidly becoming a very important mechanism of resistance both alone and with the synergistic action of the outer membrane. New drugs targeted at these pumps specifically could have a huge impact in combating antimicrobial resistance. Great care would have to be taken in trying to develop inhibitors that are selective for the microbes as humans have many similar pumps with very important functions in the body. Efforts at inhibiting these pumps are still at the early stages of research, however. Efforts are also being made to try to improve our current practices to prevent further resistance from emerging. This review has potentially outlined one of the ways in which resistance to antimicrobials is increasing. This is through the increasing use of biocides. More prudent and safe use of biocides is required if current resistance figures are to be improved. In the future, new drugs will need to be developed to inhibit the pumps and better usage practices with regard to current antimicrobials will need to be adopted in order for the current antimicrobials to continue to be therapeutically relevant.

REFERENCES

1. Poole K. Multidrug resistance in Gram-negative bacteria. Curr Opin Microbiol 2001; 4(5):500-8.
2. Roberts M. Tetracycline resistance determinants: mechanisms of action, regulation of expression, genetic mobility, and distribution. FEMS Microbiology Reviews 1996; 19:1-24.
3. George A. Multidrug resistance in enteric and other Gram-negative bacteria. FEMS Microbiology Letters 1996; 139:1-10.
4. Levy, SB. Active efflux, a common mechanism for biocide and antibiotic resistance. Journal of Applied Microbiology Symposium Supplement 2002; 92:65- 71.
5. Hosein IK, Hill DW, Jenkins LE. Clinical significance of the emergence of bacterial resistance in the hospital environment. J Appl Microbiol 2002; 92:90-97.
6. Silver S. Bacterial resistances to toxic metal ions- a review. Gene 1996; 179:9-19.
7. Markham PN, Neyfakh AA. Efflux-mediated drug resistance in Gram-positive bacteria. Current Opinion in Microbiology 2002; 4:509-514.
8. Desnottes JF. New targets and strategies for the development of antibacterial agents. TIBTECH 1996; 14:134-140.
9. McKeegan KS, Borges-Walmsley MI, Walmsley AR. The structure and function of drug pumps. Trends in Microbiology 2001; 9(2):71-79.
10. White TC, Marr KA, Bowden RA. Clinical, cellular, and molecular factors that contribute to antifungal drug resistance. Clinical Microbiology Reviews 1998; 382-402.
11. Nikaido H. Multiple antibiotic resistance and efflux. Current Opinion in Microbiology 1998; 1:516-523.
12. Murata T, Gotoh N, Nishino T. Characterization of outer membrane proteins OpmE, OpmD and OpmB of Pseudomonas aeruginosa: molecular cloning and development of specific antisera. FEMS Microbiology Letters 2002; 217(1):57-63.
13. Zgurskaya HI, Nikaido H. Multidrug resistance mechanisms: drug efflux across two membranes. Molecular Microbiology 2000; 37(2):219-225.
14. Sharff A, Fanutti C, Shi J, et al. The role of the TolC family in protein transport and multidrug efflux. European Journal of Biochemistry 2001; 268:5011-5026.
15. Murata T, Kuwagaki M, Shin T, et al. The substrate specificity of tripartite efflux systems of Pseudomonas aeruginosa is determined by the RND component. Biochemical and Biophysical Research Communications 2002; 299(2):567-572.
16. Hancock REW. The bacterial outer membrane as a drug barrier. Trends in Microbiology 1997; 5(1):37-42.
17. Russell AD. Introduction of biocides into clinical practice and the impact on antibiotic-resistant bacteria. Journal of Applied Microbiology Symposium Supplement 2002; 92:121-135.
18. Russell AD. Antibiotic and biocide resistance in bacteria: Introduction. Journal of Applied Microbiology Symposium Supplement 2002; 92;1-3.
19. Russell AD. Antibiotic and biocide resistance in bacteria: comments and conclusions. Journal of Applied Microbiology Symposium Supplement 2002; 92:171-173.
20. Poole K. Mechanisms of bacterial biocide and antibiotic resistance. Journal of Applied Microbiology Symposium Supplement 2002; 92:55-64
21. Denyer SP. Cellular impermeability and uptake of biocides and antibiotics in Gram-negative bacteria. Journal of Applied Microbiology Symposium Supplement 2002; 92:35-45.
22. Gilbert P, Allison DG, McBain AJ. Biofilms in vitro and in vivo: do singular mechanisms imply cross-resistance? Journal of Applied Microbiology Symposium Supplement 2002; 92:98-110.
23. Bambeke FV. Antibiotic Efflux Pumps. Biochemical Pharmacology 2000; 60:457-470.
24. Pechere JC. Macrolide resistance mechanisms in Gram-positive cocci. International Journal of Antimicrobial Agents 2001; 18:25-28.
25. Schmitz FJ, Higgins PG, Mayer S. Activity of Quinolones Against Gram-Positive Cocci: Mechanisms of Drug Action and Bacterial Resistance. European Journal of Clinical Microbiology and Infectious Diseases 2002; 21:647-659.
26. Munoz-Bellido JL, Munoz-Criado S, Garcia-Rodriguez JA. Antimicrobial activity of psychotropic drugs Selective serotonin re-uptake inhibitors. International Journal of Antimicrobial Agents 2000; 14:177-180.

The Complications of Jejunostomies in the Post-Operative Period

Tamalina Banerjee

ABSTRACT

Objectives: To determine the type and frequency of complications relating to jejunostomy feeding tubes following oesophagectomy for oesophageal malignancy. Methods: A retrospective analysis of 25 patients who had undergone oesophagectomy. Physicians' notes, nursing and nutrition notes were analysed and any complication relating to the jejunostomy tube was recorded. Results: Of the 25 patients reviewed, 14 (56%) had mild complications associated with the jejunostomy tube. Three (12%) experienced diarrhoea, 3 (12%) had abdominal distention, 3 (12%) bloating, 3 (12%) cramping, 1 (4%) constipation, 1 (4%) reflux. In 13 patients, all of the symptoms were mild and resolved in one to two days with treatment. One patient who developed diarrhoea died of sepsis before an outcome could be determined. Conclusion: The complications relating the jejunostomy feeding were minor, short-lived and easily treatable. These minor complications are acceptable considering the nutritional advantages that jejunostomy tubes offer patients post-operatively.

INTRODUCTION

Post-operative nutritional support of patients undergoing major surgery has been shown to have a major positive impact on subsequent recovery.[1] Enteral nutrition has been shown to be superior to parenteral nutrition in this respect by a number of studies.[2] This direct form of feeding maintains functional capacities of the intestine, including digestion and absorption of nutrients, hormone and enzyme production and maintenance of peristaltic movements.[3] It avoids the use of a central venous catheter that can lead to sepsis and pleuropulmonary accidents. It can be administered for lengthy time periods and the patient can easily adapt to enteral nutrition at home.[4] Placement of a jejunostomy tube for the purpose of enteral feeding is a surgical procedure that involves the insertion of a catheter into the lumen of the proximal jejunum. In the post-operative period however, enteral feeding by jejunostomy tube can lead to a number of complications. This study aimed to analyse the type and proportion of complications in patients who received jejunostomies while undergoing surgery for oesophageal malignancy.

METHODS

The study was a retrospective chart analysis of patients who had received jejunostomy tubes during first, second, or third-stage oesophagectomy for oesophageal carcinoma. The list of patients was obtained from a chart database. The charts were subsequently removed from the oesophageal library and reviewed. The charts were then analysed to determine the type and frequency of jejunostomy related complications, specific interventions and outcome.

Surgical Technique: The technique used in all patients for jejunostomy placement during oesophagectomy has been described in other literature.[5] In brief, a catheter is passed through the anterior abdominal wall into the lumen of the jejunum via an intramural tunnel. The tube is advanced to a distal position in order to prevent reflux. A purse-string suture is used to secure the catheter entry site. Any excess catheter is removed from the peritoneal cavity until the jejunum lies adjacent to the parietal peritoneum. The jejunum is then secured in place with a few

interrupted sutures.

Protocol for Enteral Nutrition: The feed was started on the first post-operative day in all patients. The rate of delivery commenced at 30 ml/hr and the rate was gradually increased every eight hours until the desired rate was reached. For a 70 kg person, the target volume was 100 ml/hr (2 litres over 20 hours). Development of GI symptoms occasionally necessitated the slowing or even cessation of the feed for a short period of time, which was then generally recommenced once symptoms had resolved.

RESULTS

Table 1. Complications of Jejunostomy

Complications	n=25	%
Diarrhoea	3	12
Nausea	3	12
Abdominal Distension	3	12
Abdominal Cramping	3	12
Constipation	1	4
Reflux	1	4

Twenty-five patients (22 men) of median age 58.5 (range 40-76) were studied. All patients underwent oesophagectomy for malignancy, one patient undergoing a one-stage procedure, 14 a two-stage and the remaining 10 patients a three-stage oesophagectomy. Minor GI complications arose in 12 of the 25 patients, with some patients having more than one complication (Table 1).

In all cases, duration of symptoms was short-lived and usually resolved within 24-48 hours of initiation of appropriate treatment. Nausea was treated by administration of prochlorperazine and constipation was treated with prune juice via the jejunostomy tube.

Three patients in this series developed diarrhoea (e"4 bowel motions/day) and were initially treated with loperamide. In two patients, the feeding rate was slowed from 100 mls/hr until the diarrhoea subsided. In one patient, the jejunostomy feed was stopped several times over a period of two days due to recurrent episodes. In this instance, the feeding was recommenced at normal rate once the diarrhoea had resolved. Two patients in the series experienced loose bowel motions. However, the frequency did not exceed two episodes per day and therefore they were not included as having experienced this complication. In these instances, the symptoms resolved within a day by slowing the feed rate by 20 mls/hr.

Six patients experienced abdominal distention and cramping, and in all cases the symptoms resolved within several days. Intervention consisted of either slowing the feed rate or stopping the feed temporarily. In all but one case the feed was then recommenced at the normal rate once the symptoms subsided. In these patients, recommencement was well-tolerated. One patient who had cessation of feed due to abdominal distention did not have the feed recommenced, as she died the following day as a result of overwhelming sepsis. The origin of the sepsis could not be determined.

One patient experienced some difficulty with reflux necessitating cessation of his feed. However, the feed was then recommenced approximately eight hours later and the patient experienced no further difficulties.

DISCUSSION

Enteral feeding via jejunostomy tube is considered standard practice in most hospitals for patients undergoing surgery for oesophageal malignancy. Patients with oesophageal malignancy are often malnourished and denied oral intake for one to two weeks post-operatively. Enteral feeding aims to maintain nourishment post-operatively and prevent prolonged complications that may result from lack of nutrition. It has been demonstrated in animal studies that lack of nutrients in the gut

leads to decreased mucosal integrity, bacterial translocation and sepsis.[6] Immunogenicity, hormone production and the ability to regain full absorptive capacity are also compromised by

lack of direct nutritional support.[7]

Enteral feeding is not without complications and there is considerable debate over the frequency and severity of complications that jejunostomy tubes can produce. The most severe complications include major mechanical problems, e.g. intraperitoneal leakage and catheter

occlusion.[8] Abscess formation and bowel necrosis have also occurred.[9] By far the most common complications are GI complications, e.g. diarrhoea, abdominal distention, and bloating. A large prospective study (n=500) published in the British Journal of Surgery reported the

incidence of diarrhoea as 15%, abdominal distention 5% and cramping 3%.[10] A study of catheter feeding jejunostomy in patients after major abdominal trauma concluded that 83% of the study group had one or more GI complaints compared to 50% of a control group who had GI complaints

despite not being given enteral feeding.[11]

In this retrospective chart review, 56% of patients had GI complaints which all resolved within two to three days with appropriate action. Gastrointestinal complaints are extremely common after oesophageal surgery. It is difficult to conclude from a retrospective study which GI complaints were due to the enteral feeding and which were due to the effects of the surgery. In any case, this chart review demonstrated that out of 25 patients, none had complications requiring jejunostomy replacement or removal.

CONCLUSION

In summary, jejunostomy tubes are an effective and safe way of delivering nutrition post-operatively. They produce GI complications which are generally mild and resolve quickly with non-invasive treatment. Considering the benefits of enteral feeding via jejunostomy tube, it can be concluded that the complications observed are minor and acceptable.

REFERENCES

1. Zarazaga MA. Peri-operative Nutrition. Nutr Hosp 1999; 14:1115-1195.
2. Aiko S, Yoshizumi Y, Sugiura Y et al. Beneficial effects of immediate enteral nutrition after oesophageal cancer surgery. Surg Today 2001; 31:971-978.
3. Alverdy J, Chi, HS, Sheldon GF. The effect of parenteral nutrition on gastrointestinal immunity: the importance of enteral stimulation. Ann Surg 1985; 202:681.
4. Tapia J, Murguia R, Garcia G et al. Jejunostomy: Techniques, indications, and omplications. World J Surg 1999; 23:596-602.
5. Mansell NJ. Use of a feeding jejunostomy after oesophogastric surgery. Br J Surg 1995; 82:811-813.
6. Rennie MJ. Consensus workshop on enteral feeding of ICU patients. How important is the role of glutamine? Br J Int Care 1993; 3:438-47.
7. Langkamp-Henken B, Glezer JA, Kudsk KA. Immunologic structure and function of the gastrointestinal tract. Nutr Clin Pract 1992; 7:100.

8. Sonawane RN, Thombare MM, Kumar A. Technical complications of feeding jejunostomy: a critical analysis. Trop Gastroenterol 1997; 18:127-8.
9. Eddy VA, Snell JE, Morris JA Jr. Analysis of complications and long-term outcome of trauma patients with needle catheter jejunostomy. Am Surg 1996; 62:40-44.
10. Sarr, M.G. Appropriate use, complications and advantages demonstrated in 500 consecutive needle catheter jejunostomies. Br J Surg 1999; 86:557-561.
11. Jones TN, Moore FA, Moore EE, et al. Gastrointestinal symptoms attributed to jejunostomy feeding after major abdominal trauma-a critical analysis. Crit Care Med 1989; 17:1146-50.

An Investigation into the Suitability of Ordering D-dimers for Patients with Suspected DVT in the A&E at Waterford Hospital

Oliver Tobin

ABSTRACT

Objective: The objectives of this study were to assess the suitability of ordering D-dimer assays and to investigate the need for a validated risk assessment model in the evaluation of patients with a clinical suspicion of deep venous thrombosis in patients attending the Accident and Emergency unit of Waterford Regional Hospital. Methods and Patients: Admission cards of 106 consecutive patients ,for whom D-dimer assays were ordered, were evaluated according to the Wells Criteria to determine whether the patients had a high, medium or low probability risk of having a deep venous thrombosis. (DVT) This information was correlated with initial clinical impression, presenting complaint, the result of the D-dimer test and the results of ultrasonography, if performed. Results: There were 30 positive D-dimer results returned from the 106 analysed. Of those, 19 (63.3%) had a Wells score suggesting low probability of DVT, 10 (33.3%) had a medium probability, and 1 (3%) had a high probability of DVT. For the remaining 76 negative D-dimer results, 59 (77.6%) had a low probability Wells score, 14 (18.4%) were in the medium probability group and 3 (3.9%) were in the high probability group. This study proposes that the introduction of a clinically validated model for the diagnosis of DVT/pulmonary embolism (PE) would rationalise the ordering of D-dimers and make the diagnosis of DVT/PE more evidenced based.

INTRODUCTION

D-dimer assays were developed to measure the degradation product of cross-linked fibrin. They have been primarily used to diagnose Deep Vein Thrombosis (DVT) and resultant thrombotic Pulmonary Embolism (PE). They do this by measuring the increase in specific plasma degradation products of fibrin, which is elevated due to the action of plasmin and other endogenous thrombolytic agents. Many different assays have been evaluated for their accuracy

and utility in diagnosing DVT.[1] A D-dimer result of less than 0.2ug/ml is taken to have a negative predictive value for the test. In general, an isolated positive D-dimer (greater than 0.2ug/ml) result is not useful because the test lacks specificity. D-dimer levels are elevated not only in the setting of acute thrombosis, but also in other conditions such as pregnancy, infection and malignancy. In contrast, a negative result using a sensitive D-dimer test is useful for excluding acute DVT. In an overview, Bounameaux et al. (1997) quote an overall sensitivity for D-dimer assays of 82%, with 95% confidence intervals of 77-87%. Unfortunately, commercially available D-dimer assays vary in their sensitivity and specificity and, therefore, the performance of one assay cannot be

extrapolated to another.[2] Currently, the most reliable and extensively evaluated tests are two rapid enzyme-linked immunosorbent assays (ELISAs; Instant-IA D-dimer) and a rapid whole blood assay (SimpliRED D-dimer). The sensitivity of the rapid ELISAs is over 95% and that of the

SimpliRED D-dimer assay is approximately 85%.[3] Currently the ELISA method is the one used in Waterford Regional Hospital.

The incidence of DVT is 5 per 10,000 per annum.[4] The incidence is much lower in the young and higher in the elderly. Although many patients develop DVT in the presence of risk factors, such as malignancy and immobility, DVT can also occur without obvious provocation (idiopathic DVT). Some of the patients with idiopathic DVT have an inherited or acquired thrombophilia, whereas

the remainder have no identifiable biochemical or genetic abnormality.

Making a diagnosis of DVT requires both clinical assessment and objective testing because the clinical features are non-specific and investigations can be either falsely positive or negative. The initial step in the diagnostic process is to stratify patients into high, intermediate or low-risk categories using a validated clinical model. When the clinical probability is intermediate or high and the venous ultrasound result is positive, acute symptomatic DVT is confirmed. Similarly, when the probability is low and the ultrasound result is normal, DVT is ruled out. A low clinical probability combined with a negative D-dimer result can also be used to rule out DVT, thereby obviating the need for ultrasonography. In contrast, when the clinical assessment is discordant with the results of objective testing, serial venous ultrasonography or venography is required to confirm or refute a diagnosis of DVT. Outpatients with classical findings of DVT and at least one risk factor have an 85% probability of having DVT, whereas those with atypical features and no

identifiable risk factors have only about a 5% probability of having thrombosis.[5]

Several clinical models can be found in the literature for the accurate diagnosis of DVT/PE. The important thing is to find one that is accurate and easy to implement in the clinical setting in which it is being used. One such algorithm is presented here for illustrative purposes. The algorithm presented in Figure 1 is used for the diagnosis of DVT. It is important to stress, however, that further research would need to be undertaken to find the most suitable one for Waterford Regional Hospital.

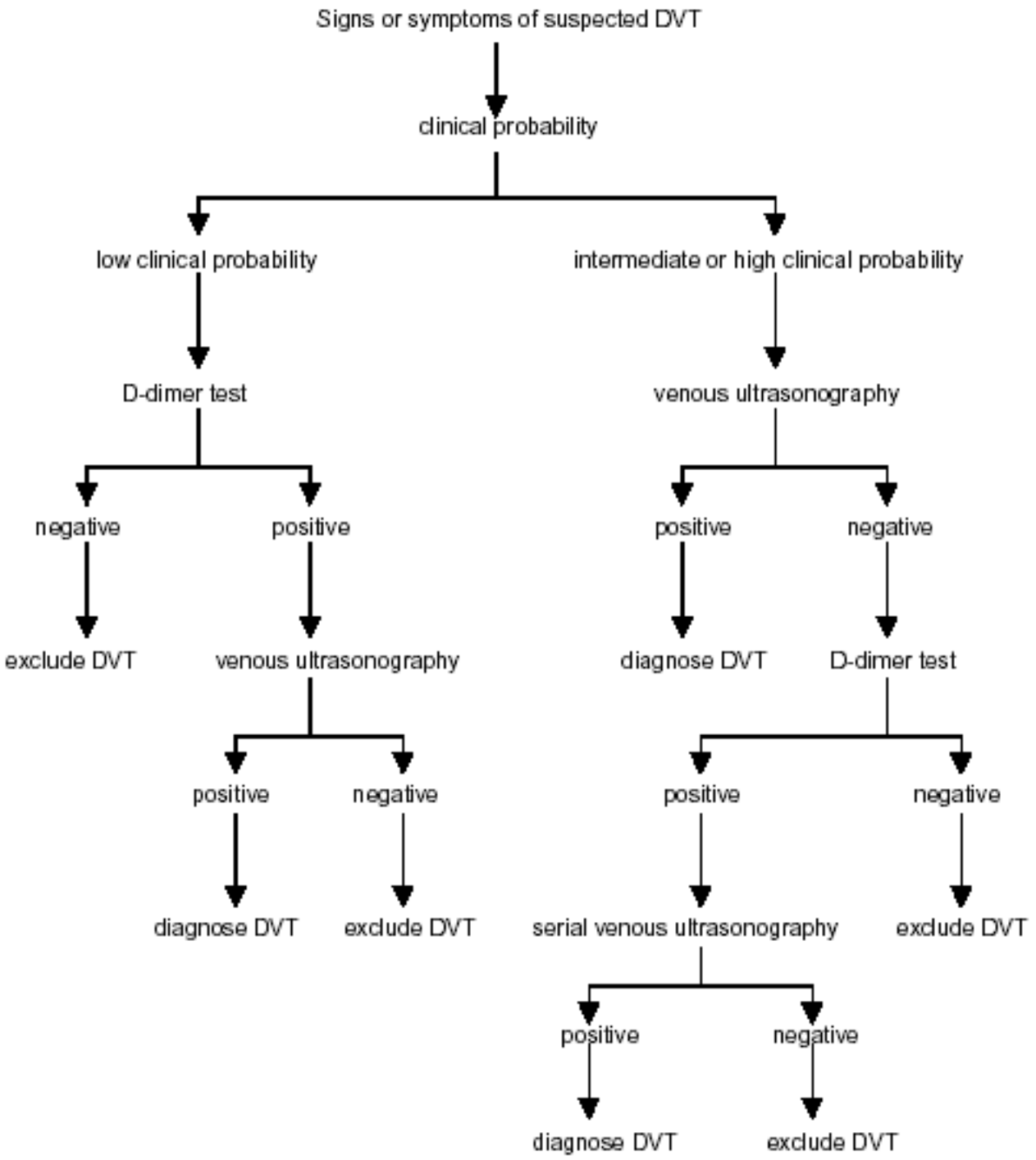
Clinical models exist also for diagnosing PE exclusively. An example is that proposed by Egermayer et. al. (1988) using respiratory rate, arterial oxygen tension and a D-dimer assay produced by the SimpliRED method. With this method a correct diagnosis is made in 95.9% of

cases.[7]

At present, a standardised, validated clinical model does not exist in Waterford Regional Hospital for the classification of risk in patients with a suspected DVT/PE or the ordering of related tests. The aims of this study were to research the ordering of D-dimer assays in Waterford Regional Hospital and to investigate the need for such a model.

Figure 1. Algorithm for diagnosing DVT using clinical assessment, venous ultrasonography, and

D-dimer testing.[6]



METHOD

Over a one month period, 111 A&E admission cards, which contained D-dimer assay orders, were assessed. The Wells criteria were applied to determine whether the patients had a high, medium

or low probability of having a DVT.[5] This was to assess the objective clinical probability of these patients having a DVT/PE. This information was correlated against initial clinical impression, presenting complaint, the result of the D-dimer test and the results of ultrasonography, if performed.

The risk factors for DVT determined by Wells et al. (2001) in the clinical evaluation of DVT are presented in Table 1. Each risk factor constitutes a score of one, and an alternative diagnosis on clinical grounds gives a score of two.5 The total score is achieved by adding these together and allows for risk stratification. Patients with a score of zero are at low risk, those with a score of one or two are at intermediate risk, and those with a score of three or greater are at high risk of having a DVT.

Table 1. Clinical model for predicting pre-test probability for DVT.[5]

Symptom	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden > 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of DVT	2

RESULTS

Of the 111 admission cards from the A&E department, 5 were excluded, as the cards were illegible. Thus there were 106 patients in this patient cohort. The presenting complaints and clinical impressions given for these patients are displayed in Table 2. Patients with an initial clinical impression other than DVT or PE were those in whom a diagnosis of neither DVT nor PE was explicitly stated on their admission card. Patients with an unspecified clinical impression were those patients who did not have a clinical diagnosis explicitly stated on their admission card.

Wells scores were calculated for all the patients in this study. According to this score system, 78 (73.5%) of the patients studied had a low probability of having a DVT (Wells Score = 0), 24 (22.6%) had a medium probability of having a DVT (Wells Score =1 or 2) and 4 (3.7%) patients had a high probability of having a DVT (Wells Score e"3).

There were 30 positive D-dimer results returned from the 106 analysed. Of those, 19 (63.3%) had a Wells score suggesting low probability of DVT, 10 (33.3%) had a medium probability, and 1 (3%) had a high probability of DVT. For the remaining 76 negative results, 59 (77.6%) had a low probability Wells score, 14 (18.4%) were in the medium probability group and 3 (3.9%) were in the high probability group.

According to Figure 2, 27% of the patient group were in the medium to high risk group of having a DVT/PE. According to the algorithm proposed by Hirsh et al. (2002), this group of patients should have had venous ultrasonography performed in the first instance. The 73% of patients in the low risk group are the patients who would most benefit from D-dimer assays in the study.[6]

Information regarding the patients with a primary diagnosis of DVT/PE on clinical grounds is presented in Table 3. Of these patients only one was admitted. The eventual outcome of one other patient is unknown. All others were discharged from A&E. Venous ultrasonography of the lower limbs was performed in four of these patients. The author was unable to establish why this was the case, although it may be because clinicians do not see D-dimers as a useful test in this situation, despite having ordered them. None of these patients had a final diagnosis of DVT/PE.

Figure 2. Wells Score Rick vs. Total D-dimers ordered.

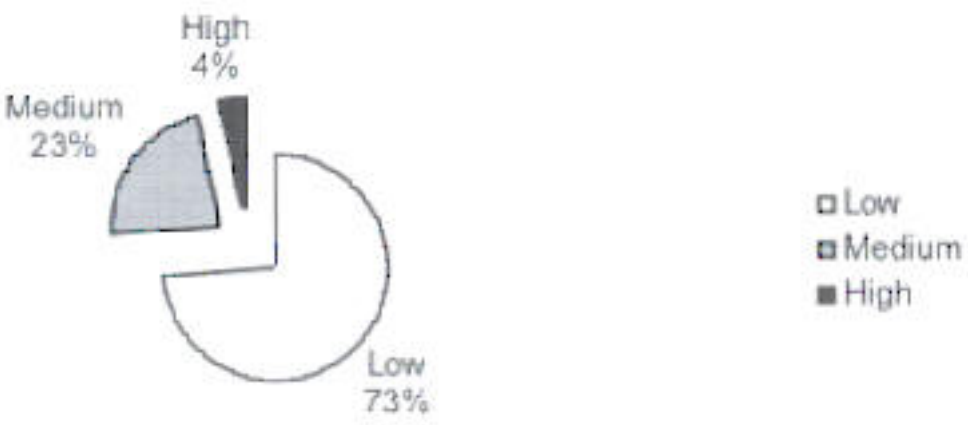


Table 2.Patients' presenting complaints and clinical impressions.

Presenting Complaint	Total Number of Patients	Patients with an Initially Indicated Clinical Impression Other than DVT/PE	Patients with an Initially Indicated Impression of DVT/PE	Unspecified Clinical Impression
Abdominal pain	18	11	0	7
Chest Pain/SOB	51	30	1	20
Leg pain	11	4	6	1
Musculoskeletal pain	3	2	0	1
Other	4	4	0	0
Paralysis/Weakness	11	4	0	7
Collapse	3	2	0	1
Haemorrhage	5	1	0	4
Total	106	58	7	41

Table 3. Patients suspected of having DVT/PE

D-dimer result	Risk (from Wells Score)	Admitted to Hospital	Doppler Performed	Presenting Complaint
<0.2 (negative)	Low	No		Chest pain/ dyspnoea
<0.2 (negative)	Intermediate	No		Leg pain
<0.2 (negative)	Intermediate	No	Negative	Leg pain
<0.2 (negative)	Intermediate	NO		Leg pain
<0.2 (negative)	Intermediate	Unknown	Negative	Leg pain
0.52 (positive)	High	Yes	Negative	Leg pain
<0.2 (negative)	High	No	Negative	Leg pain

DISCUSSION

This study was undertaken to assess the suitability of ordering D-dimer assays and to investigate the need for a validated risk assessment model in the evaluation of patients with a clinical suspicion of DVT in patients attending the A&E unit of Waterford Regional Hospital.

Of the 106 D-dimer tests ordered in this study, only 6.6% of them were done for patients with a primary suspicion of DVT/PE (Table 1). The presenting complaint and clinical impression varied widely in this cohort as can be seen in Figure 3 and Figure 4. While the majority of tests were ordered for patients with a presenting complaint of either chest pain or dyspnoea, over half of these patients were suspected to have a condition other than DVT/PE (Table 2). The high testing rates for chest pain and a clinical impression of cardiac pathology suggests that D-dimer testing is being used as a "safety net" to exclude pulmonary embolism in patients with symptoms of cardiac pathology. The very low rate of venous ultrasonography would back this up. Of the 7 patients in whom DVT/PE was suspected, 6 of them were in intermediate or high probability groups. These

six presented with leg pain, while the remaining patient with low probability presented with chest pain. This was perhaps the sole patient who presented with chest pain who would have benefited from the D-dimer assay, as he presented with low probability of having a DVT and therefore a negative D-dimer assay result would put his risk of having a DVT/PE in the next 3 months at less

than 2%.[8]

As can be seen in Figure 2, 73% of all D-dimers ordered were for patients with a low probability of DVT/PE. Only 4% of those ordered were done so for patients with a high probability of DVT/PE. If D-dimers are to be used as a primary test for the exclusion of PE, they should be correlated with

arterial oxygen tension less than 80mmHg or respiration rate greater than 20.[6] However, only 3 patients in the study group presented with a respiration rate of over 20 breaths per minute and arterial oxygen tension was not recorded.

According to the Wells score, 6.6% of the patients in the study were suspected of having a DVT/PE as their primary pathology, and 4% were in the high probability category. Ultrasonography is indicated for those patients with a high clinical probability, therefore only 2.6%of the patients in the study would have benefited from D-dimer assays for a primary suspicion of DVT/PE.

An explicit initial clinical impression of DVT/PE was only expressed in seven of the patients in the study group. However, 28 of the patients were in the medium to high risk groups as calculated by the Wells score (Table 1). This illustrates that DVT/PE is a very difficult diagnosis to make. The introduction of the clinical model would standardise the diagnostic process, which ultimately would lead to increased diagnosis of DVT/PE. If the clinical model proposed by Hirsh et al. (2002) had been used in the A&E department of Waterford Regional Hospital for the duration of the study, the number of D-dimers ordered would have been reduced by 27%. The trade off is that, if the model proposed earlier (Figure 1) were used, the 28 patients in the medium and high risk groups would have had venous ultrasonography performed which is a more expensive test.

The ordering of D-dimers in patients presenting to A&E in this study seems to be poorly selective. It is not influencing further testing procedures and presumably patient outcomes. The implementation of a validated clinical model would standardise the ordering procedure and lead to greater confidence in the diagnosis of DVT/PE.

Figure 3. Patients' presenting complaints

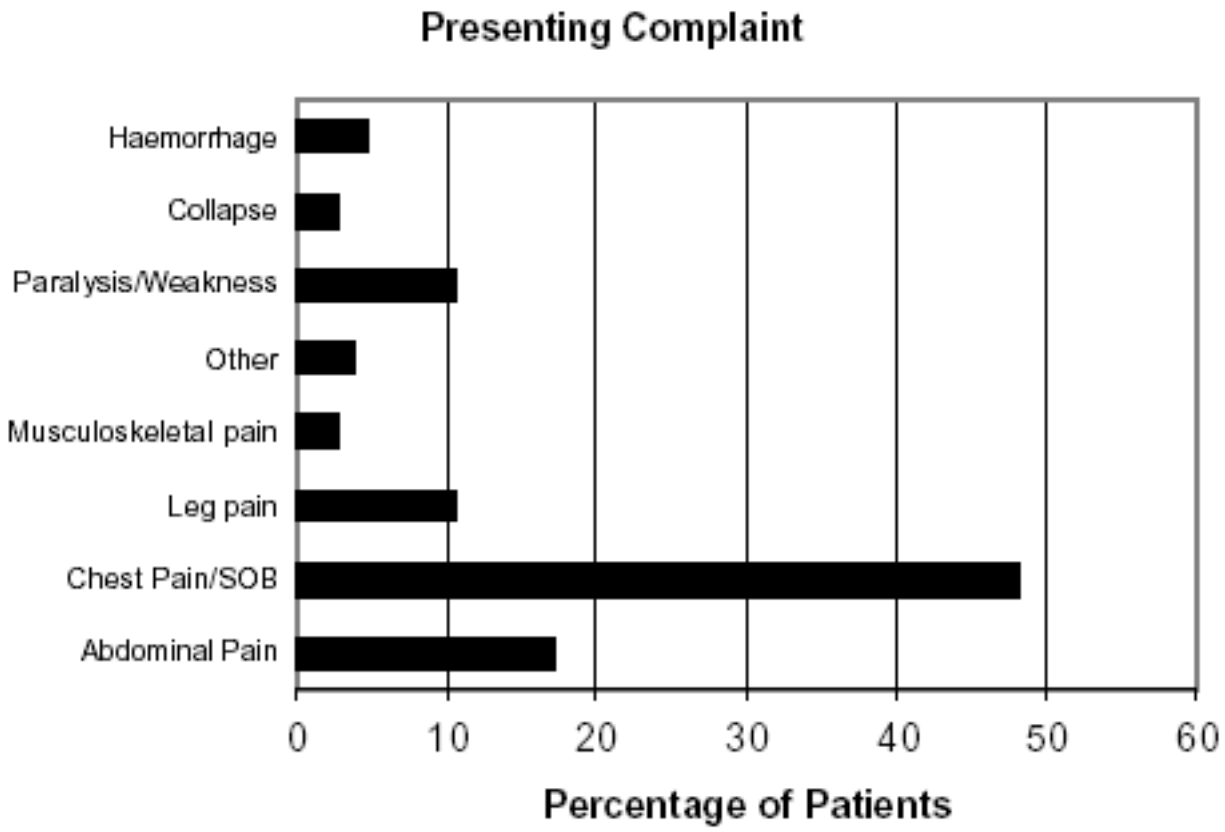
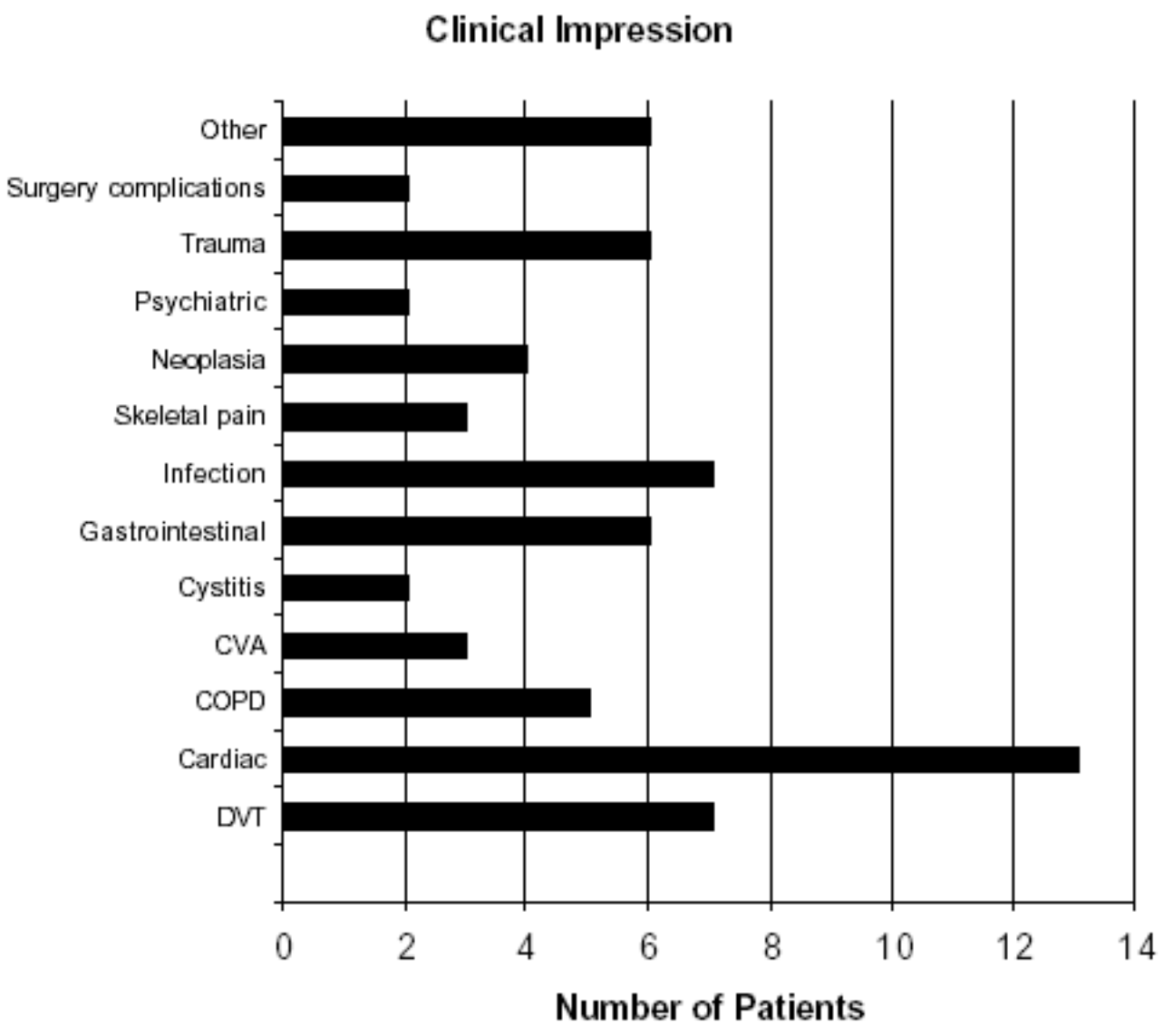


Figure 4. Clinical impression of patients



CONCLUSION

This study aimed to outline the ordering practices of D-dimer assays in Waterford Regional Hospital's A&E department. The shortcomings of this study were the relatively small sample size and the fact that the clinical outcomes of the patients in the cohort were not analysed. Despite these, it is clear that the "safety net" status of D-dimer ordering needs to be examined and more

evidenced-based ordering strategies implemented.

The impact of this is that in a nine-month period in 2001 there was an overshoot of 78,234 euro for the D-dimer budget of Waterford regional hospital. The implementation of a standard practice for ordering D-dimer assays or even a DVT/PE algorithm such as that proposed by Hirsh et.al., would regulate the investigation of DVT/PE and ultimately increase the detection rate while

decreasing budgetary overruns.[6]

ACKNOWLEDGMENTS

The author sincerely thanks Dr. Frederick Jackson and Dr. Michael Doyle who were the inspiration for this study.

REFERENCES

1. Dixon AK, Coulden RA, Peters AM. The non-invasive diagnosis of pulmonary embolism. BMJ 2001; 323(7310):412-3.

2. Bounameaux H,de Moerloose P,Perrier A,Miron MJ D-dimer testing in suspected venous thrombo-embolism:an update. Quarterly Journal of Medicine 1997; 90:437-442.

3. Lee AY, Ginsberg JS. Laboratory diagnosis of venous thromboembolism, Baillieres Clin Haematol 1998; 11:587-604.

4. Fowkes FJ, Price JF, Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. Eur J of Vasc Endovasc Surg 2003; 25(1):1-5.

5. Wells PS, Anderson DR, Rodger M. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. Annals of Internal Medicine 2001; 135(2):98-107.

6. Hirsh J, Lee AY. How we diagnose and treat deep vein thrombsis. Blood 2002; 99(9):3102-3110.

7. Egermayer P, Town GI, Turner JG. Usefulness of D-dimer, blood gas, and respiratory rate measurements for excluding pulmonary embolism. Thorax 1998; 53(10):830-4.

8. Janes S, Ashford N. Use of a simplified clinical scoring system and D-dimer testing can reduce the requirement for radiology in the exclusion of deep vein thrombosis by over 20%. Br J Haematology 2001; 112:1079-1082.

Aphasia: Do We Understand its Impact?

Niamh Ní Dhonnabháin

ABSTRACT

Objective: To establish the extent of Trinity College Dublin students' awareness of aphasia in comparison to multiple sclerosis, a disorder with lower prevalence. Methods: Three-hundred students from all six faculties in Trinity College Dublin were surveyed: Arts Humanities; Arts Letters; Business, Economics and Social Studies (BESS); Engineering and System Sciences; Health Sciences; and Science. The survey enquired if the students had "heard of aphasia", 'heard of multiple sclerosis', along with further questioning which allowed for the elaboration of their knowledge of each disorder. The scale ranked the students' knowledge as good, basic, or no knowledge. Results: Of the 300 students surveyed, 40 said they had heard of aphasia (13.3%), with 28 of these students (9.3%) meeting the criteria for "basic knowledge of aphasia". In comparison, 267 of the students surveyed (89%) said they had heard about multiple sclerosis, with 223 (74.3%) of these meeting the criteria for 'basic knowledge of multiple sclerosis'. These findings lend support to the notion that the students lack awareness and understanding of aphasia, and that there is an imbalance between the level of awareness and understanding between aphasia and multiple sclerosis.

INTRODUCTION

Aphasia is an acquired language disorder caused by injury to the left half of the brain, which

affects the generation and content of speech and its understanding.[1] It can affect all four modalities of language - reading, writing, comprehension and expression - to varying degrees. Some people with aphasia have problems primarily with expressive language (how they speak) while others have their major problems with receptive language (how they understand). Language is affected not only in its oral form of talking and understanding but also in its written form of reading and writing. Typically, reading and writing are more impaired than oral communication. The nature of the problems varies from person to person depending on many

factors but most importantly on the amount and location of the damage to the brain.[2] The impairment can be so subtle that it only manifests when the patient is put into unfamiliar surroundings and the language consists of "low frequency" words that he would be unlikely to come across in everyday life. Thus, aphasia is often called an 'invisible' disorder. There is little understanding of aphasia in both the general population and the medical community. Unfamiliarity with the disease has serious ramifications - less funding for services and research and less

empathy for those who suffer from aphasia.[3]

In this study, subjects' levels of aphasia awareness to their knowledge of multiple sclerosis (MS) were compared. There is little research done on peoples' knowledge of aphasia, yet it is a prevalent disorder. MS was chosen for comparison because it is less prevalent according to the

National MS Society and the National Aphasia Association in the United States.[4,5] In Ireland, it is not certain which disorder is more prevalent due to lack of research into the number of people with aphasia, however the number of people with MS represents 0.13% of the population (Table

1).[6] It was also chosen for similarities. MS confers physical as well as communication abnormalities. Aphasia will cause communicative and often physical abnormalities due to the nature of acquiring aphasia, for example a stroke.

Table 1. Prevalence of aphasia and multiple sclerosis

	Aphasia		Multiple Sclerosis	
	Number	%	Number	%
Ireland	Unknown	Unknown	4,735	0.13%
USA	1,000,000	0.35%	250,000 - 350,000	0.09% - 0.12%

It was predicted that awareness levels of aphasia would be lower in Ireland than in America or Britain, due to more advocacy groups and aphasia centres being available to the public in America and Britain. A previous international survey conducted in Australia, the UK and the USA

showed awareness levels are highest in populations near aphasia centres or advocacy groups.[7] The role of society is to ease the reintegration of people with aphasia by promoting the understanding of their experience in order to create a physical and social environment which will

be most conducive for communication.[7] However, if awareness of aphasia is lacking, how can society be expected to assume this role?

The opening statement of the 1988 National Aphasia Association's (NAA) survey says, "So many people don't even know the word aphasia, much less what it does to you." Ninety percent of those with aphasia who participated in this survey felt the public's awareness of this disability is

minimal.[9] The company Speakability held a telephone survey in Great Britain in 2000, and found that only 3% of the participants could give an accurate definition of aphasia. The same study revealed that only 5.4% of the participants in the study had basic knowledge of aphasia in the UK,

the USA and Australia.[4]

Aphasia can be an extremely frightening experience, exacerbated by an absence of compassion due to ignorance or miscomprehension on the part of health professionals in treating these patients. Parr et al. (1997) highlight the view of a patient with aphasia from a stroke with regards to the nursing staff:

I was furious with the nurses because…well two nurses came on one and another side of me and they…they… they discussed me…over…never…never thought of me at all. Never. I couldn't help…you know I wasn't able to speak very well at that time. I was furious with, you know – I'm

usually the person to do the speaking.[10]

This lack of understanding within the health service sector also negatively affects information the patient and his family receive concerning services from which they may benefit.

METHODS AND RESULTS

A questionnaire was given to 300 students from the third and fourth years in Trinity College Dublin (TCD). Table 2 shows 13.3% of students had heard of aphasia by name as opposed to 89% of the students who recognised MS.

Table 2. Number of students who recognise the terms aphasia and MS.

	Multiple Sclerosis	Aphasia
Yes	89% (267)	13.3% (40)
No	11% (33)	86.7% (260)

In Table 3 shows the number of students whohad heard of either illness. Knowledge of aphasia was predominantly through studying or reading about the illness. In contrast, knowledge of MS was largely through knowing someone or seeing campaigns. In addition, Table 3 highlights again the low percentage of students who have had contact in any way with aphasia.

In Table 4, students are categorised based upon their level of knowledge of aphasia. Group 1 involves students who have heard of aphasia (n=40) while Group 2 takes into account all participants (n=300) in the study, regardless. Table 5 elaborates on the levels of knowledge of each disease.

Table 3. Percentages of ways in which respondents have heard about aphasia and multiple sclerosis.

	Aphasia (n=300)		MS (n=300)	
	Number	%	Number	%
Know someone who suffers from it?	10	3.3%	93	31%
Heard of someone who suffers from it?	1	0.3%	41	13.6%
Work with / study it?	15	5%	37	12.3%
Know someone who works with / studies it?	6	2%	27	9%
Heard about it in the media?	3	1%	72	24%
Heard about it through awareness campaigns?	0	0%	68	22.6%
Read about it in books, journals, the internet etc.?	13	4.3%	46	15.3%
No Response	7	2.3%	0	0%

Table 4. Level of students' knowledge of aphasia.

	Understanding of Aphasia		
	Numbers Group 1 n=40	Group 1 % of people who have heard about aphasia	Group 2, n=300 % of overall participants in the study
Good Knowledge	9	22.5%	3%
Basic Knowledge	19	47.5%	6.3%
No Knowledge	12	30%	90.7%

Table 5. Classification of levels of knowledge of aphasia and multiple sclerosis.

	Aphasia	Multiple Sclerosis
Good Knowledge	A knowledge that aphasia is an impairment that can affect all four modalities of communication, and is caused by injury to the brain / stroke.	Knowledge that multiple sclerosis is a degenerative disease, caused by demyelination, that effects at least one of the following symptoms: fatigue, vision, co-ordination, strength, sensation, speech and swallowing, bladder control, sexual intimacy and cognitive function.
Basic Knowledge	A knowledge that at least one modality of communication can be affected by aphasia and /or that aphasia is caused by injury to the brain / stroke.	A knowledge that multiple sclerosis is associated with at least one of the following: • a degenerative disease • demyelination • one of the symptoms listed above.
No Knowledge	No knowledge of what aphasia affects, or how it is caused.	No knowledge of what multiple sclerosis is, how it is caused, or what its symptoms are.

DISCUSSION

There is some encouraging news to be found in this study. Of the 300 student sample population, 9.3% meet basic knowledge requirements, (with 3% of the participants considered to having good

knowledge), as compared with the 5.4% determined by the Simmons-Mackie survey.[7] However, since subjects were pooled from the Health Science faculty, one would hope that these students have a higher level of familiarity.

Results from the study also indicate that there was a large imbalance between aphasia recognition and awareness of multiple sclerosis, despite the fact that aphasia occurs in up to 4

times as many people in the United States.[4,5] There are a number of possible explanations for this. For example, multiple sclerosis generally affects a younger population than aphasia (although aphasia can strike at any age), so the sample population of college students who are generally a young population, might have been more likely to come into contact with MS patients. Of the total sample population, 31% indicated personal contact with someone affected by multiple sclerosis (MS), and a further 13.6% indirectly associated with an MS sufferer. Conversely, only 3.3% of the population knew someone with aphasia and 0.3% of them had heard of somebody who suffers from it. Only 1% of total respondents had heard of aphasia through the media compared with 24% concerning MS. A very disturbing finding was that 0% of the sample population have heard about aphasia through awareness campaigns in contrast to 22.6% with regards to MS. These disparities in differences of awareness of MS and aphasia due to contact with individuals or awareness campaigns are significant.

CONCLUSION

These results indicate there is not enough being done to promote knowledge of aphasia. Simmons-Mackie et al. (2002) state that the awareness of aphasia in the general public is lacking,

but one must address why this is so.[7] The public's lack of awareness points to medi apathy. From the period between 1985 to 2001, only eight articles were written in the Times and the Sunday Times (English) newspapers that mention the word ‘aphasia’. Of these eight articles, five of them detailed that aphasia is caused by a stroke or brain injury, and only three articles explained the background to aphasia. In contrast, when observing the exposure these same papers gave MS,

163 articles discussing the condition appeared from the years 1998 to 2001.[11] Why is there such a contrast between media exposure of the two disorders?

The advocates of aphasia promotion must find a way to generate enough appeal so that it will be beneficial for reporters, newspapers and television stations to research and publicise this disorder. By its very nature, suffering from aphasia can cause difficulty for those afflicted to promote awareness, and it is therefore essential that active aphasia advocacy groups be set up in this country to elevate awareness of the disorder.

REFERENCES

1. Martin EA. Oxford Concise Colour Medical Dictionary. 2nd ed. Oxford University Press; 1998.
2. Jordan L, Kaiser W. Aphasia, a Social Approach. London: Chapman and Hall; 1996.
3. Elman RJ, Ogar J, Elman SH. Aphasia: awareness, advocacy and activism. Aphasiology 2000; 14: 455-9.
4. National Multiple Sclerosis Society of the United States. MS Factsheet.
http://www.nationalmssociety.org/historical%20perspective.asp
5. National Aphasia Association (NAA). Aphasia Fact Sheet 1999.
http://www.aphasia.org/NAAfactsheet.html.
6. The Multiple Sclerosis Society of Great Britain and Northern Ireland.
http://www.mssociety.org.uk/index.html
7. Simmons-Mackie N, Code C, Armstrong E, et al. What is aphasia? Results of an international survey. Aphasiology 2002; 16: 837-48
8. Lemay M. The person with Aphasia and Society. In: Lafond D, DeGiovani R, Joanette Y, Ponzio J, Taylor-Sarno M, editors. Living with Aphasia: Psychosocial Issues. San Diego: Singular Publishing; 1993.
9. National Aphasia Association. Impact of Aphasia on Patients and Family.
http://www.aphasia.org/NAAimpact.html 1988
10. Parr S, Byng S, Gilpin S, Ireland C. Talking about Aphasia: Living with Loss of Language after Stroke. Buckingham: Open University Press; 1997.
11. The Times (English). Archives. http://www.newintarchive.co.uk/pages/welcome post.asp

Beta Blockers and Heart Failure

Deirdre Moran

Introduction

Beta-blockers were traditionally thought to be contraindicated in heart failure due to their negative inotropic properties. However, recent research has revealed the beneficial effects of treating heart failure patients with beta-blockers.

What is Heart Failure?

Heart failure is a clinical condition in which the heart is unable to pump sufficient blood around the body to meet its metabolic needs. It is characterised by abnormalities of left ventricular function and neurohormonal regulation, exercise intolerance, shortness of breath, fluid retention and

reduced longevity.[1] Heart failure can be due to systolic or diastolic left ventricular dysfunction. Most patients with heart failure have primarily systolic dysfunction. In two-thirds of patients with systolic dysfunction, the cause is coronary artery disease.2 However, patients may also have nonischaemic causes of cardiomyopathy such as hypertension, valvular heart disease, myocarditis, systemic disease, toxins, alcohol/drug abuse, or idiopathic cardiomyopathy. Depressed left ventricular ejection fraction (<40%) is the hallmark of systolic dysfunction. Diastolic dysfunction is defined as normal or preserved rest systolic function in the presence of

heart failure signs and/or symptoms.[2]

Heart failure can be viewed as three models – the cardiorenal model, the haemodynamic model

and the neurohormonal model.[3] The primary cause of the cardiorenal model of heart failure is renal hypoperfusion caused by cardiac dysfunction. This leads to oedema and volume expansion due to excessive salt and water retention. Heart failure is also associated with a reduced cardiac output and excessive peripheral vasoconstriction; these symptoms are characteristic of the

haemodynamic model of heart failure.[4] This model also describes the progressive heart failure which develops from chronically increased preload and afterload. The neurohormonal model of heart failure develops after prolonged expression of endogenous neurohormonal mechanisms. These systems are initially compensatory, but can eventually lead to toxic effects on the myocardium. The two primary neurohormonal systems involved are the sympathetic nervous system and the renin-angiotensin-aldosterone axis (R-A-A).

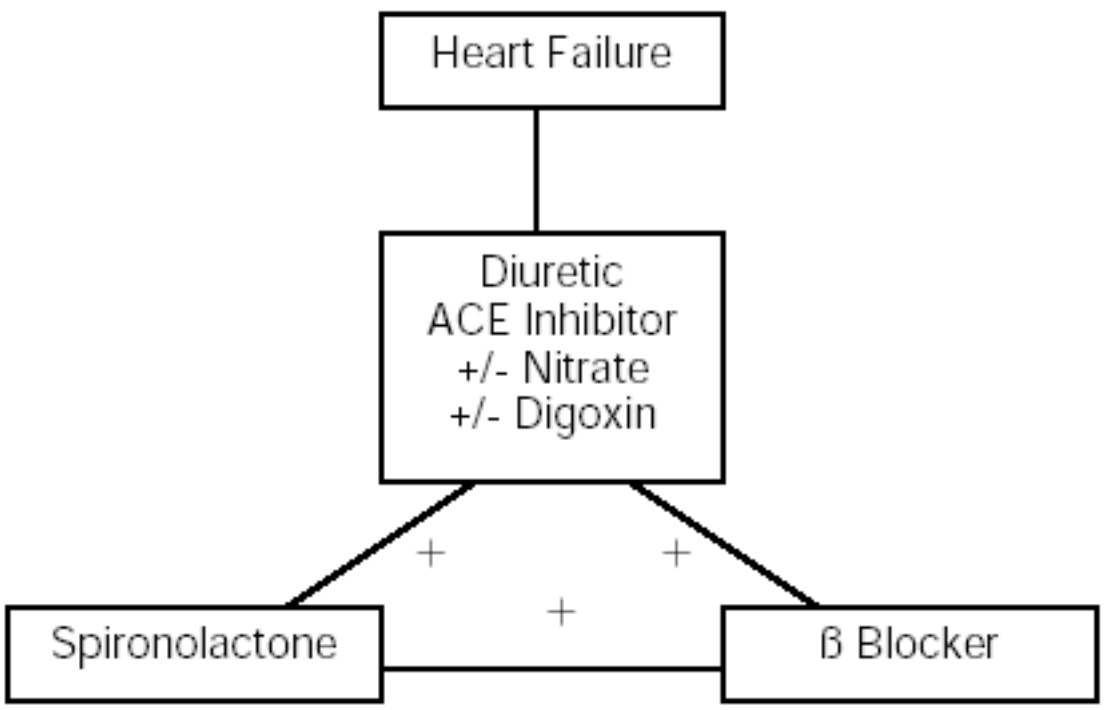
Current Treatment of Heart Failure

The treatment of heart failure is targeted at each of these three separate models (Figure 1). The primary treatments for the cardiorenal model are digitalis and diuretics. Digitalis (or its associated glycosides, e.g. digoxin) increases the contractility of the heart. Diuretics relieve pulmonary congestion and peripheral oedema by increasing urine volume, which leads to a decrease in plasma volume. The decreased plasma volume leads to a decreased venous return (preload) to the heart, which in turn decreases the cardiac workload and oxygen demand. The reduced plasma volume also leads to a decreased blood pressure. Therefore, afterload is also decreased. The haemodynamic model is treated with positive inotropic agents and peripheral vasodilators. Angiotensin-converting enzyme (ACE) inhibitors are used to counteract the adverse effects of the long-term stimulation of the R-A-A axis. They decrease the circulating levels of angiotensin II, the effect of which is to cause decreased output of the sympathetic nervous

system, increased vasodilation of vascular smooth muscle, increased levels of bradykinin and decreased retention of sodium and water. Currently, the standard therapy for heart failure involves diuretics and an ACE inhibitor, with or without digitalis glycosides. This line of therapy ignores or incompletely inhibits adrenergic activation, which is one of the primary contributors to

progressive left ventricular systolic dysfunction.[2] This 'triple' therapy also only treats the symptoms of heart failure without considering whether an actual improvement in the patient could be attained by identifying the causatory factors of the patient's heart failure. The emphasis of this review will be targeted at the treatment of the neurohormonal model of heart failure involving beta-blockers, which can inhibit the activation of the adrenergic system.

Figure 1. Treatment of Heart Failure



Adrenergic Activation in the Failing Heart

During rest and when left ventricles are normally functioning, there is no adrenergic support. However, in the failing human heart, the adrenergic system is activated. Over the short term, activation of the sympathetic nervous system has a compensatory effect on cardiac performance and is important in the maintenance of normal cardiac output. Ultimately however, the prolonged increase in circulating noradrenaline (NA) can lead to progressive damage to the failing human

heart. NA produces cardiotoxic effects which cause damage to the cardiac myocytes.[5] Persistent peripheral vasoconstriction and precipitation of ischaemia and arrhythmias are subsequent deleterious effects. NA spillover in the myocardium has been linked to life-threatening arrhythmias. The increase in heart rate, which is caused by activation of the sympathetic nervous

system, can exacerbate the discrepancy between oxygen demand and supply.[6] Progressive cell loss and death are consequences of the combination of local and systemic sympathetic nervous system activation. This leads to worsening of ventricular remodelling, characterised by changes in ventricular geometry, mass, and volume, resulting in a dilated and less contractile chamber. If this vicious cycle of adrenergic activation continues unabated, the dilation of the ventricle worsens, contractility is further reduced and ultimately these may lead to myocardial infarction or

complete ventricular failure.[4] It is important to note that by the time symptoms appear, this cycle of left ventricular dysfunction is well under way. Therefore, it is of paramount importance that diagnosis be made as early as possible to optimise the chances of successful treatment of heart failure.

Within the myocardium, there are 3 types of adrenergic receptor – a1, b1 and b2. The b1 group of receptors normally predominate. However, in the failing heart, 35-40% of the total number of b receptors are b2 because of selective downregulation in the b1 subtype. There is also a concomitant upregulation in the numbers of a1 receptors in the failing heart. Cardiac overexpression of b2 receptors results in depressed systolic function and a cardiomyopathy phenotype, whereas the increased levels of a1 receptors produces concentric hypertrophy of the

ventricle.[5] These data indicate that chronic activation of the adrenergic system can lead to damage to the myocardium. This is the reason that beta-blockers for the treatment of heart failure has now become a distinct reality, as they are capable of inhibiting the sympathetic nervous system's effects on the heart. Traditionally, it was thought that beta-blockers were contraindicated in heart failure patients due to their negative inotropic properties. This was thought to render an already compromised heart even weaker through beta-blockade.7 However, several clinical trials have been conducted using beta-blockers in combination with diuretics and ACE inhibitors and have resulted in improvements in left ventricular function, symptoms and survival, as well as a

reduction in admission to hospital.[8]

Types of Beta-Blockers

Beta-blockers can be divided into three categories, dependent on their properties. 'First-generation' compounds such as propranolol, are non-selective beta-blockers and block b1 and b2 receptors with equal affinity. These compounds have no other important pharmacological

effects other than beta-blockade.[5] The 'second-generation' beta-blockers can be considered to be 'cardioselective' as they have much greater affinity for b1 than b2 receptors. Examples of second-generation beta-blockers are metoprolol and bisoprolol. The final category of beta-blockers – the 'third-generation' – includes carvedilol and bucindolol. Carvedilol is a non-selective, vasodilatory agent with the unique property of having an a-blocking moiety as well as

an antioxidant effect.[6] The moderate vasodilatory properties of carvedilol are due to the blockade of the a1 receptors. Bucindolol is also a non-selective beta-blocker with vasodilator properties. The third-generation beta-blockers, therefore, provide a more comprehensive anti-adrenergic effect than do second-generation beta-blockers, due to the fact that they block both b1 and b2 receptors, reduce cardiac and/or systemic adrenergic drive, do not upregulate downregulated b1

receptors and can block a1 receptors.[5]

Clinical Studies

Several studies have been conducted into the effects of beta-blockade on the condition of the heart failure patient. The CIBIS-II study (cardiac insufficiency bisoprolol study) compared the second-generation drug bisoprolol to placebo. Its findings reported a highly significant reduction

in all cause mortality.[9] The patients included in the study were from New York Heart Association classes III and IV [Classification of the New York Heart Association is as follows: I=no symptoms, II=mild, III=moderate, IV=severe]. Bisoprolol was shown to be superior to placebo for morbidity

and mortality.[8] This study showed a 34% reduction in mortality and a 20% decrease in the risk of hospital admissions to hospital for any reason. The trial was stopped prematurely because of a significant mortality benefit in patients treated with bisoprolol. There have been two trials conducted on the effects of carvedilol, one in Australia and New Zealand (ANZ), the other in the US. The US study was the first to show a mortality advantage with beta-blockers given in chronic

heart failure.[1] These studies supported the contention that carvedilol improves survival and reduces the rate of hospitalisation and worsening heart failure with patients who have heart failure

caused by coronary heart disease and those with primary cardiomyopathy.[10] Carvedilol is indicated for the treatment of heart failure in patients with clinically stable NYHA functional class II

or III.[11] Both of these studies found that carvedilol was superior to placebo for morbidity and

mortality.[8] Carvedilol is currently the only beta-blocker approved for the treatment of chronic heart failure in the US, UK and most other countries. It was approved as a result of the delay in progression of the myocardial disease process and the lowering of the combined risk of morbidity

plus mortality seen in both of these trials.[5] In another study, metoprolol was used in dilated cardiomyopathy (MDC) with patients with mild to moderate heart failure. The outcome of this study was an improved clinical state without effect on survival and a reduction in the need for

transplantation in patients with dilated cardiomyopathy.[8] In addition, metoprolol, compared with placebo, improved left ventricular function, quality of life, hospitalisations, and exercise tolerance. Another trial involving metoprolol was the metoprolol randomised intervention trial in congestive heart failure. This trial included patients with classes II-IV heart failure. The results of this trial showed a reduction in mortality resulting from sudden death or progressive pump failure. Also, mortality was reduced across most demographic groups. including age, nonischaemic and

ischaemic causes and levels of ejection fractions.[5] Metoprolol, therefore, was found to decrease the risk of death and of the combined end point of total mortality and all cause hospital

admissions.[12]

Beta-blockers appear to have an effect as great as or greater than that of ACE inhibitors. However, in most of the trials detailed above, the patients were already taking ACE inhibitors so the benefits of beta-blockade could be in addition to those of ACE inhibitors. Reduction of

mortality by the combination of treatments has been shown to be 46%.[5] This is obviously a highly significant improvement in the progress of successful treatment for chronic heart failure.

Cautions and Side-Effects

Beta-blockers must be administered with careful supervision and initially, the practitioner may need to consult a cardiologist. This is because beta-blockers can cause worsening of heart failure before improvement is seen. Left ventricular ejection fraction tends to worsen initially but

subsequently improves after 6 to 12 months of therapy.[10] Other drugs used in the treatment of heart failure do not cause a similar improvement in left ventricular ejection fraction. Therefore, the strategy for administering all beta-blocking agents for the treatment of heart failure is to start at low doses and to gradually increase the dose over weekly or biweekly intervals. Metoprolol and carvedilol have half-lives which dictate that they must by given twice-daily, whereas bisoprolol can be given once per day. The former compound is highly lipophilic, extensively metabolised and cleared by the liver, whereas the latter compound is less lipophilic and is cleared by both the liver and the kidney. The bioavailability of all of these agents is quite low (20-50%) due to the

extensive first-pass hepatic metabolism experienced by the agents.[5] Carvedilol may result in an increase in serum digoxin concentrations in patients receiving digoxin. Therefore, frequent alterations in concomitant therapy may be a necessity.

While in the short-term, beta-blockade can cause a depression of cardiac function, which leads to a temporary worsening of symptoms, this does not seem to outweigh the long-term therapeutic benefits. Primary adverse effects may include fluid retention, hypotension and bradycardia. Carvedilol can produce substantial vasodilation, which is usually asymptomatic but can be accompanied by dizziness or light-headedness. This effect usually disappears upon repeated dosing. Both selective and non-selective beta-blockers can slow the heart rate and cardiac conduction, and as a result, may cause bradycardia and heart block. If the heart rate decreases to fewer than 50 beats per minute or second-degree or third-degree heart block develops, the

dose of beta-blocker should be decreased.[2]

What patients are suitable for Beta-Blocker Therapy?

The current recommendations for determining candidates suitable for beta-blocker therapy

stipulate that the subjects should have a mild to moderate compensated heart failure from nonischaemic or ischaemic cardiomyopathies, with stable NYHA class II to III symptoms on standard treatment (diuretics and an ACE inhibitor), and may be used in conjunction with digitalis

or vasodilators.[2] Subjects should not have a contraindication to beta-blockade such as asthma. If beta-blockers are given to subjects with decompensated heart failure, the myocardial

depression that accompanies initiation of therapy can be life-threatening.[5] Also, NYHA functional class IV heart failure should be considered a relative contraindication for beta-blocker therapy as the evidence from the literature does not conclusively suggest a benefit in this population and the

potential for grave harm exists.[6] Therefore, careful selection of patients with heart failure suitable for beta-blocker therapy is essential.

Conclusion

The administration of beta-blockers for the treatment of heart failure appears to have its benefits in certain categories of heart failure patients. Previously, beta-blockers were believed to be a contraindication in the treatment of heart failure due to their negative inotropic properties. However, through extensive research and clinical trials, beta-blockers have now become part of the recognised treatment process for heart failure. Beta-blockers can antagonise the effects of an overactive sympathetic nervous system, which is responsible for many of the disease processes leading to the progression of heart failure. Several studies have highlighted the successful clinical effects of beta-blockers – decreased mortality and decreased risk of hospitalisation for the treatment of heart failure. Beta-blockers reduce total and cardiovascular mortality, as a result of a

reduction in pump failure mortality and sudden death.[13] While standard 'triple' therapy for heart failure has improved the quality of life of heart failure patients, this type of therapy only relieves symptoms, which is the reason for success of beta-blocker therapy. Although the beta-blocker data does not demonstrate a 'cure' for heart failure, it has shown that substantial improvement in the prognosis of heart failure can be obtained. There are risks associated with the administration of beta-blockers; they can produce initial worsening of heart failure and must be given under expert supervision. Beta-blockers are also contraindicated in chronic obstructive pulmonary disease and they can cause arrhythmias if therapy is discontinued abruptly. However, these risks are small in comparison to the proven benefits, which can include slowed disease progression and improvement of symptoms. Although initial treatment can put additional demands on the primary care physician, the extra effort can prove worthwhile, especially if comparison is made to the high rates of morbidity and mortality among patients receiving standard treatment. It is hoped that with further trials, the use of beta-blockers in heart failure can reach a conclusion in which the beta-blockers involved are used optimally to produce significant improvements in the life of the heart failure patient.

REFERENCES

1. Lonn E. Drug treatment in heart failure. BMJ 2000; 320:1188-1192.
2. Abraham WT. Beta-blockers: The new standard of therapy for mild heart failure. Archives of Internal Medicine 2000; 160(9):1237-1247.
3. Pepper GS. Sympathetic activation in heart failure and its treatment with beta-blockade. Archives of Internal Medicine 1999; 159(3):225-234.
4. Mann DL. Mechanisms and models in heart failure. Circulation 1999; 100(9):999-1008.
5. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. Circulation 2000; 101(5):558.
6. Mehra MR, Uber PA, Aditya KK. Using beta-blockers in patients with heart failure. Patient Care 1999; 33(6):205-209.
7. Eagle KA. Update in cardiology. Annals of Internal Medicine 2000; 133(6):439-446.
8. Gibbs CR, Davies MK, Lip GYH. Management:digoxin and other inotropes, b-blockers and antiarrhythmic and antithrombotic treatment. BMJ 2000; 320:495-498.

9. Cleland JG, McGowan J, Clark A, et al. The evidence for beta-blockers in heart failure. BMJ 1999; 318:824-825.
10. Gheorghiade M, Cody RJ, Francis GS et al. Current medical therapy for advanced heart failure. Heart & Lung 2000; 29(1):16-32.
11. Vanderhoff BT, Ruppel HM, Amsterdam PB. Carvedilol:The new role of beta-blockers in congestive heart failure. American Academy of Family Physicians 1998; 58(7):1627-34.
12. Strauss SE. Geriatric medicine. BMJ 2001; 322:86-89.
13. Bonet S. Beta-adrenergic blocking agents in heart failure:benefits of vasodilating and nonvasodilating agents according to patients' characteristics:a meta-analysis of clinical trials. Archives of Internal Medicine 2000; 160(5):621-627.

Controversy in the Surgical Management of Achalasia Cardia

Lara Herbert and Cliona Lorton

INTRODUCTION

Achalasia Cardia is a primary oesophageal motility disorder, characterised by a hypertensive lower oesophageal sphincter (LOS) which fails to relax on swallowing, and by aperistalsis of the body of the oesophagus.[1, 2]

The aetiology of the disease remains unknown. Epidemiological findings rule out an infectious cause, and there appears to be minimal genetic influence.[3, 4] A viral cause is plausible but as of yet electron microscopy has failed to detect viral particles in the vagus nerve or in the oesophageal intramural nerve plexus.[5] The incidence of the disease is 1-2 per 200,000 per year, with both sexes equally affected.[6] Onset of the disease is typically between the ages of 20 and 50.

The principal lesion is denervation of the oesophageal smooth muscle.[7] While muscular abnormalities are also present, these appear to be secondary to the neural deficit. A decreased number of ganglion cells in the oesophageal intramural nerve plexus has been found in patients with achalasia, and the extent of this loss corresponds to the duration of the disease.[8,9] There may also be degenerative changes in the vagus nerve, both in its branches to the oesophagus and in the dorsal motor nucleus.[10] The interaction between nerve plexus and vagus nerve lesions is not yet clear.[8] In both cases, the loss predominantly concerns inhibitory neurons. [8,9,10] This would explain the increased basal LOS pressure as well as the inadequate sphincteric relaxation observed on swallowing. Degeneration of the oesophageal ganglion cells leads to permanent aperistalsis as the disease progresses and favours oesophageal dilatation.[7]

Progressive dysphagia is the most common presenting symptom. It generally concerns both liquids and solids from the outset. The second most common symptom is the regurgitation of undigested food during or shortly after a meal. Approximately 36% of patients present with sub/retrosternal pain and a similar percentage with heartburn.[11] Weight loss is a very common finding in patients with achalasia due to decreased food intake, and is a good indicator of the chronicity and severity of the condition. Patients may complain of nocturnal coughing if there is overspill of oesophageal contents into the trachea, which is increased in the supine position.

Pulmonary infiltrates resulting from aspiration constitute a rare, but severe, complication.[7]

Diagnosis of achalasia cardia is based on history, barium swallow with fluoroscopy, upper endoscopy and oesophageal manometry.

Pseudoachalasia can occur in a number of conditions, most commonly in gastric adenocarcinoma.[12] The mechanism may be infiltration of the oesophageal nerve plexus or constriction of the distal oesophagus by the tumour mass. Endoscopy can be used to rule out this differential diagnosis, which is more common among older patients, who usually present with marked weight loss. Oesophageal squamous cell carcinoma, lymphoma, lung carcinomas and a number of other malignancies can also cause pseudoachalasia. Other conditions which can mimic achalasia include Chaga's disease, amyloidosis, sarcoidosis, oesophageal stricture,

chronic idiopathic intestinal pseudo-obstruction and post-vagotomy disturbance.

TREATMENT

As the degenerative neural lesion of this disease cannot be corrected, treatment is directed at palliation of symptoms and prevention of complications. Effective peristalsis is rarely restored by successful treatment, but improved oesophageal emptying and a decrease in oesophageal diameter are generally expected.

Four palliative treatments are available: pharmacotherapy, botulinum toxin injection, pneumatic dilatation and myotomy. They all aim to decrease LOS pressure and improve emptying by gravity.

Pharmacotherapy :

Smooth muscle relaxants alleviate symptoms and improve oesophageal emptying in up to 70% of patients. Nitrites, such as sublingual isosorbide dinitrite, and calcium channel blockers, such as diltiazem, nifedipine and verapamil, have this effect.

The role of pharmacological agents in the long-term management of achalasia is unclear. It is not known whether their long-term use prevents dilatation and complications. This treatment option is suitable for patients with medical conditions that interfere with pneumatic dilatation or myotomy. Also, patients with severe weight loss can be treated pharmacologically until a healthy nutritional status can be re-established, making them better candidates for other forms of treatment.

Botulinum Toxin:

Botulinum toxin type A is derived from the controlled fermentation of Clostridium botulinum. The toxin binds to presynaptic cholinergic neuronal receptors, is internalised, and irreversibly interferes with acetylcholine release, probably by preventing the neurotransmitter vesicle docking

and fusing with the axonal membrane.[13]

Pasricha and colleagues first demonstrated the similar ability of botulinum toxin to decrease LOS

basal tone and improve symptoms in patients with achalasia. [14]

An initial, beneficial response at the level of the LOS occurs in 90% of patients, but symptoms

reappear within a year in many initial responders.[15] Side effects of this treatment are rare, but include chest discomfort for a few days after the injection and an occasional rash.

The best use of botulinum toxin injection in achalasia is still being explored, but this seemingly safe approach with little apparent morbidity may be of great advantage when a short-term treatment response is desired.

Dilatation:

Forceful dilatation of the gastroesophageal sphincter to a diameter of approximately 3 cm is necessary to tear the circular muscle and to ensure a lasting reduction in LOS pressure. Many types of dilators have been developed for this purpose, but it is pneumatic dilators which are conventionally used today.

The technique of dilatation, inflation pressure and duration of inflation varies. Water-soluble contrast material is used to detect distal oesophageal leaks. Surgical consultation is undertaken if perforation is evident. Small perforations are managed conservatively with broad-spectrum

antibiotics.[16] Clinical deterioration e.g. shock, sepsis, haemorrhage or a finding of free-flowing

barium into the mediastinum, requires immediate thoracotomy and repair.

At least 60% of patients have a good response and success rates exceeding 95% have been

reported.[17] The response rate varies with patient age, (younger patients do not do as well as older patients), and duration of symptoms, (those with a shorter history do not respond as well), but it does not seem to be related to the degree of oesophageal dilatation or tortuosity. The efficacy of this procedure is decreased by as much as half with each subsequent dilatation.

Morbidity is mostly related to oesophageal perforation, a complication in approximately 5% of

patients, but surgical repair is required in less than half of these cases.[17] Perforation may be more likely in severely malnourished patients, which raises the possibility that re-establishment of

a good nutritional status decreases the complication rate following dilatation.[18]

Surgery:

The goal of surgical therapy in achalasia is to decrease LOS resting pressure without completely compromising its competency against gastroesophageal reflux (GOR).

The Heller procedure was described in 1913 and now a modification of this procedure is used

most commonly in the surgical management of achalasia.[19,20] An anterior myotomy is performed by dividing the circular muscle of the oesophagus down to the level of the mucosa. The myotomy extends less than 1cm onto the stomach and to several centimetres above the palpable region of the lower sphincter. The transthoracic approach is preferred, as it helps confirm the diagnosis, allows careful palpation and inspection of the oesophagus, and enables the surgeon to extend the myotomy proximally as far as is necessary. Open myotomies have good results in 80-90% of

patients.[21,22] They decrease the LOS pressure more reliably, and therefore have a greater efficacy than pneumatic dilatation.[23]

Minimally invasive surgical procedures are becoming a preferable alternative to open myotomy,

allowing the Heller myotomy to be performed thoracoscopically and laparoscopically .[24,25,26] Shorter hospitalisation, less pain and early resumption of activity are the benefits of the minimally

invasive approach, which remains as effective as the open techniques in the relief of dysphagia.[27] Complications of minimally invasive surgery include: anterior gastric perforation, mucosal perforation at the gastroesophageal (GO) junction and, most significantly, GOR.

Surgery is not necessary for a patient who has few symptoms and minimal oesophageal dilatation. It is, however, required for those with dilatation and food retention to prevent serious pulmonary complications and, of course, to provide symptomatic relief.

Pre-Operative Evaluation:

- Symptomatic Evaluation

  The severity of the symptoms is scored by the patient by questionnaire before and after surgery.

- Barium Swallow

  This should be the first test performed in the evaluation of dysphagia. It usually shows a "bird’s beak" narrowing at the GO junction and oesophageal dilatation proximal to the narrowing.

- Endoscopy

Endoscopy should follow a barium swallow to rule out pseudoachalasia. It excludes gastroduodenal abnormalities, peptic malignancy and stricture.

- Oesophageal Manometry

  Typical manometrical findings are the absence of oesophageal peristalsis and a hypertensive LOS which fails to relax completely in response to swallowing.

- Prolonged Ambulatory pH Monitoring

  Prolonged pH monitoring is performed to determine if abnormal reflux is present. In patients who have a positive test result, it is essential to distinguish between true reflux and increased acidity due to stasis and fermentation.[28]

Post-Operative Follow-Up:

Patients are re-examined 2-6 weeks after surgery. Oesophageal manometry and pH monitoring are performed 2-3 months after the operation. Subsequently, patients are contacted for symptomatic evaluation.

Comparisons between therapies:

Pneumatic dilatation, pharmacotherapy and botulinum toxin injection are easy to use, usually well-tolerated and relatively cheap treatment options in achalasia. Surgery generally gives longer-lasting results as well as more complete relief of symptoms. Non-operative therapy is recommended initially. Patients are only referred for surgery if they remain symptomatic after 3 attempts at pneumatic dilatation.

Two studies done by Patti et al. (2001) and a study by Stewart et al. (1999 - comparing thoracoscopic to laparoscopic myotomies) indicate that laparoscopic myotomy is the superior approach, due shorter operative times and shorter duration of hospitalisation, as well as a more effective relief of dysphagia.[28,29,30]

THE CONTROVERSY

In the surgical treatment of achalasia, a balance must be found - there must be a sufficient decrease in oesophageal obstruction to provide symptomatic relief, but an excessive decrease in LOS pressure results in GOR. An anti-reflux procedure is sometimes added to avoid this. Laparoscopic procedures are either combined with a Floppy Toupet Fundoplication attached to the sides of the myotomy or a Dor fundoplication, known as the laparoscopic Heller-Dor fundoplication. There is, nonetheless, considerable debate surrounding the actual therapeutic value of such an addition.

Arguments against an Anti-reflux procedure after oesophageal myotomy:

It is clear that adding a complete fundoplication increases resistance at the GO junction and defeats the objective of the myotomy i.e. to decrease this resistance. There is, however, evidence that even partial fundoplication procedures, e.g. Toupet and Dor techniques, increase LOS resistance and could compromise the effectiveness of the myotomy. Ellis et al. (1984) have achieved excellent relief of dysphagia with Heller myotomy alone, with only 9-15% of patients having unsatisfactory results.[31]

Richards et al. (1999) studied gastroesophageal reflux in 75 patients who had been treated by myotomy without fundoplication. They discovered that there was only a very weak correlation between patients' perceptions of their GOR (heartburn symptoms), as evaluated by a

questionnaire, and objective measurement of reflux by a distal pH sensor.[32] This proves that heartburn symptoms are not a reliable indicator of GOR in achalasia patients and should not be used as a justification to perform a fundoplication procedure with myotomy.

Furthermore, the same author found that confirmed pathological acid reflux, present in only 13%of patients, does not conform to the usual Gastro-Oesophageal Reflux Disease (GORD) pattern. Reflux events in achalasia patients occur less frequently, are of a longer duration and happen

predominantly when the patient is supine.[33] This suggests that it is inadequate clearance of fermented food and/or refluxed acid, rather than true acid reflux, which is responsible for post-myotomy heartburn. This theory is strengthened by the finding, corroborated by Ellis, that the patients most likely to have such symptoms were those with the highest LOS pressures i.e. higher

resistance across the GO junction·[34] Thus a fundoplication procedure, aimed at increasing this resistance, could potentially worsen heartburn symptoms. Indeed, pathological acid reflux following myotomy with fundoplication has been found by Patti et al.(2001) and by Csendes et al.(1981) in 17% and 19% of patients respectively. This (shows that fundoplication clearly does not fully solve the problem of post-myotomy reflux. Bonavina et al (1992)., meanwhile, achieved a very impressive 8.6% incidence of reflux when myotomy was performed without an anti-reflux

procedure.[37]

Finally, the risk-benefit ratio of adding an anti-reflux procedure must be considered. Patti et al. noteed a risk of technical problems with a Dor fundoplication and suggest that these may be avoided by skilled surgery and meticulous attention to detail.35 However, surgeons may not perform these procedures with sufficient regularity to ensure this. A simpler procedure plainly reduces the risk of technical hitches.

As previously mentioned, Richards et al.(2001) report pathological acid reflux in 13% of patients

when myotomy is performed without an associated fundoplication.[33] Routine addition of an anti-reflux procedure would thus treat 87% of patients needlessly. This is particularly pointless when one considers the fact that medication frequently suffices to control reflux symptoms in this 13%. The dysphagia which results from an insufficiently lowered LOS pressure, meanwhile, requires far more drastic treatment measures, namely pneumatic dilatation or even further surgery.

Arguments in favour of an Anti-reflux procedure after oesophageal myotomy:

Iatrogenic GORD has only recently been given proper consideration and recognition. There are therefore a limited number of studies objectively documenting oesophageal acid exposure after treatment for achalasia. Those that are available reveal some interesting trends (Tables 1 and 2).

Table 1. Postoperative pH studies after transthoracic limited myotomy without fundoplication for the treatment of achalasia

Reference	Year	No. of patients	Postoperative pH positive result
Ellis et al.[32]	1984	103	8/19 (42%)
Shoenut J, Duerksen DA[40]	1997	15	6/15 (40%)
Patti et al.[28]	1997	10	6/10 (60%)
Total			20/44 (45%)

Table 2. Postoperative pH studies following laparoscopic myotomy and fundoplication for the treatment of achalasia

Reference	Year	No. of patients	Postoperative pH positive result
Bonavina et al.[45]	1995	193	7/81 (8.6%)
Mitchell et al.[46]	1995	14	0/5
Anselmino et al.[47]	1997	43	2/35 (5.7%)
Patti et al.[30]	1998	30	1/10 (10%)
Total			10/131 (7.6%)

Relevant to the "pro-anti-reflux procedure" argument is the fact that reflux-induced stricture after an oesophagea myotomy is a severe problem, and usually requires oesophagectomy for relief of symptoms.

Long-term data stress the need for anti-reflux protection. Malthaner et al. (1994) reported on long-

term clinical results in 35 patients with achalasia.[22] These patients had undergone primary oesophageal myotomy and Belsey hemifundoplication at Toronto General Hospital. The minimum follow up time was 10 years Excellent results were found in 95% of patients at 1 year, declining to 68% after 10 years. It was concluded that there was a deterioration of the initially good results after surgical myotomy and hiatal repair, and that most of the deterioration was due to the

complication of GOR.[38] In another study, Ellis reported his experience with transthoracic short oesophageal myotomy without an anti-reflux procedure. 179 patients were analysed at a mean follow-up of 9 years, ranging from 6 months to 20 years. Overall, 89 % of patients were improved at 9 years post-operatively. Ellis also noted deterioration in good results with time. The fact that his clinical data was similar to findings in the Toronto study suggests the likelihood that reflux

played a significant role in his results as well.[34]

Another relevant finding of several recent studies is that a post-treatment sphincter pressure of

less than 10mmHg is required for long term relief of dysphagia.[39,40] This is relevant because it shows that near complete disruption of the sphincter is required to relieve dysphagia in the long term.

In one of the largest studies reported yet, Bonavina et al. (1992) report good to excellent results with transabdominal myotomy and Dor fundoplication. 94% of 198 patients had excellent/good outcomes after a mean follow-up of 5.4 years. A remarkable 81% of patients returned for post-operative 24-hour pH studies, of which only 7 (8.6%) had a positive test result. Oesophageal diameter was significantly decreased post myotomy, as was LOS pressure (40.5 +/- 9.7 to 11.7

+/- 4.7 mmHg).[37]

Zaninotto et al. (2000) reported results in 100 patients who underwent a laparoscopic Heller-Dor procedure. 70% of patients reported no dysphagia and 22 % complained of only occasional difficulty swallowing. 7 patients were salvaged by post-operative pneumatic dilatation. Of note, 24-

hour oesophageal pH monitoring showed abnormal reflux in only 5 (6.5%) of 63 patients tested.[41]

These studies confirm that laparoscopic Heller-Dor fundoplication achieves excellent medium-term results.

Patti et al. (1999) compared the outcome of 30 patients who had undergone laparoscopic myotomy with a Dor anterior fundoplication to that of 30 patients who had undergone thoracoscopic myotomy without anti-reflux repair. Dysphagia was well-relieved by both the laparoscopic and thoracoscopic groups (77% and 70% success rates respectively). 20% of patients in the group who did not have a fundoplication had a positive post-operative 24-hour pH

study result compared to only 3% following the Heller-Dor procedure.[30]

CONCLUSION

GOR is uncommon in achalasia patients who have not undergone surgery and most evidence suggests that pH proved-reflux is minimised by the addition of a partial fundoplication to a myotomy. Studies show that abdominal myotomy combined with fundoplication provides excellent symptomatic outcomes in both the short- and the long-term in patients with achalasia. Perhaps it is better to perform a partial fundoplication with a myotomy in a single operation, and thereby reduce the risk of reflux, than to risk post-operative reflux, its complications and with them, further radical surgery.

On the other hand, why complicate a surgical procedure with addition of fundoplication when such an addition risks compromising the very outcome of the surgery (i.e. by re-increasing the LOS pressure reduced by the myotomy)? Also, the fundoplication procedure has not yet been definitely proven to prevent GOR and, in any case, may be unnecessary in the majority of patients.

It is evident that there is an urgent need for in-depth study of this question. Only a randomised controlled trial of Heller myotomy, with and without an anti-reflux procedure, including full patient evaluation by questionnaire, manometry and 24 hour pH studies can provide a satisfactory answer.

REFERENCES

1. Cohen S, Lipshutz W. Lower esophageal sphincter dysfunction in achalasia. Gastroenterology 1971; 61(6):814-20.
2. Castell DO. Achalasia and diffuse esophageal spasm.Arch Intern Med 1976; 136(5):571-9.
3. Niwamoto H, Okamoto E, Fujimoto J, et al. Are herpes virus or measles virus associated with esophageal achalasia? Dig Dis Sci 1995; 40(4):859-64.
4. Eckrich JD, Winans CS. Discordance for achalasia in identical twins. Dig Dis Sci 1979; 24(3):221-4.
5. Robertson CS, Martin BA, Atkinson M. Varicella-zoster virus DNA in the oesophageal myenteric plexus in achalasia. Gut 1993; 34(3):299-302.
6. Mayberry JF, Atkinson M. Studies of incidence and prevalence of achalasia in the Nottingham area. Q J Med 1985; 56(220):451-6.
7. Feldman M, Sleisenger MH, Scharschmidt BF. Sleisenger & Fordtrans Gastrintestinal and Liver Disease: Pathophysiology, Diagnosis and Management. 6th Ed. Philadelphia; London: WB Saunders; 1998

8. Cassella RR, Brown AL Jr, Sayre GP, et al. Achalasia of the esophagus: Pathologic and etiologic considerations. Ann Surg 1964; 160:474.

9. Csendes A, Smok G, Braghetto I, et al. Gastroesophageal sphincter pressure and histological changes in distal esophagus in patients with achalasia of the esophagus. Dig Dis Sci 1985; 30(10):941-5.

10. Higgs B, Kerr FWL, Ellis FH Jr. The experimental production of esophageal achalasia by electrolytic lesions in the medulla. J Thorac Cardiovasc Surg 1965; 50(5):613-25.

11. Patti MG, Diener U, Molena D. Esophageal achalasia: preoperative assessment and postoperative follow-up. J Gastrointest Surg 2001; 5(1):11-2.

12. Sivak MV Jr., Scleuterman DA. Gastroenterologic Endoscopy. 2nd Ed. Philadelphia; London: Saunders; 2000

13. Jankovic J. Botulinum toxin in movement disorders. Curr Opin Neural 1994; 7(4):358-66.

14. Pasricha PJ, Ravich WJ, Hendrix TR, et al. Intrasphincteric botulinum toxin for the treatment of achalasia. N Engl J Med 1995; 322(12):774-8.

15. Pasricha PJ, Rai R, Ravich WJ, et al. Botulinum Toxin for achalasia: long-term outcome and predictors of response. Gastroenterology 1996; 110(5):1410-5.

16. Swedlund A, Traube M, Siskind BN, et al. Nonsurgical management of esophageal perforation from pneumatic dilatation in achalasia. Dig Dis Sci 1989; 34(3):379-84.

17. Reynolds JC, Parkman HP. Achalasia. Gastroenterol Clin North Am 1989; 18(2):223-55.

18. Fennerty MB. Esophageal perforation during pneumatic dilatation for achalasia: a possible association with malnutrition. Dysphagia 1990; 5(4):227-8.

19. Scott HW Jr, DeLozier JB 3rd, Sawyers JL, et al. Surgical management of esophageal achalasia. South Med Journal 1985; 78(11):1309-13.

20. Pai GP, Ellison RG, Rubin JW, et al. Two decades of experience with modified Heller's myotomy for achalasia. Am Thorac Surg 1984; 38(3):201-6.

21. Vantrappen G, Hellemans J, Deloof W, et al. Treatment of achalasia with pneumatic dilatations. Gut 1971; 12(4):268-75.

22. Vantrappen G, Hellemans J. Treatment of achalasia and related motor disorders. Gastroenterology 1980; 79(1):144-54.

23. Csendes A, Velasco N, Braghetto I, et al. A prospective randomised study comparing forceful dilatation and esophagomyotomy in patients with achalasia of the esophagus. Gastroenterology 1981; 8(4):789-95.

24. Pellegrini C, Wetter LA, Patti M, et al. Thoracoscopic esophagomyotomy. Initial experience with a new approach for the treatment of achalasia. Ann Surg 1992; 216(3):291-9.

25. Swanstrom LL, Pennings J. Laparoscopic esophagomyotomy for achalasia. Surg Endosc 1995; 9(3):286-92.

26. Holzman MD, Sharp KW, Ladipo JK, et al. Laparoscopic surgical treatment of achalasia. Am J Surg 1997; 173(3):308-11.

27. Ancona E, Anselmino M, Zaninotto G, et al. Eesophageal achalasia: laparoscopic versus conventional open Heller-Dor operation. Am J Surg .1995; 170(3):265-70

28. Patti MG, Arcerito M, Tong J, et al. Importance of preoperative and postoperative pH monitoring in patients with esophageal achalasia. J Gastrointest Surg 1997; 1(6):505-510.

29. Stewart KC, Finley RJ, Clifton JC, et al. Thoracoscopic versus laparoscopic modified Heller myotomy for achalasia: efficacy and safety in 87 patients. J Am Coll Surg 1999; 189(2):164-170.

30. Patti MG, Arcerito M, De Pinto M, et al. Comparison of thoracoscopic and laparoscopic Heller myotomy for achalasia. J Gastrointest Surg 1998; 2(6): 561-6.

31. Ellis FH Jr, Crozier RE, Watkins E Jr. Operation for esophageal achalasia. Results of esophagomyotomy without an anti-reflux operation. J Thorac Cardiovasc Surg 1984; 88(3):344-51.

32. Richards WO, Clemments RH, Wang PC, et al. Prevalence of gastroesophageal reflux after laparoscopic Heller myotomy. Surg Endosc 1999; 13(10):1010-4.

33. Richards WO, Sharp KW, Holzman MD. An anti-reflux procedure should not routinely be added to a Heller myotomy. Journal of Gastrointestinal Surgery 2001; 5(1):13-16.

34. Ellis FH Jr. Oesophagmyotomy for achalasia: a 22-year experience. Br J Surg 1993; 80(7):882-5.

35. Patti MG, Pellegrini CA, Horgan S, et al. Minimally invasive surgery for achalasia: an 8 year experience with 168 patients. Ann Surg 1999; 230(4):587-94

36. Csendes A, Braghetto I, Mascaro J, et al. Late subjective and objective evaluation of the results of esophagomyotomy in 100 patients with achalasia of the esophagus. Surgery 1988; 104(3):469-75.

37. Bonavina L, Nosadini A, Bardini R, et al. Primary treatment of esophageal achalasia. Long-term results of myotomy and Dor fundoplication. Arch Surg 1992; 127(2):222-7.

38. Malthaner RA, Tood TR, Miller L, et al. Long term results in surgically managed esophageal achalasia. Ann Thorac Surg 1994; 58(5):1343-7.

39. Eckardt VF, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilatation. Gastroenterology 1992; 103(6):1732-8.

40. Ponce J, Garrigues V, Pertejo V, et al. Individual predictors of response to pneumatic dilation in patients with achalasia. Dig Dis Sci 1996; 41(11):2135-41.

41. Zaninotto G, Costantini M, Molena D, et al. Treatment of esophageal achalasia with laparoscopic Heller myotomy and Dor partial anterior fundoplication: prospective evaluation of 100 consecutive patients. J Gastrointest Surg 2000; 4(3):282-9.

Huntington's Disease: Pathogenesis and Treatment

Alison Hosey

INTRODUCTION

Huntington's disease (HD) is an autosomal, progressive and dominantly-inherited neurodegenerative disorder, characterised by abnormalities of movement, emotion and cognition. It claims its name from the physician, George Huntington, who first described the illness in 1872. The most important pathological feature is selective neuronal loss, primarily in the striatum and cerebral cortex. A major breakthrough occurred in 1993, with the discovery that the mutation causing the disease is the expansion of the CAG trinucleotide repeats in exon 1 of the gene

encoding the protein huntingtin.[1] CAG codes for the amino acid, glutamine, thus the mutation produces an expanded stretch of glutamine residues that are attached to the amino terminal of the huntingtin protein.

HD affects 4-10 per 100,000 individuals of Caucasian origin.[2] A HD genetic test is now available that can show if someone has inherited the mutation. There is usually a delayed onset of the disease with symptoms typically beginning between the ages of 35 and 50; however, the disease

may manifest itself from childhood to old age.[3] Disease onset is insidious. Early complaints include clumsiness, difficulty in balance, minor involuntary movements, lack of concentration and often a depressed or irritable mood. As the disease progresses, chorea (meaning "mad dance") becomes a prominent involuntary movement, along with difficulty in voluntary motor activities, weight loss and difficulties in speech. Cognitive deficits and psychiatric symptoms may prevent patients from fulfilling everyday responsibilities, e.g. retaining employment. Patients in the later stages of the disease generally have severe chorea, resembling monoclonic jerks and progressive disturbances in voluntary movement. Patients at this point are severely rigid, bed-ridden and largely non-verbal with global dementia. They often have difficulty swallowing, which can lead to death, either directly by suffocation or indirectly by starvation.

Death usually occurs 15-20 years after the onset of symptoms. Earlier death may occur as a direct result of the disease. The suicide rate in HD patients is 12.7%, which as indicated by epidemiological and phenomenological evidence, is a result of emotional depression and affective mood disorder caused by the disease rather than a direct reaction to changes in life circumstances. Premature death may also occur from a fall as a result of motor abnormalities. A small number of patients have been known to survive 3-4 decades after onset of the disease.

PATHOGENESIS

Genetics:

The gene for huntingtin is comprised of 67 exons in humans. It is located between the markers D4S127 and D4S180 on chromosome 4p16.3. The gene spans a genomic region of over 200kb.

Huntingtin is a 350kDa protein with no strong homology to known proteins.[3] In normal huntingtin, the number of CAG repeats ranges from 6 to 35, whereas with individuals with the dominant HD mutation, the repeat length varies from 36 to 121.

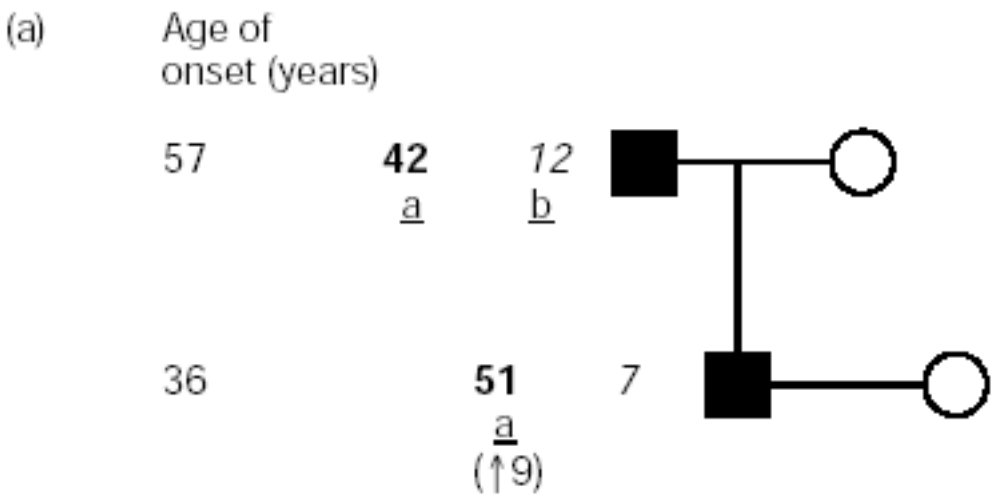
The age of onset of HD is inversely correlated with CAG repeat length. Adult onset generally occurs with repeat lengths of 36-50, while juvenile onset is often seen with greater than 60

repeats. In the past, it was thought that HD had full penetrance, that is, for individuals with the mutant allele the likelihood of them attaining the disease is 100%. However, it subsequently came to light that for individuals carrying an allele with 36-40 repeats there may be less than 100% penetrance and for repeats of 36-37 triplets, it may be in the order of 50%.

A feature that distinguishes the trinucleotide expansion is the non-Mendelian form of inheritance;

the repeat length can grow in each successive generation.[4] This phenomenon known as anticipation occurs with the expansions of the CAG repeat during paternal transmission. In clinical samples of affected parent-child pairs, there was no significant change in the age of onset with maternal transmission, but a mean advance of 8 years occurred with paternal transmission. The net result is a skew towards earlier ages of onset in successive generations of a family driven by paternal transmission.

Figure 1.



(a) Expansion in huntingtin decreases the age of onset in those affected. A representative two-generation pedigree of a HD family. Squares are males; circles are females. Black boxes indicate affected individuals. Numbers in bold represent the CAG repeat number in each allele of the affected family members. Small underlined letters represent the alleles present in father-to-son transmission. The italic green repeat number is a normal allele inherited from the mother. The number in brackets represents the size of the CAG expansion during inheritance.
(b) The relationship between HD pathology and CAG repeat number. In the schematic representation of the HD gene (left), the open bar represents the coding region, huntingtin. The small black bar indicates the position of the CAG repeat stretch located within the N-terminal portion of the coding sequence. The inverted triangle represents an increasing number of CAG repeats. The white base represents unaffected individuals with 6-29 CAG repeats with the black

area representing affected individuals with 36-120 repeats.[4]

Neuropathology:

HD post-mortem neuropathology shows a general atrophy of the brain, but the most prominent atrophy is found in the caudate nucleus and putamen (which together comprise the corpus striatum portion of the basal ganglia). In advanced cases, the total brain weight is reduced by 25-30%. Severe loss of medium spiny neurons, especially those synthesising enkephelin and

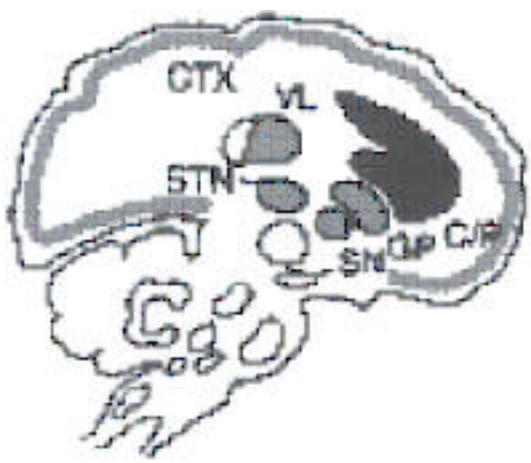
GABA, is most prevalent in the striatum.[3] Substantial neuronal loss is evident in the globus pallidus and subthalamic nucleus. Degeneration in the cerebral cortex is also found with

widespread loss of neurons, especially in layer VI, but also significantly in layers III and V. [5] Thus, the major degeneration, which normally occurs first in the striatum, leads to chorea, and the subsequent loss in the cerebral cortex causes dementia. Inclusion bodies comprised of huntingtin protein, found in the nucleus and cytoplasm in the neurons of HD patients and transgenic mice, indicate that these aggregates may play a major role in the pathogenesis of HD.

There is evidence of regenerative changes and plasticity in the diseased brain as it tries to

compensate for lost neurons.[3] Compared to control brains, surviving neurons in HD patients' brains have more dendrites, a greater density and larger size of dendritic spines, and a greater somatic area.

Figure 2. Affected Brain Regions



Dark regions indicate the major areas of neuronal loss in HD patients. (C/P = caudate/putamen, CTX = cortex, GP = globus pallidus, STN = subthalamic nucleus, VL = ventrolateral thalamic

nucleus, SN = substantia nigra.) [4]

Gain-of-function mutant huntingtin and loss of normal huntingtin function - a hypothesis of the pathogenesis of HD:

Wild-type or normal huntingtin protein is important for development. Mice with targeted deletions in the HD gene demonstrate developmental abnormalities rather than a progressive neurological

disorder. Embryos of huntingtin homozygous knock-out mice die by day 7.5.[6] Studies have shown that a single copy of the huntingtin gene is sufficient for correct brain development, regardless of the length of the CAG repeat. Thus, mutant huntingtin can substitute for its wild-type (normal) counterpart during development, consistent with the fact that homozygous HD patients do not present with developmental defects.

Mutant huntingtin, by virtue of the expanded polyglutamine moiety, has structural similarities to known transcription factors. One of the most specific antibodies recognising the expanded form of huntingtin is the IC2 antibody, originally raised against TATA-binding protein (TBP), (a transcriptional activator). Normal huntingtin is localised in the cytoplasm but mutant huntingtin, in addition to being found in the cytoplasm is localised in the nucleus. Although polyglutamine repeat length seems to be one feature governing nuclear entry of huntingtin, another is the length of the whole molecule. Shorter fragments of huntingtin are translocated to the nucleus more

efficiently with longer fragments tending to form aggregates in the cytoplasm.[7] This finding is

further supported using antibodies directed at the N-terminus of huntingtin, which can detect the inclusions in the nucleus, but antibodies directed at internal epitopes of huntingtin cannot detect the inclusions. Thus, it seems that huntingtin within the inclusions is a truncated N-terminal fragment. Another possibility is that the full-length huntingtin protein is misfolded so that the

internal epitopes are sequestered.[3] Popular hypothesis is that the full-length mutant protein is cleaved by caspases (the apoptotic proteases) to yield the N-terminal fragment before

translocating to the nucleus.[6]

Mutant huntingtin can recruit transcription factors into the inclusion bodies. For example, recruitment of CREB-binding protein (CBP), (a transcriptional co-activator), and TBP into aggregates has been shown in vitro as well as in human HD post-mortem brains. CBP has been identified as a critical component of neuronal responses to neurotrophins. It is therefore possible that the sequestration of CBP results in a diminished response to trophic factors, which are

essential to neuronal survival.[8] In addition, mutant huntingtin can recruit normal huntingtin into insoluble aggregates both in vitro and in vivo, suggesting that an important pathogenic effect might lie in the sequestration of normal huntingtin resulting in seclusion of its functions. Wild-type huntingtin has a protective anti-apoptotic effect in cells. One report indicates that the anti-apoptotic effects of huntingtin occur via sequestration of HIP1, a pro-apoptotic molecule

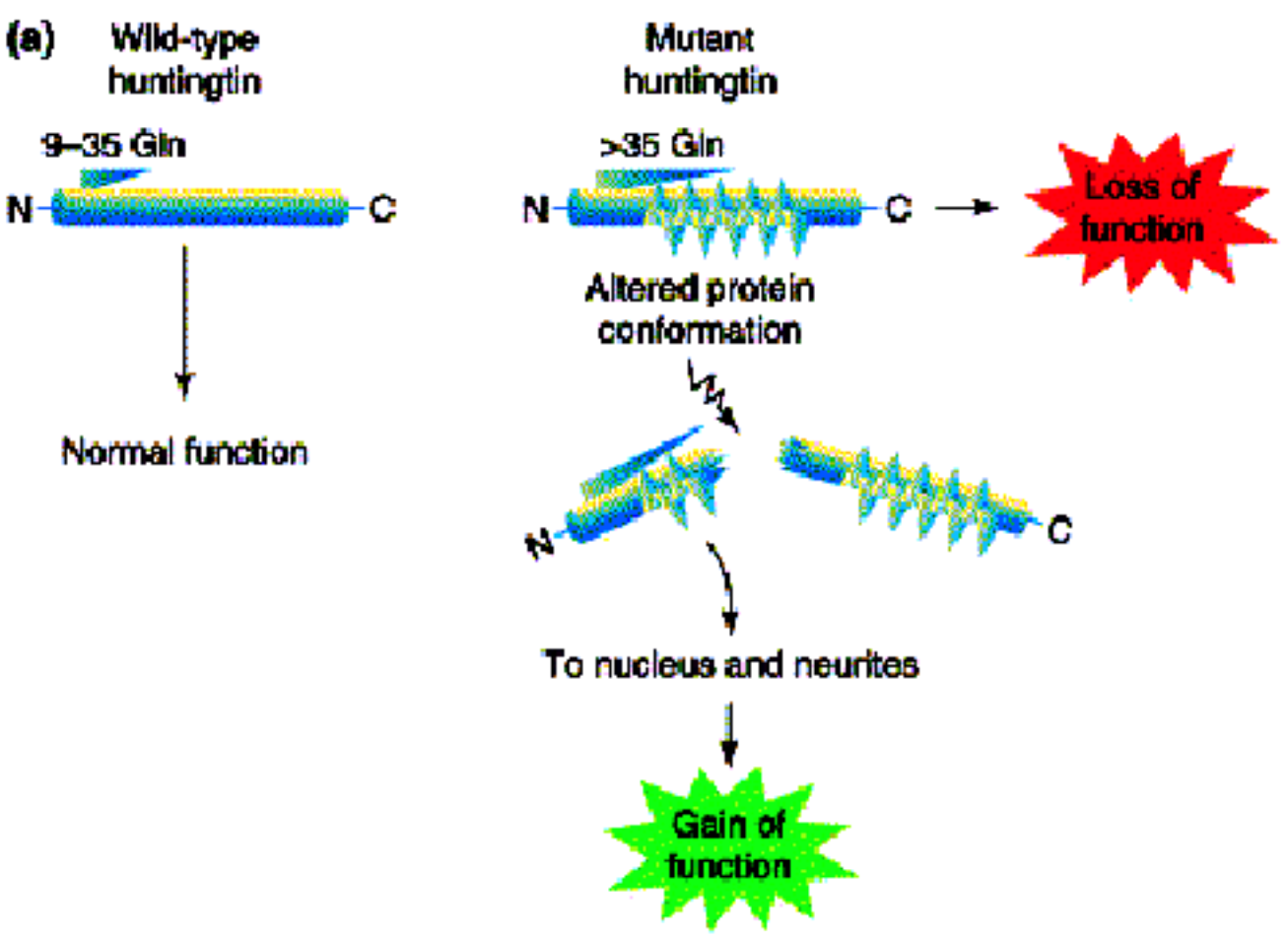
containing a novel-death effector domain.[6] It interacts efficiently with wild-type huntingtin but not with mutant huntingtin. Given the specific distribution of HIP1 in the brain, the researchers suggested that the inability of mutant huntingtin to modulate HIP1 contributes to the amplification cascade of cell death signals in HD. Thus, HD might be viewed as a double disease, that is, caused by both a new toxic property of the mutant protein and by a loss of the neuroprotective activity of normal huntingtin.

The huntingtin gene is expressed ubiquitously, not only throughout the brain but also in the peripheral tissues. But although peripheral abnormalities have been described, HD is primarily a disease of the CNS. The regional selectivity of the striatal medium spiny neurons to degeneration remains inadequately accounted for. The explanation could be that the genes whose transcription is altered by mutant huntingtin are especially relevant to neuronal function. Human HD and transgenic mouse models demonstrate downregulation of certain neurotransmitter receptor genes

that occur at the level of mRNA expression.[7] Therefore, it is possible that the mutant huntingtin exerts its toxic effects by affecting the expression of a set of genes that are important in neural and striatal functioning. The altered expression of this set of genes probably leads to the cellular dysfunction and eventual neuronal death that occurs in HD. In addition, it is thought that the neurotransmitter, dopamine, may have potentially toxic actions that contribute to the vulnerability

of the striatum.[9]

Figure 3. Potential mechanism of cell death in HD.



Processing of mutant huntingtin would generate an amino-terminal fragment that translocates into the nucleus and a carboxy-terminal portion that remains in the cytoplasm. Some full-length protein might also move into the nucleus, albeit with less affinity. The generation of amino-terminal fragments and inclusion bodies would coincide with increased toxic activity in cells. At the same time, (a) extension of the CAG repeat would cause a loss of function in the mutant protein and/or (b) the mutant protein could act negatively on the functions of the wild-type

protein.[6]

Mitochondrial dysfunction:

In cells expressing mutant huntingtin, mitochondria do not readily take up cationic dyes that

depend on intact charge gradients.[4] This data indicates that the mitochondrial membrane potential is impaired. 3-nitropropionic acid (3-NP) is an irreversible inhibitor of the enzyme, succinate dehydrogenase, which is found both in complex II of the mitochondrial respiratory chain and the citric acid cycle. In rats, systemic administration of 3-NP causes neurobehavioural and pathological abnormalities consistent with HD and in HD patients, the striatum has severe deficiencies in complexes II and III. In affected striatal and cerebral regions of the brain, glucose metabolism is decreased and precedes bulk tissue loss in HD patients. Taken together, these data point towards impairment in mitochondrial function as a contributing factor in HD.

THERAPIES

To alleviate symptoms:

The CARE-HD (Coenzyme Q10 and Ramacemide Evaluation in HD) is an NIH funded study involving 347 HD patients treated over a five-year period with a combination of Coenzyme Q10 (CoQ10) and Ramacemide hydrochloride (R). CoQ10 is an essential co-factor of the electron transport chain, as well as a potent free radical scavenger in lipid and mitochondrial membranes. R is a non-competitive, low affinity NMDA receptor antagonist that was successfully used in mouse models of epilepsy. In transgenic mouse models, high doses of dietary supplements of CoQ10/R enhanced motor performance, albeit transiently, and weight gain was evident compared to placebo controls. However, similar studies in humans to date did not achieve statistical

significance compared with placebo.[10]

In HD patients, magnetic resonance imaging confirms that creatine (a free radical scavenger, a

substrate for the enzyme creatine kinase and a precursor for ATP) is depleted.[4] Due to the possible role of energy dysregulation in pathogenesis, creatine was examined for possible neuroprotective effects in two transgenic mouse models of HD. The researchers found that creatine delays weight loss, improves motor performance, reduces the formation of intracellular

inclusions, delays striatal atrophy and significantly improves survival.[8] However, in human clinical trials efficacy has yet to be proven.

Caspases are cysteine proteases that play an important role in the execution of programmed cell death (apoptosis). It has been suggested that the aggregations of mutant huntingtin might induce

activation of important initiator caspases-8, -9, and -10.[11] Initiator caspases are responsible for cleavage and activation of downstream effector caspases, such as caspase-3. In cell-culture models, transcripts of huntingtin in which the caspase cleavage sites are mutated, demonstrate less nuclear localisation and show increased survival·[7] Caspase-3 cleavage of mutant huntingtin generates the small N-terminal fragment that forms nuclear inclusions. Such cells readily undergo apoptosis. Caspase inhibitors might provide protection by blocking a general cell death

pathway and/or by preventing the formation of the toxic N-terminal fragment.[4] Caspase inhibitors have been shown to exert neuroprotective effects and significantly improve survival in transgenic HD mice. One such inhibitor is minocycline, which is a derivative of the antibiotic tetracycline that crosses the blood-brain-barrier and inhibits caspases 1 and 3. Clinical trials are ensuing.

Potential cures:

Inhibition of protein expression of the mutant allele is one approach being taken. This inhibition is expected to be beneficial only if expression from the normal allele is preserved. Anti-sense oligonucleotides targeting the methionine initiation codon and exon 1 (the –25 to +35 region of the promotor) can inhibit expression of the stable incorporated green-fluorescent-huntingtin in a

cultured cell line to roughly half that of untreated cells·[4] Whether this is sufficient to rescue cell survival during long-term culture remains to be seen, and more importantly, whether it will be effective in targeting neural tissue in whole animals.

In animal HD models, behavioural signs analogous to HD can be improved by transplantation of embryonic striatal tissue into the degenerated striatum. In primates, striatal grafts have been shown to survive and improve motor function. In a report by Freeman et al. (2000), the post-mortem histological analysis of foetal striatal grafts implanted in the striatum of one patient who

died 18 months after implantation from reasons unrelated to surgery, were described.[12] The authors demonstrated that immature foetal striatal tissue could survive and differentiate into mature striatal tissue in the HD brain. Notably, the disease process did not appear to induce HD-like neurodegeneration within the cell implants and there was no evidence of immune rejection of

the cell implants by the host. These neuropathological results are timely because a French team, working in parallel, found in a pilot study that striatal grafts produce long-lasting motor, cognitive

and functional benefits in grafted HD patients.[13] Thus, striatal transplantation may be a viable treatment for HD.

CONCLUSION

For each new observation of the mechanism of HD, there is a possible therapeutic intervention. Thus, to broaden the therapeutic perspectives, it is important to identify all possible routes of disease manifestation. Many hypotheses exist today based on recent laboratory and clinical studies for the pathogenesis of HD, from mitochondrial dysfunction to loss of wild-type huntingtin function and to the deleterious functioning of mutant huntingtin. Thus, the rapid advances in understanding the pathogenesis, experimental therapeutics and neural transplantation predict a bright future for finding a cure for this devastating disease.

REFERENCES

1. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosome. Cell 1993; 72:971-983.
2. Reddy PH, Williams M, Tagle DA. Recent advances in understanding the pathogenesis of Huntington's disease. Trends Neurosci 1999; 22(6):248-255.
3. Ross CA, Margolis RL. Huntington's disease. Clin Neurosci 2001; 1:142-152.
4. McMurray CT. Huntington's disease: new hope for therapeutics. TINS 2001; 24:S32-S38.
5. Bradford HF. Chemical neurobiology: an introduction to neurochemistry. New York: W.H. Freeman & Company, 1986.
6. Cattaneo E, Rigamonti D, Goffredo D. Loss of normal huntingtin function: new developments in huntingtin's disease research. Trends Neurosci 2001; 24(3):182-188.
7. Cha JJ. Transcriptional dysregulation in Huntington's disease. Trends Neurosci 2000; 23(9):387-392.
8. Beal MF, Hantraye P. Novel therapies in the search for a cure for Huntington's disease. Proc Natl Acad Sci USA 2001; 98(1):3-4.
9. Jackel RJ, Maragos WF. Neuronal cell death in Huntington's disease: a potential role for dopamine. Trends Neurosci 2000; 23:239-245.
10. Schilling G, Coonfield ML, Ross CA, et al. Coenzyme Q10 and ramacemide hydrochloride ameliorate motor deficits in a Huntington's disease transgenic mouse model. Neurosci Lett 2001; 315(3):149-153.
11. Rigamonti D, Sipione S, Goffredo D, et al. Huntingtin's neuroprotective activity occurs via inhibition of procaspase-9 processing. J Biol Chem 2001; 276:14545–14548.
12. Freeman TB, Cicchetti F, Hauser RA, et al. Transplanted fetal striatum in Huntington's disease: Phenotypic development and lack of pathology. Proc Natl Acad Sci USA 2000; 97(25):13877-13882.
13. Bachoud-Levi AC, Remy P, Nguyen JP, et al. Motor and cognitive improvements in patients with Huntington's disease after neural transplantation. Lancet 2000; 356(9246):1975-1979.