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EDITORIAL

Paroxysmal atrial fibrillation: why patients experience different symptoms from the same arrhythmia?

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ABSTRACT

A careful evaluation and interpretation of the symptoms of the patient with atrial fibrillation should be the first step in selecting a treatment modality. Arrhythmia burden is not equal to symptoms. Some patients will have and continue to have symptoms not related to the occurrence of arrhythmias. Recognition of these patients is important in the treatment of atrial fibrillation.

KEYWORDS

Arrhytmia, atrial fibrillation, thromboembolic symptoms

The success of treatment in a patient with atrial fibrillation depends on a subtle balance between the evaluation and interpretation of the symptoms due to atrial fibrillation in that specific patient and the prevention of thromboembolic complications.

Prevention of thromboembolic complications has recently become quite simple. An indication for oral anticoagulation is present if a patient has a high-risk profile: age above 75 years, or age <75 years with left ventricular hypertrophy and hypertension, a previous transient ischaemic attack or cerebrovascular accident and/or diabetes mellitus. Once the criteria for anticoagulation are met, the patient will have a lifelong need for treatment, irrespective of the rhythm (sinus or paroxysmal, persistent or permanent atrial fibrillation). It can be said: 'once atrial fibrillation, always atrial fibrillation'. The patient with lone atrial fibrillation (no structural heart disease) below the age of 65 should either have no preventive treatment or low-dose aspirin since the risk of thromboembolic complications is very low.[1-3]

Evaluation of the symptoms of atrial fibrillation should be done systematically. Is the patient having palpitations: are they fast or mainly irregular or does the patient feel both? When does he/she have these palpitations? Is there a relation with exercise or body position (lying, sitting or standing)? Is chest pain or chest discomfort present and when is this feeling most prominent. Is there dizziness or (near) syncope? Is polyuria present when the patient has palpitations? Is there a feeling of fatigue after the atrial fibrillation has stopped and how long does this feeling remain present? Sometimes to your surprise the patient with atrial fibrillation has none of the above-mentioned symptoms at all and the discovery of atrial fibrillation is coincidental. This especially occurs in the elderly patient on routine check-up.
The most invalidating symptom of atrial fibrillation is a decrease in exercise tolerance. This may vary from a diminished peak exercise (during sport/bicycling) to intolerance for slight exercise (walking a flight of stairs or even just walking). Generally, the younger the patient, the more prominent the decrease in exercise tolerance will be.

Whether the treatment of atrial fibrillation will be successful depends on an appropriate interpretation of the patient's symptoms. Why is this so complicated? Patients with clear symptoms of atrial fibrillation do not only have symptomatic episodes of atrial fibrillation but will also have many asymptomatic episodes of atrial fibrillation. This may

even amount to up to 70% of the total burden of atrial fibrillation! In general it might be the case that there is no clear correlation between the number of attacks of atrial fibrillation and the patient's symptoms. Some have recurrent attacks of atrial fibrillation but hardly notice them, or at least are not limited in their daily functioning by these attacks. Others have one or two short-lasting episodes of atrial fibrillation and cannot function in their work or in their social environment! Is this related to the type of personality?
In this issue Van den Berg *et al*. report on whether traits of the personality may be helpful in evaluating the success of treatment of atrial fibrillation.[4] They investigated whether neuroticism is more frequently present in patients with atrial fibrillation in comparison with age-matched controls. A high score on the neuroticism scale indicates persons who are anxious and may have vague complaints about their health. In the present study patients were included with paroxysmal atrial fibrillation with 'lone atrial fibrillation' or atrial fibrillation in the setting of hypertension. Nearly 70% were males.

Interestingly, they found no differences in the degree of neuroticism in the study group as a whole in comparison with the age- and sex-matched control group. So patients with paroxysmal atrial fibrillation have, on average, a 'normal' degree of neuroticism.[4] However, in those persons with a high level of neuroticism, social functioning and mental health scored low. This caused a clear negative impact on the quality of life. This negative impact even seemed to be independent of the presence or absence of atrial fibrillation! In other words: if the arrhythmia burden in patients can be diminished this may not necessarily lead to improvement of quality of life in a patient with a high degree of neuroticism. Evaluation of any intervention for the social functioning and mental health in these patients will be difficult if it is possible at all.

Evaluation and interpretation of the symptoms of patients with atrial fibrillation should be done meticulously. Which symptoms have the greatest negative impact on the patient's quality of life and what are the patient's expectations? One should take time to make a proper evaluation. Only then the appropriate therapy can be selected and both physician and patient can be satisfied with the treatment option that has been selected.

REFERENCES

1. Rockson SG, Albers GW. Comparing the guidelines: anticoagulation therapy to optimize stroke prevention in patients with atrial fibrillation. JACC 2004;43:929-35.
2. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834-40.
3. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
4. Van den Berg MP, Ranchor AV, van Sonderen FLP, van Gelder IC, van Veldhuisen DJ. Paroxysmal atrial fibrillation, quality of life and neuroticism. Neth J Med 2005;63:170-4.

Smeets. Paroxysmal atrial fibrillation.

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REVIEW

Hepatitis C virus and human immunodeficiency virus coinfection: where do we stand?

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ABSTRACT

Both human immunodeficiency virus (HIV) and hepatitis C (HCV) are globally infecting millions of people. Since these viruses are both transmitted through blood-blood contact the rate of coinfection is as high as 30% and among iv drug users in the Western world 70%. In the Netherlands, 8% of HCV-infected patients are coinfected with HIV. After the successful introduction of antiretroviral therapy (HAART) the survival of patients with HIV has increased considerably. Coinfection leads to accelerated progression of liver cirrhosis and liver failure but conflicting evidence exists about the effect of HCV on the natural course of HIV. Four randomised controlled trials have shown that treatment with pegylated interferon plus ribavirin leads to an overall sustained viral response (SVR) rate between 27 and 44%. Divided by genotype the SVR is between 14 and 38% in genotype 1 (and 4) while between 53 and 73% for genotype 2 and 3. These percentages are calculated based on an intention-to-treat analysis. Although lower than in HCV-monoinfected patients this is much higher than achieved with conventional interferon. However, coinfected patients with genotypes 2 and 3 also need to be treated for 48 weeks in contrast to monoinfected patients. As the number and severity of side effects is low, coinfected patients now have a substantially better option for treatment.

KEYWORDS

Hepatitis C, human immunodeficiency virus, treatment, viral kinetics

INTRODUCTION

Hepatitis C virus (HCV) is a global health problem with an estimated 170 million people (3% of the total population) infected with this virus worldwide.[1] In the United States nearly four million and in Europe more than five million people are infected with hepatitis C.[2,3] At least 20% of these patients are expected to develop cirrhosis of the liver and approximately 25% of them will eventually die from hepatic failure or require liver transplantation.[4,5] At the end of 2003 the human immunodeficiency virus (HIV) had infected an estimated 37.8 million people worldwide causing devastating economic, social and cultural problems.[6] HIV (a retrovirus) and HCV (a flavivirus) are both RNA viruses. Both viruses are transmitted through blood-blood contact while transmission of HIV is much more effective through sexual intercourse than HCV.[7] Coinfection among patients is as high as 30% both in Europe and the United States.[8-10] The group of patients most at risk in the Western world is iv drug users, where the prevalence of coinfection is as high as 80 to 90%.[11-13] Among 6000 HIV positive patients in the Netherlands only 8% have HCV antibodies.[14] Due to a widespread needle exchange and education programme the rate of coinfection is lower than in other parts of Europe.[15]

Since the introduction of highly active antiretroviral therapy (HAART) in 1996, the survival of patients with HIV has increased considerably.[16,17] The mortality caused by opportunistic infections has declined shifting the focus of treatment to cardiovascular and liver-related pathology. Coinfection of HCV and HIV is leading to long-term complications of liver disease such as cirrhosis, liver failure and hepatocellular carcinoma. In this subgroup of patients it is becoming a serious problem with a high morbidity

and currently the leading cause of death among coinfected patients.[18,19]

In recent years, with the introduction of pegylated interferon, the treatment of hepatitis C has undergone major changes. The enhanced bioavailability leading to a prolonged serum half-life, allowing once-weekly administration, results in a higher sustained virological response (SVR) than with conventional interferon.[20,21] An SVR is defined as an undetectable HCV-RNA (<50 U/ml) at 24 weeks of follow-up after 48 weeks of treatment.

In a recent publication by Vrolijk *et al.*[22] in this journal, an excellent overview of the current treatment modalities for hepatitis C (non-coinfected) infected patients was given. Recently a few trials have been published on the treatment of hepatitis C in coinfected patients.[23-26]

The focus of this paper will be on the current available knowledge of virological interaction, viral kinetics and treatment in coinfected patients.

VIROLOGICAL INTERACTION BETWEEN THE TWO VIRUSES

The progression of hepatitis C monoinfection to cirrhosis and hepatocellular carcinoma is known to be slow, taking decades to develop. This depends on individual variables such as duration of infection, age at time of infection, male sex, amount of alcohol consumption, metabolic disorders and HIV coinfection.[27-34]

Effects of HIV infection on the natural history of liver cirrhosis

Multiple studies have examined the effects of HIV infection on the natural history of chronic hepatitis C infection. This is mostly studied in patients with haemophilia since HAART only became widely available eight years ago. An advantage of studying rates of progression in patients with haemophilia is that the date of HCV exposure is often known. Patients with haemophilia, coinfected with HCV and HIV, develop hepatic decompensation or liver failure more frequently than haemophiliacs with hepatitis C only (8 and 14% *vs* 0 and 1%).[35,36]

Graham *et al.*[37] performed a meta-analysis of eight studies looking at histological proven cirrhosis (n=4) or decompensated liver disease (n=2) or both (n=2) in both iv drug users and patients with haemophilia. The combined adjusted relative risk (RR) was 2.14 (95% CI 1.15-3.97) demonstrating that coinfected patients progress faster to hepatic cirrhosis. Also the risk of decompensated liver disease increased sixfold. Other authors have shown that coinfection leads to a higher rate of hepatocellular carcinoma and that progression to liver failure is shortened to six to ten years.[38-42] One explanation for this faster progression could be the immune compromised state of these patients. Bonnacini[43] has shown in a summary of six previous articles that the rate of progression is inversely correlated to the CD4 count. A CD4 cell count lower than 500 cells/mm^3 is associated with in an increased risk for advanced fibrosis (OR 3.2, 95% CI 1.1-9.9).[44] The accelerated progression of fibrosis is more significant among patients with lower CD4 counts.[45] It can also be postulated that the difference in progression rate in hepatitis C is caused by the different HCV genotypes. However, two large studies have shown no effect of HCV genotype on fibrosis progression.[46,47] A further two studies show that genotype 1 is closely associated with more severe histological liver damage[48] and an increase in liver-related deaths.[49]

Effects of HIV and HAART on HCV load

It is known that HCV/HIV coinfected patients have a higher HCV-RNA concentration than HCV-monoinfected patients. Spontaneous clearance of HCV occurs in 20% of cases in monoinfected patients *vs* 5 to 10% for coinfected patients.[50] The immune response to hepatitis C is important in clearing the virus from the blood. This is done by CD4+ T helper cells, cytotoxic T lymphocytes and production of interferon.[51] With HIV infection CD4+ lymphocytes show defective proliferation and apoptosis resulting in an impaired host immune response to HCV-infected cells leading to a higher HCV-RNA concentration.[52]

As stated above, the amount of CD4 cells is a prognostic variable for progression to liver cirrhosis. Therefore the effect of highly active antiretroviral therapy (HAART) on disease progression is interesting. Given the fact that HAART increases the number of CD4+ T cells (immune reconstitution), it can be postulated that progression to liver cirrhosis should halt. However, it is known that the total HCV-RNA load in untreated patients does not correlate with progression of liver cirrhosis. There are conflicting data on this immune reconstitution phenomenon. A retrospective study in France[53] shows a favourable effect of protease inhibitor (PI) therapy on the progression of liver fibrosis. A total of 63 patients were treated with PIs compared with 119 PI-naive patients. The cirrhosis rates were 2 *vs* 5%, 5 *vs* 18% and 9 *vs* 27% (p=0.0006) calculated at 5, 15 and 25 years, respectively. This effect was not seen in patients on nucleoside-based regimes only. An observational study by Qurishi *et al.*[54] based on a twelve-year follow-up showed in a Kaplan-Meier analysis that patients treated with HAART have a lower liver-related mortality. Recently, Mariné-Barjoan *et al.*[55] showed that treatment with HAART had a favourable effect on liver fibrosis in coinfected patients. These observations favour the early initiation of antiretroviral therapy in coinfected patients to stimulate immune reconstitution and thus viral suppression leading to slower progression of liver disease. Interestingly, HAART-treated patients have a significantly greater increase in HCV-RNA load than patients treated with antiretroviral therapy (only nucleosides) or untreated patients. In contrast, Martin-Carbonero *et al.*[45] found that immune reconstitution caused by antiretroviral therapy has no effect on the accelerated progression of liver fibrosis. In the later studies HCV-RNA load was found to increase after initiation of HAART and it steadily increase over time. These observations raise questions about the possible mechanism of antiviral therapy halting progression of liver cirrhosis. Many questions still remain to be answered.

Effects of HCV on HIV

Conflicting results have also been reported about the effect of chronic hepatitis C on progression of the natural history of HIV infection. Together with two early studies[56,57] Greub *et al.*[11] showed in the Swiss cohort that HCV/HIV-coinfected patients progressed faster to AIDS and death then patients with HIV infection only. The authors also noted a blunted CD4 cell response after initiation of HAART. In contrast, in a prospective study of 1995 HIV-positive patients in the USA, no difference was detected in progression to an AIDS-defining illness, progression to a CD4 cell count below 200/µl or survival between coinfected or HCV-negative patients.[58] Moreover no difference was detected in the probability of experiencing a CD4 cell count increase of more than 50 cells/mm^3 between coinfected and HCV-negative patients one, two and three years after initiation of HAART. Three more studies, European and American, also showed no difference in increased progression to an AIDS-defining illness or death between HCV positive or negative patients.[9,59,60] Soriano *et al.*[61] concluded in their recent review that HCV might act as a co-factor in HIV-positive patients by immune stimulation and possibly CD4 depletion causing a blunt response to antiretroviral therapy. However, they observed that the evidence was really poor.

VIRAL KINETICS

Lessons learned from viral kinetics in HIV have generated an enormous amount of research into HCV dynamics. HCV has a high replication rate of 1 x 10^{12} virions/day and a half-life of only three hours.[62,63] Viral load levels of HCV remain relatively stable over time but are higher in HIV-infected patients.[64,65] The decline in HCV-RNA after initiation of interferon (INF) and ribavirin treatment on both monoinfected and coinfected patients shows a biphasic pattern (*figure 1*).[66,67] This first phase is rapid and occurs within 24 to 48 hours after the start of treatment. At that time the viral production and release of HCV is blocked. This reflects the sensitivity of the virus to interferon.[66] The second phase is slower and more variable in time, reflecting the rate of immune-mediated clearance of HCV-infected cells. In genotypes 2 and 3 the slope in the first and second phase is steeper than for genotypes 1 and 4 resulting in a higher SVR after treatment.[67] The steepness of the slope in both phases is a good predictor for achieving SVR after treatment. With conventional interferon dosing needs to be frequent because of the short serum half-life leading to large fluctuations in serum concentrations and therefore less steepness of the slope in both phases. The chemical modification of IFN by the covalent attachment of a polyethylene glycol (PEG) molecule results in a changed pharmacodynamic profile. The prolonged half-life results in a higher steady serum concentration of INF resulting in a steeper first and second phase.

In coinfected patients the second phase seems to be less steep then in hepatitis C monoinfected patients.[68] In contrast, two studies found no biphasic pattern in the majority of patients. Talal *et al.*[69] administered conventional interferon monotherapy to 12 coinfected patients while achieving an early virological response in only three patients and a sustained virological response in one patient. Torriani *et al.*[70] analysed a substudy of the APRICOT trial using pegylated interferon. No biphasic pattern was seen in nine out of ten patients coinfected with HIV and HCV. Recently a triphasic model of viral kinetics has been reported by Hermann *et al.*[71] In 34 patients with chronic hepatitis C, they found the typical first phase, a flattened or slowed second phase and a third phase in 61% of patients. The rate of decline during this third phase was significantly faster in those patients receiving ribavirin. Therefore, Herrmann hypothesised that this third phase may be a result of the addition of ribavirin leading to an upregulation of the immune system by ribavirin. In a recent study on the antiviral action of ribavirin in hepatitis C, this effect was not noted.[72] The exact role of ribavirin in the viral decay needs further study.

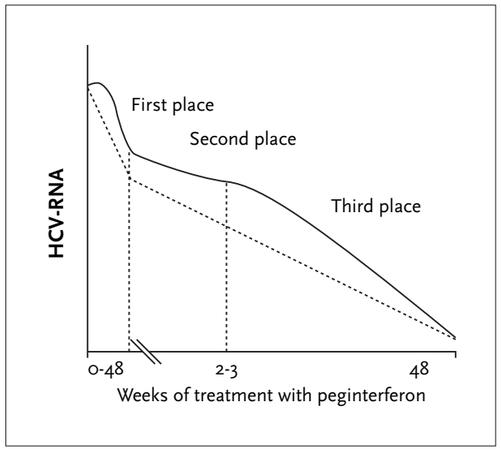

Figure 1
A schematic picture of a biphasic model for HCV monoinfected patients and of the recently reported triphasic model for HCV/ HIV coinfected patients
Straight line for coinfected patients and dashed line for HCV monoinfected patients.

TREATMENT OF COINFECTED PATIENTS

The treatment of coinfected patients with HCV and HIV is challenging because of the low response rates to interferon and ribavirin. Therapy with interferon-based regimes are known to cause significant side effects such as flu-like symptoms and general symptoms of fatigue, malaise and weight loss.[20,73,74] Psychiatric disorders, particularly depression, occur with an incidence of 20 to 30% affecting treatment adherence and sometimes requiring interferon dose reduction or discontinuation.[75] Also autoimmune thyroiditis is reported to occur with a relative risk of 4.4.[76] Therefore, patients should be carefully instructed about the occurrence of the above-mentioned side effects and followed up closely by their physicians.

Clinical trials

Recently two studies were published in the New England Journal of Medicine, one study in AIDS and one study in the JAMA describing the result of peginterferon alpha-2a (Pegasys) or alpha-2b (Pegintron) with ribavirin in coinfected patients with HCV and HIV. Results of sustained virological response are summarised in *table 1*. The first is the APRICOT study (AIDS Pegasys Ribavirin International Coinfection trial),[23] a randomised multicentre placebo-controlled blinded trial with 868 patients. Patients were assigned to either IFN alpha-2a plus ribavirin, PEG-IFN plus placebo or PEG-IFN plus ribavirin 800 mg. Irrespective of the genotype all patients were treated for 48 weeks followed by a 24-week observation period. All patients were HIV positive and had a CD4 cell count >200 cells/mm^3 or between 100 to 199 cells/mm^3 but than with a viral load of <5000 copies per ml. HAART had to be stable six weeks prior to entry with no changes expected within the next eight weeks. Thereafter changes in antiretroviral therapy were permitted. The SVR was 12% for the conventional interferon plus ribavirin group, 20% for the peginterferon group and 40% for the peginterferon plus ribavirin group. A multiple logistic-regression model resulted in two variables independently increasing the odds of achieving SVR. Those were an HCV genotype other than 1 (OR 3.37, CI 1.96-5.80) and baseline HCV-RNA levels of less than 800,000 IU (OR 3.56, CI 2.00-6.36). Parameters related to HIV infection, such as CD4 cell count and use of HAART, were not significant. Serious adverse events were low between 5 and 10% and not statistically significant among the treatment arms. Grade 4 haematological abnormalities were more frequent in the peginterferon groups. HCV treatment resulted in a slightly lower CD4 cell count but the percentage of cells was not affected.

The second trial is the ACTG 5071[24] trial which included 133 patients who were randomised to peginterferon alpha-2a (Pegasys) plus ribavirin in a dose-escalation schedule from 600 mg/day to 1000 mg/day or IFN plus dose-escalated ribavirin. As with the other trials a high percentage of genotype 1 was noted (78%). Patients had a well-controlled HIV infection with a mean CD4 count of 475 cells/mm^3 and 86% received HAART. The overall SVR was 27% for the peginterferon group *vs* 12% for the conventional interferon group. Divided by genotype, differences in SVR with peginterferon were as expected, 73% for genotypes 2 and 3 while only 14% for genotype 1. Again side effects and adverse events were similar in both arms. Premature treatment discontinuation was 12% in both groups mainly because of depression and abnormal laboratory values. One case of clinical pancreatitis was noted leading to discontinuation of treatment. This patient was receiving didanosine. Similar to the APRICOT study no effect of HCV therapy on HIV progression was noted, with even a slight increase in the percentage of CD4 cells.

Laguno *et al.*,[26] in a small single-centre study, reported their results of peginterferon alpha-2b (Pegintron) plus ribavirin compared with interferon alpha-2b plus ribavirin in 95 patients. The dose of ribavirin was adjusted to body weight with 600 mg when the body weight was <60 kg, 1000 mg when it was 60 to 75 kg and 1200 mg when it was >75 kg. Both groups were treated for 48 weeks. Twenty-one patients (22%) with genotype 2 or 3 and a HCV-RNA load below 800,000 IU were treated with peginterferon (n=14) or conventional interferon (n=7) only for 24 weeks. Of the patients, 88% received antiretroviral therapy and the mean CD4 count was 560 x 10^6/l. The SVR was 44% in the peginterferon group *vs* 21% in the interferon group with the SVR higher on treatment. In the peginterferon group genotypes 1 and 4 reached an SVR of 38 *vs* 53 and 47% for genotypes 2 and 3. No further remarks were made about the difference in duration of treatment in relation to the SVR. Altogether, 15% of the treated patients, nine in the peginteferon group and five in the interferon group, discontinued treatment because of serious adverse events such as flu-like symptoms, psychiatric disorders, lactic acidosis and severe anaemia. Haematological abnormalities required dose modification in 13% of patients with anaemia, while with neutropenia and thrombocytopenia this was 9 and 3%, respectively. In both treatment arms this did not reach statistical significance.

The RIBAVIC trial[25] with 416 patients is a randomised controlled study of PEG-IFN alpha-2b (Pegintron) plus ribavirin 800 mg *vs* conventional IFN plus ribavirin 800 mg. The incidence of iv drug use was 79%. Of the treated patients, 82% received antiretroviral therapy with a nucleoside reverse transcriptase inhibitor (NRTI) backbone. The overall reported SVR was 27 *vs* 20% and varied with genotype; genotypes 1 and 4 being 17% and genotypes 2 and 3 being 44%. In the later genotypes no significant difference was noticed between the reached SVR between peginterferon and conventional interferon. Adverse events were similar in both groups and treatment discontinuation was as high as 39%. Symptomatic mitochondrial toxicity, including symptomatic hyperlactatemia, lactic acidosis and acute pancreatitis, occurred in 11 patients (3%) nine of whom were on peginterferon. All these patients received didanosine.

Table 1
Treatment characteristics

	SUSTAINED VIROLOGICAL RESPONSE				
	SVR OVERALL		SVR PEG-INF + RIBAVIRIN		
REFERENCE	INF + RIBAVIRIN	PEG-INF + RIBAVIRIN	GENOTYPE 1 AND 4	GENOTYPE 2 AND 3	SIDE EFFECTS/ADVERSE EVENTS
APRICOT[23]	12%	40%	29%	62%	Grade 4 haematological abnormalities more frequent in the peginterferon groups; AEs in all groups between 5-10%; CD4 cells decreased in all groups but percentage increased slightly
ACTG[24]	12%	27%	14%	73%	Similar frequency of side effects in both groups; 12% prematurely discontinue treatment in both arms
Laguno *et al.*[26]	21%	44%	38%	53%	15% prematurely discontinue treatment with 9 in PEG-INF arm and 5 in INF arm; AEs not statistically significant among treatment groups
RIBAVIC[25]	20%	27%	17%	44%	AEs 33% (65 INF and 62 PEG); treatment discontinuation 39% (73 INF and 76 PEG); no significant decrease in CD4 cells

What can be learned?

Comparing these four trials is difficult because of the different brands of interferon, the baseline characteristics of the participants, sample size and the dose of ribavirin. Also the duration of treatment in genotypes 2 and 3 differed with 48 weeks in the APRICOT study while only 24 weeks for patients with a low HCV-RNA load in the study by Laguno *et al.* One interesting observation is the wide range in reported SVR. It is not yet clearly understood why the overall SVR in the APRICOT trial and the study by Laguno is 40 to 44 *vs* 27% in the RIBAVIC and ACTG trials. One explanation might be the difference in black patients between the different trials (33% in the ACTG trial *vs* 10% in the APRICOT trial while no numbers are mentioned in the other two trials). The brand of interferon does not explain the differences because both the higher and the lower SVR were achieved with both peginterferons. Currently a head-to-head study with both Pegasys and Pegintron (IDEAL study) is ongoing, but results will not become available for years. Another point is the difference in dosing regime of ribavirin. In the ACTG study a dose-escalated range is used because of fear for haematological side effects caused by ribavirin. The investigators also allowed the use of haematological growth factors. Laguno *et al.* used much higher doses of ribavirin up to 1200 mg (weight based) without reporting more adverse haematological events while not using granulocyte colony stimulating factor or erythropoietin. In chronic hepatitis C monoinfection the preferred dose of ribavirin is weight-based 1000 to 1200 mg/day.[73] Recently, the PRESCO study was published by Nunez *et al.*[77] treating coinfected patients with peginterferon alpha-2a and ribavirin 1000 to 1200 mg for 12 or 18 months for genotypes 1 and 4, and 6 or 12 months for genotypes 2 and 3. An overall viral response (ITT) after 48 weeks of treatment of 63% was reported with viral response of 50 and 44% for genotypes 1 and 4, respectively. Data on the impact of extended periods of therapy on SVR are not yet available. Exclusion criteria as mentioned above were also used in this study, only patients with higher CD4 counts of >300 cells/µl were accepted for treatment. The authors conclude that proper selection of patients, good monitoring and compliance and higher doses of ribavirin lead to an SVR in coinfected patients approaching those of HCV-monoinfected patients. Therefore, in view of the low reported haematological side effects, the optimal treatment dose of ribavirin appears to be 1000 to 1200 mg/day weight-based, especially in patients infected with genotypes 1 and 4.

The concept of an early virological response (EVR) published by Davis *et al.*, defined as a 2 $\log_{10}$ decline in HCV-RNA load or undetectable levels of HCV-RNA at week 12 of therapy, safely predicts those patients who will reach SVR and those who will not.[78] Patients who fail to achieve an EVR will not clear the virus and will not reach a SVR. So they are being treated with peginterferon unnecessarily, at a high cost and at risk considering the possible adverse events. Treatment is therefore stopped at week 12. In the APRICOT, ACTG and RIBAVIC trials this stopping rule is confirmed with only two out of 85 patients, none of 63 patients and one of 159 patients, respectively, not achieving an EVR at 12 weeks but reaching a sustained virological response at the end of treatment.

In the four mentioned studies exclusion criteria applicable as contraindications to treatment were signs of decompensated liver cirrhosis, a major depression and signs of an autoimmune disease. Also, if patients had a CD4 count below 100 per mm^3, anaemia, thrombocytopenia or low neutrophil counts they were not eligible for treatment.

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Therefore, these patients should only be treated cautiously with peginterferon and ribavirin, and monitored closely. Another important issue is the interaction between ribavirin and antiretroviral therapy. Ribavirin, a nucleoside analogue, is known to inhibit mitochondrial polymerase gamma and to promote the intracellular conversion of didanosine to its active metabolite thereby leading to an increased and cytotoxic level of didanosine.[79] The clinical syndrome of mitochondrial toxicity is symptomatic hyperlactataemia, lactic acidosis and pancreatitis. There is accumulating evidence warning against the concomitant use of didanosine and ribavirin.[79-81] Although not reported in the APRICOT trial, the other three trials confirm that this combination leads to the clinical syndrome of mitochondrial toxicity. The same mechanism of action can account *in vitro* for other nucleoside analogues such as zidovudine and stavudine but this has so far not been proven to be clinically significant.[79,82]
In conclusion, patients with HVC genotype 1 and HIV coinfection treated with PEG-IFN plus weight-based ribavirin 1000 to 1200 mg/day can achieve an overall SVR between 27 to 44% as compared with standard IFN plus RBV. These sustained virological response rates are lower compared with the SVR in patients only infected with HCV. Although side effects are numerous and therapy is demanding for both patients and physicians, treatment with peginterferon and ribavirin is currently the best option for coinfected patients. For genotypes 2 and 3, in contrast to monoinfected patients, a duration of therapy of 48 weeks is currently advised. The most common side effects of treatment are flu-like symptoms and depression, but this does not usually lead to treatment discontinuation. Adverse events are mild to moderate and can be treated with dose modification or with the use of haematological growth factors.

Where do we stand?

So where do we stand in treating hepatitis C and HIV coinfected patients? Over the last years knowledge about viral kinetics, viral interaction and treatment in coinfected patients is accumulating rapidly. This results in a better virological insight into how these viruses interact and in how to treat this subgroup of patients safely and successfully. There is still debate about the exact impact of HCV on the natural course of HIV and about the effects of HAART on HCV-RNA levels. In contrast, it is clear that coinfection with HIV leads to a faster progression of liver cirrhosis in hepatitis C infected patients. With numbers of patients increasing, it is vital that better treatment options are found.
The current optimal treatment strategy is pegylated interferon in combination with ribavirin for 48 weeks. There is still debate about the optimal dose of ribavirin in view of liver toxicity. The right time to start treatment is another key question to be resolved in the near future. What is emerging from these studies is that patients are eligible for treatment when they have moderate disease meaning a CD4 cell count above 200 cells/mm^3, a stable regime of HAART without didanosine and signs of portal fibrosis or more (but not decompensated liver disease) on liver biopsy. There is still debate about when to start treatment in coinfected patients with no signs of fibrosis or only showing signs of inflammation. According to the British guidelines[83] there are two options, namely defer treatment and repeat a liver biopsy in two to three years time or start treating hepatitis C. Considering the increased progression rate to cirrhosis and fibrosis in coinfected patients some experts in the field advocate starting hepatitis C treatment in this category of patients as soon as possible preferably before starting HAART. On the other hand cure rates are low, side effects often occur and only one treatment modality is currently available. International standards are currently not available. It is generally agreed that a CD4 cell count lower than 200 cells/mm^3 is a contraindication for hepatitis C treatment and that first the effect of HAART should be awaited. Also patients with decompensated liver cirrhosis are not candidates for treatment because peginterferon is contraindicated in this subgroup of patients. Treatment modalities are changing rapidly. Analogue to the antiretroviral therapy in HIV patients, new nucleoside analogues and protease inhibitors are being developed. They will be introduced into clinical practice within the coming years.

REFERENCES

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345(1):41-52.
2. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341(8):556-62.
3. Trepo C, Pradat P. Hepatitis C virus infection in Western Europe. J Hepatol 1999;31(suppl 1):80-3.
4. National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 1997;26(3 suppl 1):S2S-10.
5. Seeff LB, Hoofnagle JH. Appendix: The National Institutes of Health Consensus Development Conference Management of Hepatitis C 2002. Clin Liver Dis 2003;7(1):261-87.
6. UNAIDS. Report on the Global AIDS Epidemic. 2004.
7. Terrault NA. Sexual activity as a risk factor for hepatitis C. Hepatology 2002;36(5 suppl 1):S99-105.
8. Soriano V, Rodriguez-Rosado R, Garcia-Samaniego J. Management of chronic hepatitis C in HIV-infected patients. AIDS 1999;13(5):539-46.
9. Staples CT Jr, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. Clin Infect Dis 1999;29(1):150-4.
10. Waldrep TW, Summers KK, Chiliade PA. Coinfection with HIV and HCV: more questions than answers? Pharmacotherapy 2000;20(12):1499-507.

11. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet 2000;356(9244):1800-5.
12. Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clin Infect Dis 2002;34(6):831-7.
13. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. JAMA 2002;288(2):199-206.
14. Ruys TA, Reesink HW, Lange JM. [Coinfection with hepatitis C virus and HIV]. Ned Tijdschr Geneeskd 2003;147(42):2056-60.
15. Hepatitis B and Hepatitis C in the EuroSIDA Cohort: Prevalence and Effect on Mortality, AIDS Progression and Response to HAART. 11th Conference on retroviruses and opportunistic infections; San Francisco, CA: 2004.
16. Detels R, Tarwater P, Phair JP, Margolick J, Riddler SA, Munoz A. Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. AIDS 2001;15(3):347-55.
17. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338(13):853-60.
18. Monga HK, Rodriguez-Barradas MC, Breaux K, et al. Hepatitis C virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. Clin Infect Dis 2001;33(2):240-7.
19. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis 2001;32(3):492-7.
20. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347(13):975-82.
21. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358(9286):958-65.
22. Vrolijk JM, de Knegt RJ, Veldt BJ, Orlent H, Schalm SW. The treatment of hepatitis C: history, presence and future. Neth J Med 2004;62(3):76-82.
23. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004;351(5):438-50.
24. Chung RT, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med 2004;351(5):451-9.
25. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA 2004;292(23):2839-48.
26. Laguno M, Murillas J, Blanco JL, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS 2004;18(13):F27-36.
27. Datz C, Cramp M, Haas T, et al. The natural course of hepatitis C virus infection 18 years after an epidemic outbreak of non-A, non-B hepatitis in a plasmapheresis centre. Gut 1999;44(4):563-7.
28. Mathurin P, Moussalli J, Cadranel JF, et al. Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal alanine transaminase activity. Hepatology 1998;27(3):868-72.
29. Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. Am J Gastroenterol 2002;97(9):2408-14.
30. Pessione F, Degos F, Marcellin P, et al. Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. Hepatology 1998;27(6):1717-22.
31. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349(9055):825-32.
32. Poynard T, Ratziu V, Benmanov Y, Di M, V, Bedossa P, Opolon P. Fibrosis in patients with chronic hepatitis C: detection and significance. Semin Liver Dis 2000;20(1):47-55.
33. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J Hepatol 2001;34(5):730-9.
34. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. Hepatology 1998;28(3):805-9.
35. Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr 1993;6(6):602-10.
36. Telfer P, Sabin C, Devereux H, Scott F, Dusheiko G, Lee C. The progression of HCV-associated liver disease in a cohort of haemophilic patients. Br J Haematol 1994;87(3):555-61.
37. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis 2001;33(4):562-9.
38. Benhamou Y, Bochet M, Di M, V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology 1999;30(4):1054-8.
39. Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology 2001;34(6):1193-9.
40. Garcia-Samaniego J, Rodriguez M, Berenguer J, et al. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. Am J Gastroenterol 2001;96(1):179-83.
41. Lesens O, Deschenes M, Steben M, Belanger G, Tsoukas CM. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. J Infect Dis 1999;179(5):1254-8.
42. Verucchi G, Calza L, Manfredi R, Chiodo F. Human immunodeficiency virus and hepatitis C virus coinfection: epidemiology, natural history, therapeutic options and clinical management. Infection 2004;32(1):33-46.
43. Bonacini M, Puoti M. Hepatitis C in patients with human immunodeficiency virus infection: diagnosis, natural history, meta-analysis of sexual and vertical transmission, and therapeutic issues. Arch Intern Med 2000;160(22):3365-73.
44. Puoti M, Bonacini M, Spinetti A, et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and human immunodeficiency virus. J Infect Dis 2001;183(1):134-7.
45. Martin-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. Clin Infect Dis 2004;38(1):128-33.

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46. Pol S, Fontaine H, Carnot F, Zylberberg H, et al. Predictive factors for development of cirrhosis in parenterally acquired chronic hepatitis C: a comparison between immunocompetent and immunocompromised patients. J Hepatol 1998;29(1):12-9.
47. Puoti M, Bonacini M, Spinetti A, et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and human immunodeficiency virus. J Infect Dis 2001;183(1):134-7.
48. Garcia-Samaniego J, Soriano V, Castilla J, et al. Influence of hepatitis C virus genotypes and HIV infection on histological severity of chronic hepatitis C. The Hepatitis/HIV Spanish Study Group. Am J Gastroenterol 1997;92(7):1130-4.
49. Yee TT, Griffioen A, Sabin CA, Dusheiko G, Lee CA. The natural history of HCV in a cohort of haemophilic patients infected between 1961 and 1985. Gut 2000;47(6):845-51.
50. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected patient. Clin Liver Dis 2003;7(1):179-94.
51. Freeman AJ, Marinos G, French RA, Lloyd AR. Immunopathogenesis of hepatitis C virus infection. Immunol Cell Biol 2001;79(6):515-36.
52. Fauci AS, Schnittman SM, Poli G, Koenig S, Pantaleo G. NIH conference. Immunopathogenic mechanisms in human immunodeficiency virus (HIV) infection. Ann Intern Med 1991;114(8):678-93.
53. Benhamou Y, Di M, V, Bochet M, et al. Factors affecting liver fibrosis in human immunodeficiency virus- and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy. Hepatology 2001;34(2):283-7.
54. Qurishi N, Kreuzberg C, Luchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet 2003;362(9397):1708-13.
55. Marine-Barjoan E, Saint-Paul MC, Pradier C, et al. Impact of antiretroviral treatment on progression of hepatic fibrosis in HIV/hepatitis C virus co-infected patients. AIDS 2004;18(16):2163-70.
56. Dorrucci M, Pezzotti P, Phillips AN, Lepri AC, Rezza G. Coinfection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. Italian Seroconversion Study. J Infect Dis 1995;172(6):1503-8.
57. Wright TL, Hollander H, Pu X, et al. Hepatitis C in HIV-infected patients with and without AIDS: prevalence and relationship to patient survival. Hepatology 1994;20(5):1152-5.
58. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. JAMA 2002;288(2):199-206.
59. Haydon GH, Flegg PJ, Blair CS, Brettle RP, Burns SM, Hayes PC. The impact of chronic hepatitis C virus infection on HIV disease and progression in intravenous drug users. Eur J Gastroenterol Hepatol 1998;10(6):485-9.
60. Llibre JM, Garcia E, Aloy A, Valls J. Hepatitis C virus infection and progression of infection due to human immunodeficiency virus. Clin Infect Dis 1993;16(1):182.
61. Soriano V, Puoti M, Sulkowski M, et al. Care of patients with hepatitis C and HIV co-infection. AIDS 2004;18(1):1-12.
62. Layden TJ, Lam NP, Wiley TE. Hepatitis C viral dynamics. Clin Liver Dis 1999;3(4):793-810.
63. Neumann AU, Lam NP, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science 1998;282(5386):103-7.
64. Gordon SC, Dailey PJ, Silverman AL, Khan BA, Kodali VP, Wilber JC. Sequential serum hepatitis C viral RNA levels longitudinally assessed by branched DNA signal amplification. Hepatology 1998;28(6):1702-6.
65. Nguyen TT, Sedghi-Vaziri A, Wilkes LB, et al. Fluctuations in viral load (HCV RNA) are relatively insignificant in untreated patients with chronic HCV infection. J Viral Hepat 1996;3(2):75-8.
66. Ferenci P. Predicting the therapeutic response in patients with chronic hepatitis C: the role of viral kinetic studies. J Antimicrob Chemother 2004;53(1):15-8.
67. Zeuzem S. The kinetics of hepatitis C virus infection. Clin Liver Dis 2001;5(4):917-30.
68. Soriano V, Nunez M, Camino N, et al. Hepatitis C virus-RNA clearance in HIV-coinfected patients with chronic hepatitis C treated with pegylated interferon plus ribavirin. Antivir Ther 2004;9(4):505-9.
69. Talal AH, Shata MT, Markatou M, et al. Virus dynamics and immune responses during treatment in patients coinfected with hepatitis C and HIV. J Acquir Immune Defic Syndr 2004;35(2):103-13.
70. Torriani FJ, Ribeiro RM, Gilbert TL, et al. Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) dynamics during HCV treatment in HCV/HIV coinfection. J Infect Dis 2003;188(10):1498-507.
71. Herrmann E, Lee JH, Marinos G, Modi M, Zeuzem S. Effect of ribavirin on hepatitis C viral kinetics in patients treated with pegylated interferon. Hepatology 2003;37(6):1351-8.
72. Pawlotsky JM, Dahari H, Neumann AU, et al. Antiviral action of ribavirin in chronic hepatitis C. Gastroenterology 2004;126(3):703-14.
73. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha-2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140(5):346-55.
74. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358(9286):958-65.
75. Hauser P. Neuropsychiatric side effects of HCV therapy and their treatment: focus on IFN alpha-induced depression. Gastroenterol Clin North Am 2004;33(suppl I):S35-50.
76. Prummel MF, Laurberg P. Interferon-alpha and autoimmune thyroid disease. Thyroid 2003;13(6):547-51.
77. Nunez M, Maida I, Berdun MA, et al. Efficacy and safety of pegylated interferon alpha-2a plus ribavirin for the treatment of chronic hepatitis C in HIV-coinfected patients: the PRESCO trial. Washington, DC, Program and abstracts of the 44th Interscience Conference of Antimicrobial Agents and Chemotherapy.
78. Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. Hepatology 2003;38(3):645-52.
79. Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. Clin Infect Dis 2004;38(8):e79-80.
80. Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. Lancet 2001;357(9252):280-1.
81. Bruno R, Sacchi P, Filice G. Didanosine-ribavirin combination: synergistic combination in vitro, but high potential risk of toxicity in vivo. AIDS 2003;17(18):2674-5.
82. Landau A, Batisse D, Piketty C, Jian R, Kazatchkine MD. Lack of interference between ribavirin and nucleosidic analogues in HIV/HCV co-infected individuals undergoing concomitant antiretroviral and anti-HCV combination therapy. AIDS 2000;14(12):1857-8.
83. Nelson M, Matthews G. British HIV Association (BHIVA) guidelines for treatment and management of HIV and Hepatitis C coinfection. http://www.bhiva.org/guidelines/2004/HCV/index.html. 2004.

ORIGINAL ARTICLE

Blood glucose awareness training in Dutch type 1 diabetes patients: one-year follow-up

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ABSTRACT

Background: American studies have shown positive effects of Blood Glucose Awareness Training (BGAT) on the recognition of hypoglycaemia. We evaluated the effects of BGAT among Dutch patients, and compared individual training with training in the original group format.
Methods: Fifty-nine type 1 diabetes patients participated in BGAT in either a group (n=37) or an individual (n=22) setting. Before and one year after training they performed up to 70 measurements, two to four a day, at home on a handheld computer. During each measurement they estimated their blood glucose (BG), indicated whether they would be participating in traffic and raised their BG on the basis of their estimation, and then measured their BG. The incidence of severe hypoglycaemia and traffic accidents was also assessed.
Results: BGAT had positive effects on hypoglycaemic awareness, decisions not to drive and to raise the blood glucose during hypoglycaemia, severe hypoglycaemic episodes and traffic accidents. The accuracy of BG estimations only improved after group training, while after individual training patients tended to measure more or more extremely high BG values.
Conclusion: The training improved awareness of hypoglycaemia, and seems worthy of implementation in the Netherlands.

KEYWORDS

Awareness, driving, hypoglycaemia, handheld computers, traffic accidents, training

INTRODUCTION

In type 1 diabetes mellitus, intensive insulin therapy is effective in delaying late complications of the diabetes,[1] but also increases the frequency of hypoglycaemia.[2] Timely recognition and correction of hypoglycaemia is important to avoid severe hypoglycaemic episodes. A quarter of the patients with type 1 diabetes have difficulty recognising hypoglycaemia in time,[3] they suffer from 'reduced hypoglycaemic awareness'.
Cox *et al.*[4-9] developed 'Blood Glucose Awareness Training' (BGAT) to help patients recognise, correct, anticipate and prevent blood glucose (BG) values outside of the normal range. During eight group sessions, information is provided on autonomic symptoms, neuroglycopenic symptoms, mood symptoms, hyperglycaemic symptoms, and the influence of stress, food, insulin and exercise on the BG. Participants exchange experiences and do exercises, for instance to examine the effect of neuroglycopenia on cognitive and motor performance. In between the sessions, patients keep a symptom diary to examine the relationship between their personal symptoms and blood glucose levels. They estimate their BG level before measuring it, and get direct feedback on the accuracy of their estimation from a coloured grid with safe and dangerous estimation zones. In the short term, BGAT improved the ability to estimate BG levels[5,7-9] and the detection of hypoglycaemia[5] in American samples. A Dutch adaptation of BGAT improved BG estimations, the number of hypoglycaemic readings, and fear of hypoglycaemia directly after the training.[10] In the longer term (12 months or more), BGAT reduced the number of road traffic accidents,[4,6] while positive effects on other measures (such as hypoglycaemia detection) were maintained.[4] There were no differences between the effects six months and 12 months after BGAT.[4] The present study evaluated the effects of a Dutch adaptation of BGAT-III (3rd version of BGAT),[11] and compared training in the original group format with individual training, which may be more easily incorporated into the hospital routine, and more tailored to an individual patient's situation, preferences and concerns. Shortly after BGAT, only handheld computer measures were collected. We observed no significant effects on the recognition of hypoglycaemia or any other measure, with the exception of wiser decisions to raise the BG and not to drive during hypoglycaemia.[12] Aims of the present study were to assess the effects of BGAT one year after training on (handheld computer) measures of BG perception, decisions not to drive and to raise the BG during hypoglycaemia; diabetes regulation; and on (questionnaire) measures of hypoglycaemia related worry, severe hypoglycaemia, and self-monitoring of the blood glucose (SMBG). We furthermore assessed possible differences between the effects of individual and group BGAT.

MATERIALS AND METHODS

Patients

Patients in the sample participated in a research project on reduced hypoglycaemic awareness.[13] They were diagnosed with type 1 diabetes mellitus before the age of 40 and at least two years prior to invitation, had become insulin dependent within 18 months after diagnosis, used multiple injections a day or continuous subcutaneous insulin infusion (CSII), were under 65 years of age, and had no serious physical or psychological comorbidity. All 123 patients in the original sample were invited to participate in the training. Baseline characteristics of participants and those who declined participation are displayed in *table 1*.

Participants were a mean of five years older (p=0.05) and had more impaired hypoglycaemic awareness than patients who did not participate in BGAT (p=0.00-0.03).

The intervention

BGAT-III was adapted and translated into Dutch by the Dutch Psychosocial Diabetology Working Group.[11] The original eight classes were reduced to six weekly sessions. The chapters on food, insulin and exercise were integrated into one chapter, as it was assumed that these topics were covered well enough by the standard diabetes education available for every patient in the Netherlands.
Group BGAT was offered in the evenings, to small groups of five to nine patients, by a diabetes educator and a psychologist. The six weekly sessions lasted 1.5 to 2 hours. Individual BGAT was offered in the daytime, and consisted of up to six 30-minute sessions with a diabetes educator. While the same manual was used for both interventions, individual training was more tailor-made: topics of specific importance to an individual patient received more attention, and appointments were scheduled in accordance with the patient.

Procedure

Patients were interviewed at the hospital, completed questionnaires, and a blood sample was sent to the laboratory for HbA_{1c} assessment (HPLC technique).[15] They then performed up to 70 handheld computer (HHC, Psion P-250, Hoofddorp, the Netherlands) measurements at home, two to four measurements a day, over a four to six week period.

Table 1
Mean (SD) baseline characteristics

	NO TRAINING (N=64)[a]	GROUP BGAT (N=37)	INDIVIDUAL BGAT (N=22)	P TRAINING *VS* NO TRAINING[b]	P GROUP *VS* INDIVIDUAL[b]
Age (years)	39.3 (11.8)	43.7 (9.2)	42.5 (11.1)	0.05	0.65
Gender	45% male	68% male	50% male	0.08	0.18
Education[c]	5.1 (2.2)	5.6 (1.9)	4.8 (2.1)	0.74	0.14
Duration of DM (years)	20.2 (10.9)	23.9 (9.4)	21.3 (12.1)	0.17	0.36
HbA_{1c} (%)	7.9 (1.4)	7.5 (1.4)	7.5 (1.0)	0.11	0.93
Neuropathy[d]	1.4 (1.7)	1.4 (1.8)	1.3 (1.4)	0.86	0.84
CSII	6%	11%	5%	0.64	0.40
Hypo awareness 0-10[e]	6.4 (2.8)	4.0 (2.4)	5.2 (2.7)	0.00	0.09
BG level of detecting hypo[e]	3.7 (1.0)	2.7 (1.0)	2.7 (0.8)	0.00	0.97
Accuracy index[f]	19.0 (22.5)	7.7 (15.4)	13.1 (16.2)	0.01	0.21
Recognised hypoglycaemia[f] (%)	45.6 (31.0)	31.7 (22.8)	34.8 (25.6)	0.03	0.67
No. of severe hypos last year[e]	3.0 (6.2)	6.6 (7.0)	6.6 (6.9)	0.03	0.98

[a]Participants who did not receive blood glucose awareness training (BGAT) were not included in the present study (see discussion). [b]Significance of independent sample t-test, except for gender and CSII: significance of χ^2 test. [c]Educational level ranged from 1 (primary school) to 8 (university). [d]Three cardiovascular function tests were used: heart rate response to standing up, heart rate response to deep breathing and blood pressure response to standing up.[14] A higher score reflects more severe autonomic neuropathy. [e]Self-report.[14] [f]Handheld computer data.

They were instructed to perform these HHC measurements when they habitually checked their blood glucose, and when they expected their blood glucose to be high or low. During every HHC measurement, they estimated their BG, indicated whether they would raise their BG and whether they would participate in traffic on the basis of their estimation, and then determined their blood glucose level. They were lent a One Touch Profile blood glucose memory meter (Lifescan, Beerse, Belgium) to obtain uniform measurements. The study was not randomised because of practical considerations. Resources were limited, and some patients were not able to attend the group meetings during the evenings, while others were unable to attend individual sessions during the day. Therefore patients chose either group or individual BGAT, conform clinical practice. After BGAT, patients again performed HHC measurements and one year after BGAT they were asked to perform HHC measurements and to again complete questionnaires. All participants gave their written informed consent, and the Medical Ethics Committee of Leiden University Medical Centre (LUMC) approved the study.

Outcome measures

Handheld computers

Only handheld computer (HHC) measurements that were not preceded by another measurement within two hours were used to calculate the aggregated HHC measures. Only data of patients with at least 30 measurements were used.

- Accuracy index (AI): This measure was developed, used and described by Cox *et al.*[4-9] It reflects the clinically relevant accuracy of blood glucose estimations on the HHC. The AI ranges from -100% to +100%, higher values indicate higher accuracy.
- Percentage of recognised hypoglycaemic episodes: The percentage of estimates below 3.9 mmol/l or within 20% of the measured BG, when the actual BG was lower than 3.9 mmol/l.
- Percentage of recognised hyperglycaemic episodes: The percentage of estimates above 10 mmol/l or within 20% of the measured BG when the actual BG was above 10 mmol/l.
- Low blood glucose index (LBGI):[16,17] The LBGI reflects the number and/or extent of low BG readings on the handheld computer. BG values >6.25 mmol/l receive a weighting of zero, while values of 6.25 mmol/l receive progressively increasing weights, until 100 at a BG of 1.1 mmol/l. These weights are then averaged. A higher LBGI reflects more frequent, or more severe, hypoglycaemia.
- High blood glucose index (HBGI):[16,17] The HBGI reflects the number and/or extent of high BG readings on the HHC. It is calculated in the same way as the LBGI, but now readings <6.25 mmol/l receive zero weighting, and readings at 6.25 mmol/l progressively increasing weighting, up to 100 at a BG of 33.3 mmol/l. A higher HBGI reflects more frequent, or more severe, hyperglycaemia.
- Blood glucose risk index (BGRI):[16,17] LBGI + HBGI. The BGRI increases with the number and/or extent of extreme BG values (HHC).
- Judgement on driving during hypoglycaemia: The percentage of decisions to drive while the actual BG was below 3.6 mmol/l.
- Judgements on raising the BG during hypoglycaemia: The percentage of decisions to raise the BG (HHC) while the actual BG was below 3.9 mmol/l.

Questionnaire measures

- Frequency of self-monitoring of the blood glucose (SMBG) was assessed by the open questions: 'How many days of the week do you measure your BG? On these days, how often do you measure your BG?' The mean number of measurements a day was calculated.
- Frequency of severe hypoglycaemic episodes during the preceding year was assessed by the open question: 'During the last year, how often did you experience a severe hypoglycaemic episode during the day which you were unable to correct by yourself?' The same question was asked about episodes during the night. The numbers of episodes during the day and night were added up.
- Fear of hypoglycaemia (HFS): The Hypoglycaemia Fear Survey (HFS-95) worry subscale[18,19] is a validated measure of hypoglycaemia-related worry. Patients answer 13 items on a 0 (never) to 4 (always) scale. Scores range from 0 to 52, high scores reflect increased worry about hypoglycaemia.
- Traffic accidents: 'During the previous 12 months, how often have you been involved in a traffic accident?' (open question)

Statistics

SPSS 6.0 was used to analyse the data. All variables were normally distributed, except for SMBG. Nonparametric tests were used for this variable. Descriptive statistics and frequencies were used to describe the sample. T-tests (Mann-Whitney U) and χ^2 tests were used to assess differences between participants *vs* nonparticipants and patients in group *vs* patients in individual training. Repeated measures analysis (2 (time: pre BGAT *vs* one year after BGAT) x 2 (treatment: group *vs* individual training) ANCOVA, with the baseline value as a covariate) was used to assess the significance of change over time and the possible differential effect of individual and group treatment. P<0.05 was considered significant. When the time x treatment interaction was significant, post hoc within-group comparisons were made, by means of paired t-tests.

RESULTS

Fifty-nine patients participated in BGAT, 37 in a group and 22 in an individual setting. Baseline characteristics of the participants were displayed in *table 1*. No baseline differences between patients in group training *vs* patients in individual training emerged, but there was a trend for patients in individual training to self-report higher awareness of hypoglycaemia (p=0.09). Differences between them at more objective measures of hypoglycaemic awareness did not reach significance.

Handheld computer data

Valid handheld computer measurements both at baseline and at follow-up were completed by 36 patients (61%; 24 group, 12 individual). *Table 2* shows baseline and follow-up HHC data and HbA_{1c}, the significance of change after BGAT (time effect), and the significance of the differential effect of the two treatment conditions (interaction term).

After BGAT, the percentage of recognised hypoglycaemic episodes (p=0.02), decisions not to drive during hypoglycaemia (p=0.01) and decisions to raise the BG during hypoglycaemia (p=0.02) improved.
The change in scores after group and individual BGAT differed significantly for two measures: the accuracy index (p=0.04) and the high blood glucose index (p=0.03). Post hoc comparisons showed that the accuracy index improved after group BGAT (5.3 to 18.8, p=0.005), but not after individual BGAT (13.6 to 11.7, p=0.75). The high blood glucose index tended to deteriorate after individual BGAT (HBGI 11.4 to 13.4, p=0.09), but not after group BGAT (10.7 to 9.9, p=0.25).

Questionnaire data

Questionnaires were returned by 49 patients (83%, 31 group, 18 individual). *Table 3* shows their baseline and follow-up scores on the questionnaire variables, the significance of change after BGAT (time effect), and the significance of the differential effects of the two treatment conditions (interaction term).

After BGAT, the number of severe hypoglycaemic episodes decreased (p=0.001), patients more often performed self-monitoring of the BG (SMBG, p=0.000), and patients were less often involved in a traffic accident (p=0.04) than before training. There were no significant differences between the effects of individual or group BGAT on the questionnaire measures.

DISCUSSION

To our knowledge, this is the first study to assess long-term effects of BGAT in a European sample. American long-term studies on the effects of BGAT reported improved detection of high and low BG readings; wiser judgments concerning BG corrections and not driving during hypoglycaemia; reduced ketoacidosis, severe hypoglycaemia, and traffic accidents; improved quality of life and diabetes knowledge and reduced worry about hypoglycaemia one year after the training;[4] fewer car crashes at a mean of five years after the training;[6] and improved BG estimations and hypoglycaemic awareness a mean of five years after training when patients had received a booster training.[6] The present study partly replicated these positive results, despite a modest sample size. We observed significant

Table 2

Mean (SD) handheld computer scores and HbA_{1c} before and one year after blood glucose awareness training (BGAT)

	GROUP BGAT (N=24)		INDIVIDUAL BGAT (N=12)				
	BASELINE	FOLLOW-UP	BASELINE	FOLLOW-UP	P TIME	P INTERACTION	N
Accuracy index (%)	5.3 (15.2)	18.8 (18.9)	13.6 (11.7)	11.7 (10.6)	0.12	0.04	36
Recognised hypoglycaemic episodes (%)	27.9 (24.6)	42.1 (23.7)	35.3 (33.7)	42.4 (25.6)	0.02	0.40	34[a]
Recognised hyperglycaemic episodes (%)	33.9 (23.4)	38.9 (27.5)	40.1 (20.0)	39.8 (18.7)	0.55	0.49	36
HbA_{1c} (%)	7.3 (1.2)	7.3 (1.3)	7.2 (0.9)	7.5 (1.1)	0.30	0.22	44
Low blood glucose index	3.8 (1.4)	4.2 (3.0)	4.1 (2.7)	3.1 (1.8)	0.61	0.15	36
High blood glucose index	10.7 (4.8)	9.9 (6.4)	11.4 (4.6)	13.4 (7.1)	0.33	0.03	36
Blood glucose risk index	14.5 (4.6)	14.1 (5.8)	15.5 (3.7)	16.5 (6.3	0.61	0.31	36
Not driving during hypoglycaemia (%)	43.5 (29.7)	57.8 (27.8)	36.1 (29.8)	47.2 (27.1)	0.01	0.73	35[b]
Raising BG during hypoglycaemia (%)	51.3 (29.7)	64.3 (33.5)	41.5 (31.1)	54.9 (27.9)	0.02	0.98	35[b]

Significance of change after BGAT ('time') and significance of the difference in effect of the treatment conditions ('interaction'). [a]Two patients measured less than two hypoglycaemic episodes. [b]One patient did not measure any hypoglycaemic episodes.

Table 3
Mean (SD) questionnaire scores at baseline and one year after blood glucose awareness training (BGAT)

	GROUP BGAT		INDIVIDUAL BGAT				
	BASELINE	FOLLOW-UP	BASELINE	FOLLOW-UP	P TIME	P INTERACTION	N_a
HFS worry[b]	20.2 (11.3)	18.9 (10.1)	19.4 (11.3)	17.9 (11.9)	0.29	0.95	46
Severe hypoglycaemia[c]	7.9 (7.5)	1.7 (2.4)	6.6 (7.6)	.3 (8.5)	0.001	0.26	26
SMBG[d]	2.4 (2.0)	3.2 (1.7)	2.4 (1.5)	3.7 (1.6)	0.000	0.28	49
Traffic accidents[e]	0.3 (0.4)	0.1 (0.4)	0.6 (0.5)	0.2 (0.4)	0.04	0.32	33

Significance of change after BGAT ('time') and differential effect of the treatment conditions ('interaction'). [a]49 patients returned questionnaires, smaller n's are the result of missing data. [b]HFS = hypoglycaemia fear survey. [c]Number of reported severe hypoglycaemic episodes per year. [d]SMBG = times a day of self-monitoring of blood glucose. [e]Number of reported traffic accidents per year.

positive effects on the recognition of hypoglycaemia, decisions not to drive and to raise the BG during hypoglycaemia, the frequency of severe hypoglycaemic episodes, self-monitoring of the blood glucose, and traffic accidents. The present study had no control group and was not randomised. It is therefore uncertain if the observed improvements were due to the training *per se*. Nonparticipants were younger and tended to be more often female than participants, but did not differ from participants in diabetes-related characteristics. Unreported data of a small available control sample of patients who had not participated in BGAT showed that while participants improved, controls remained stable or deteriorated on most outcome measures. This strengthens our conclusion that BGAT may have had beneficial effects. Data on these control subjects were not presented here because at baseline, controls differed from participants in hypoglycaemic awareness, as was shown in *table 1*. They are available from the authors on request. Other studies also show that it is unlikely for patients to improve their BG estimations with the passing of time alone.[7] For these reasons, we are quite confident that the observed improvements could be attributed to BGAT.

The effects of training in the original group format were compared with the effects of individual training, and two differences emerged. Group training had positive effects on the accuracy of BG estimations while individual training did not. Furthermore, after individual training, patients tended to measure more frequent, and/or more extreme, high BG levels than at baseline (an undesired effect). Both findings indicate that group training was superior to individual training. Possibly the group process fostered an attitude change and the acceptance of information. The possible relationship between reduced awareness of hypoglycaemia (and even type 1 diabetes) and driving mishaps has been an area of recent debate.[20-28] In the present study, directly after BGAT, participants decided less often to participate in traffic when their BG was low.[12] At follow-up, the rate of traffic accidents was reduced compared with baseline. In an American sample, reductions in traffic accidents were also reported six and 12 months after BGAT.[4] Although traffic accidents were measured by means of retrospective self-report, in our opinion, it seems unlikely that after BGAT patients would be unable to remember accidents to a lesser degree, or that they would be more reluctant to report accidents. We think it is likely that BGAT was able to reduce the rate of traffic accidents among participants.

While the present follow-up data showed positive results of BGAT, the data directly after training did not.[10] Intuitively, training effects would be expected to abate (rather than increase) with time, when no follow-up booster is provided. Directly after the training, changes in outcome measures were in the right direction, but did not reach statistical significance. Maintenance of BGAT effects up to one year after the training was also reported in two American studies.[4,6] We can think of two further explanations for the fact that the effects of the training were only significant at the follow-up measurement. First, directly after BGAT, after the baseline assessment and keeping the symptom diary during the training, patients were reluctant to use the handheld computers again. They were a bit 'fed up' with the effort of keeping note of BG readings and estimations, and answering additional questions. This may have influenced the results. Second, about a year after the training, one of the patients mentioned that right after the training, she was alert to specific symptoms that would tell her that her BG was low. At times she misjudged her BG level on the basis of these separate symptoms. After a while, however, she developed a type of 'overall feeling', which helped her to recognise hypoglycaemia more readily. During the year after the training, on the basis of her experience in monitoring BG symptoms, she may have developed intuition (skilled pattern recognition, understanding without a rationale),[29] which takes time to develop, and is generally considered an element of expertise.

CONCLUSION

We observed significant improvements in clinically relevant measures one year after BGAT, despite a modest sample size. Group training should be preferred over individual training, but individual training also improved hypoglycaemic awareness. This adapted version of BGAT seems worthy of implementation in the Netherlands.

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REFERENCES

1. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 1997;46:271-86.
2. The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 1991;90:450-9.
3. Gerich JE, Mokan M, Veneman T, Korytkowski M, Mitrakou A. Hypoglycemia unawareness. Endocr Rev 1991;12:356-71.
4. Cox D, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): Long term benefits. Diabetes Care 2001;24:637-42.
5. Cox D, Gonder-Frederick L, Polonsky W, Schlundt D, Julian D, Clarke W. A multicenter evaluation of Blood Glucose Awareness Training-II. Diabetes Care 1995;18:523-8.
6. Cox DJ, Gonder-Frederick L, Julian DM, Clarke W. Long term follow-up evaluation of Blood Glucose Awareness Training. Diabetes Care 1994;17:1-5.
7. Cox DJ, Gonder-Frederick L, Julian D, et al. Intensive versus standard BG awareness training (BGAT) with insulin-dependent diabetes: mechanisms and ancillary effects. Psychosom Med 1991;53:453-62.
8. Cox DJ, Gonder-Frederick LA, Lee JH, Julian DM, Carter WR, Clarke WL. Effects and correlates of Blood Glucose Awareness Training among patients with IDDM. Diabetes Care 1989;12:313-8.
9. Cox DJ, Carter WR, Gonder-Frederick LA, Clarke WL, Pohl SL. Blood Glucose Discrimination Training in insulin-dependent diabetes mellitus (IDDM) patients. Biofeedback Self Regul 1988;13:201-17.
10. Ter Braak EWMT, de Valk HW, de la Bije YF, van der Laak MF, van Haeften TW, Erkelens DW. Response to training in blood glucose awareness is related to absence of previous hypoglycaemic coma. Diabetes Care 2000;23:1199-200.
11. Snoek FJ, van der Ven NCW. Bewust van je bloedglucose: de Hypoglykemie Preventie Training. Introductie van een nieuwe cursus voor insuline afhankelijke diabetespatiënten. EADE Nieuwsbrief 1997;4:134-6.
12. Broers S, le Cessie S, van Vliet KP, Spinhoven Ph, van der Ven NCW, Radder JK. Blood glucose awareness training in Dutch type 1 diabetes patients. Short-term evaluation of individual and group training. Diabet Med 2002;19:157-61.
13. Broers S, van Vliet KP, Everaerd W, le Cessie S, Radder JK. Modest contribution of psychosocial variables to hypoglycaemia awareness in type 1 diabetes. J Psychosom Res 2002;52:97-106.
14. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985;8:491-8.
15. Mosca A, Carpelli A. Automated determination of glycated haemoglobin with a new high performance liquid chromatograph analyser. Clin Chem 1986;32:202-3.
16. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke W. Symmetrization of the blood glucose measurement scale and applications. Diabetes Care 1997;20:1655-8.
17. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke W. Assessment of risk for severe hypoglycemia among adults with IDDM. Validation of the low blood glucose index. Diabetes Care 1998;21:1870-5.
18. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation and utilization. Diabetes Care 1987;10:617-22.
19. Snoek FJ, Pouwer F, Mollema ED, Heine RJ. De angst voor hypoglykemie vragenlijst (AHV). Interne consistentie en validiteit. Gedrag & Gezondheid 1996;24:287-93.
20. Cox D, Clarke W, Gonder-Frederick L, Kovatchev B. Driving mishaps and hypoglycaemia: risk and prevention. Int J Clin Pract Suppl. 2001;123:38-42.
21. Cox DJ, Penberthy JK, Zrebiec J, et al. Diabetes and driving mishaps: frequency and correlations from a multinational survey. Diabetes Care 2003;26:2329-34.
22. Adams KM. Driving and diabetes: one piece of the picture. Diabetes Care 2003;26:2464-5.
23. Cox DJ, Gonder-Frederick L, Clarke W. Driving decrements in type I diabetes during moderate hypoglycemia. Diabetes 1993;42:239-43.
24. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Julian DM, Clarke WL. Progressive hypoglycaemia's impact on driving simulation performance. Occurrence, awareness and correction. Diabetes Care 2000;23:163-70.
25. Barry-Bianchi S. "Real-life" driving behavior while hypoglycemic? Diabetes Care 2000;23:1210-2.
26. Burden AC, Spiers N. Progressive hypoglycemia's impact on driving simulation performance: occurrence, awareness, and correction. Diabetes Care 2000;23:1866-7.
27. Marrero D, Edelman S. Hypoglycemia and driving performance: a flashing yellow light? Diabetes Care 2000;23:146-7.
28. Frier BM. Hypoglycemia and driving performance. Diabetes Care 2000;23:148-50.
29. Benner P, Tanner C. Clinical judgement: how expert nurses use intuition. Am J Nurs 1987;87:23-31.

ORIGINAL ARTICLE

Paroxysmal atrial fibrillation, quality of life and neuroticism

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ABSTRACT

Background: Paroxysmal atrial fibrillation (AF) is associated with significant impairment of quality of life (QoL), which is to a large extent independent of objective measures of disease severity. We sought to investigate the potential role of neuroticism in the impairment of QoL in patients with paroxysmal AF.

Methods: The study group (AF group) comprised 73 patients with paroxysmal AF (mean age 55.5 ± 13.3 years, 50 males). On average, patients had a three-year history of one symptomatic paroxysm a week lasting two hours. QoL was assessed using the Medical Outcomes Study Short Form (SF-36) and neuroticism was assessed using the short-scale Eysenck Personality Questionnaire (EPQ).

Results: The degree of neuroticism in the AF patient group did not differ from the degree of neuroticism in a group of age- and sex-matched controls (mean EPQ score on neuroticism 4.1 ± 3.0 and 3.9 ± 3.1, respectively; p=NS). Within the AF group, multivariate regression analyses showed that QoL in the physical domain (SF-36 physical functioning, physical role function, vitality and pain subscales) was not related the degree of neuroticism. In contrast, significant inverse relations were observed between scores on the mental health and social functioning subscales and the degree of neuroticism (β coefficients p<.05), independent of age, sex and symptoms.

Conclusion: Based on the present study, patients with paroxysmal AF appear to have on average a degree of neuroticism similar to age- and sex-matched controls. However, the impairment of QoL in these patients, in particular regarding social functioning and mental health, seems to be related to a relatively high degree of neuroticism, independent of age and sex.

KEYWORDS

Atrial fibrillation, neuroticism, quality of life

INTRODUCTION

Atrial fibrillation (AF) is a very common arrhythmia, and its prevalence is still increasing. Two studies have recently been published with a primary focus on the impact of paroxysmal AF on quality of life (QoL);[1,2] both studies used the Medical Outcomes Study Short Form (SF-36). The two studies were consistent: patients with paroxysmal AF were characterised by rather low QoL across all domains (physical and social functioning, and mental health) compared with healthy controls. Of interest is that in both studies QoL only marginally depended on objective measures of disease severity (New York Heart Association functional class, left ventricular function) and even arrhythmia burden (frequency and duration of paroxysms, as based on the history) played a minor role. Instead, it was shown that the presence of cardiac symptoms associated with paroxysms of AF was predictive for impaired QoL.[2] For instance, chest pain and dizziness were associated with a low score on the physical role function subscale, which is probably not surprising. On the other hand, although loss of QoL is greater in severely symptomatic patients, even mildly symptomatic AF patients have a lower overall perception of well-being ('global life satisfaction').[3] In conclusion, the impairment of QoL in patients with AF is still only partly explained, and other factors should be considered. We hypothesised that neuroticism might be implicated in the impairment of QoL in patients with AF. Neuroticism is a stable personality trait, which gives an indication of the emotional stability of a person. Persons with high scores on neuroticism scales tend to be anxious and to have more worries in general, and neuroticism has proved to be an important predictor of psychological distress, both in the presence and the absence of stressful circumstances.[4] More specifically, persons with a high degree of neuroticism often have vague complaints about their health, which are not readily attributable to objective somatic disease,[5] but which may nonetheless have a negative impact on their QoL. The aim of the present study was to investigate the potential role of neuroticism in the impairment of QoL in patients with paroxysmal AF.

MATERIALS AND METHODS

Patient selection and study design

The study group consisted of patients who had participated in a previous study on QoL.[2] Briefly, all consecutive patients from the outpatient clinic with paroxysmal AF, aged >18 years, were considered eligible for the study. Paroxysmal AF was defined as proposed by Gallagher and Camm:[6] paroxysms had to terminate either spontaneously or after treatment with an antiarrhythmic drug. The presence of AF was based on electrocardiographic evidence, including ambulatory (Holter) monitoring. Lone AF was inferred when routine cardiac investigations (echocardiogram, ergometry) did not reveal structural heart disease. Patients with hypertension were considered to have structural heart disease. In the first study[2] a set of questionnaires was administered to the patients, including questionnaires on QoL, symptomatology and personality. Data thus collected were entered into a database, and in the present study we used this database focussing on personality, that is, neuroticism. The study was performed in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. Informed consent was obtained from all patients.

Quality of life and symptomatology

Details have been described previously.[2] Briefly, QoL was measured by the SF-36,[7] which is a widely used, thoroughly validated, standardised, generic health survey, consisting of eight subscales that measure physical functioning, bodily pain, role limitations due to physical or emotional problems, social functioning, as well as sense of vitality, mental health and general health. These scales together cover the three major domains of QoL, i.e. physical and social functioning, and mental health. Scores of each subscale are transformed to a scale ranging from 0 to 100, with lower scores representing a lower QoL. The following symptoms were incorporated in the analysis: palpitations, dyspnoea, dizziness and chest pain. Patients were asked to rate these symptoms as they occurred during AF according to severity; none-to-mild or moderate-to-severe.

Neuroticism

Neuroticism was assessed using the revised, short-scale Eysenck Personality Questionnaire (EPQ), with a validated Dutch translation (*table 1*).[8,9] Neuroticism is quantified using a set of 12 questions, to be answered with yes or no. The total score thus ranges from 0 to 12, a higher score signifying a higher degree of neuroticism.

Table 1
Eysenck personality questionnaire (revised, short scale)

Does your mood often go up and down?	Yes	No
Do you ever feel 'just miserable' for no reason?	Yes	No
Are you an irritable person?	Yes	No
Are your feelings easily hurt?	Yes	No
Do you often feel 'fed-up'?	Yes	No
Would you call yourself a nervous person?	Yes	No
Are you a worrier?	Yes	No
Would you call yourself tense or 'highly-strung'?	Yes	No
Do you worry too long after an embarrassing experience?	Yes	No
Do you suffer from 'nerves'?	Yes	No
Do you often feel lonely?	Yes	No
Are you often troubled about feelings of guilt?	Yes	No

Yes = 1; No = 0. Total score is calculated by adding the scores on the individual questions.

Data analysis

First, in order to determine the relative degree of neuroticism in the AF patients, the EPQ scores on neuroticism were compared with scores in controls individually matched for age and sex, using t-tests for independent samples. The control subjects were taken from a previously established control group consisting of 849 randomly selected adults.[9] The analyses were performed for the two groups as a whole, as well as for subgroups according to age and sex. Second, in order to determine whether (impaired) QoL was related to the degree of neuroticism, multivariate regression analyses were performed. For each of the four symptoms, the independent contributions of the particular symptom and neuroticism to the QoL scores on any of the eight subscales were examined, thereby controlling for age and sex. Mean values ± the standard deviation were calculated for normally distributed variables and median values with range were used for non-normal distributions. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

The study group comprised 73 patients. Clinical characteristics are given in *table 2*. Most patients were male and in

the majority no structural heart disease was apparent (lone AF). Almost half of the patients with structural heart disease had hypertension. None of the patients had congestive heart failure. Mean echo parameters were within the normal range. Self-reported arrhythmia burden in terms of the duration of the paroxysms ranged from 15 minutes to two days, whereas the frequency ranged from two paroxysms a year to five a week. On average, patients had a three-year history of one paroxysm a week lasting two hours. Most patients (70%) were on an antiarrhythmic agent to suppress their arrhythmia ('rhythm control'), whereas the remaining patients (30%) were not taking any medications or only medication for control of ventricular rate during AF ('rate control').

Table 2
Clinical characteristics

N	**73**
Age (years) ± SD	**55.5 ± 13.3**
Sex	
Male (%)	50 (68)
Female (%)	23 (32)
Underlying heart disease	
Ischaemic heart disease (%)	12 (16)
Valvular heart disease (%)	7 (10)
Hypertension (%)	11 (15)
Lone atrial fibrillation (%)	43 (59)
Arrhythmia burden	
Total duration (years) (range)	3.0 (0.2-30)
Frequency of paroxysms/week (range)	1.00 (0.04-5)
Duration of paroxysms (hours) (range)	2.00 (0.15-48)
Echo parameters	
Left ventricular end-diastolic dimension (mm)	47 ± 5
Left ventricular end-systolic dimension (mm)	32 ± 6
Left atrial dimension, parasternal (mm)	35 ± 6
Left atrial dimension, apical (mm)	54 ± 7
Medication	
Class I antiarrhythmics (%)	27 (37)
Class III antiarrhythmics (%)	24 (33)
Beta-blockers (%)	25 (34)
Digoxin (%)	7 (10)
No medication (%)	17 (23)

Neuroticism
All patients fully completed and returned the questionnaires. Mean total score in the AF group was 4.1 ± 3.0 and mean total score in the control group was 3.9 ± 3.1, the difference not being statistically significant. Also in the subgroups according to mean age and sex no statistically significant differences were found between the AF group and the control group. These data imply that the degree of neuroticism in the AF patients was similar to that in the controls.

Symptoms, neuroticism and quality of life
Regression coefficients indicating the independent relation between symptoms and neuroticism on the one hand and the eight QoL scales on the other, for each symptom separately, are presented in *table 3*. In the physical domain (physical functioning, physical role function, vitality and pain subscales) impaired QoL was significantly related to symptom severity for almost all symptoms (β coefficients p<0.05), but not to the degree of neuroticism. For example, scores on physical functioning were lower in the patients with moderate-to-severe palpitations as opposed to patients with none-to-mild palpitations (β coefficient -0.26, p=0.01), whereas the degree of neuroticism did not play a role (β coefficient -0.03, p=0.81). In contrast, significant inverse relations were observed between scores on the mental health and social functioning subscales and the degree of neuroticism (β coefficients p<.05), whereas in this instance QoL was not related the severity of any of the symptoms. For example, scores on mental health did not differ in the patients with moderate-to-severe palpitations as opposed to patients with none-to-mild palpitations (β coefficient -0.01, p=0.95). Instead, scores on mental health were significantly lower when the degree of neuroticism was higher (β coefficient -0.74, p<0.01). Regarding the emotional role function subscale, the results varied, both symptoms and neuroticism being implicated in some but not all instances. Finally, no relation was observed between general health and neuroticism nor between general health and symptoms.

Table 3
Relation of QoL with symptoms and neuroticism

		PHYSICAL FUNCTION-ING		SOCIAL FUNCTION-ING		PHYSICAL ROLE FUNCTION		EMOTIONAL ROLE FUNCTION		MENTAL HEALTH		VITALITY		PAIN		GENERAL HEALTH	
		β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P
Palpitations	Neuroticism	-.03	.81	-.39	<.01	-.07	.53	-.19	.12	-.74	<.01	-.02	.89	.06	.59	-.09	.44
	Palpitations	-.26	.01	.05	.69	-.27	.02	-.17	.17	-.01	.95	-.38	.07	-.18	.13	-.08	.48
Dyspnoea	Neuroticism	-.09	.36	-.39	<.01	-.16	.15	-.23	.06	-.74	<.01	-.28	0.2	.01	.92	-.12	.30
	Dyspnoea	-.26	.01	-.07	.55	-.43	<.01	-.12	.31	-.07	.43	-.32	<.01	-.28	.02	-.16	.16
Dizziness	Neuroticism	-.02	.86	-.35	<.01	-.06	.61	-.18	.14	-.70	<.01	-.25	.04	.06	.59	-.07	.56
	Dizziness	-.26	.02	-.16	.17	-.31	<.01	-.20	.10	-.19	.03	-.16	.18	-.18	.12	-.19	.10
Chest pain	Neuroticism	-.04	.68	-.21	.12	-.10	.41	-.20	.10	-58	<.01	-.25	.04	.08	.48	-.09	.43
	Chest pain	-.33	<.01	.10	.59	-.28	.02	-.21	.09	.19	.16	-.25	.04	-.39	<.01	-.16	.17

Each symptom was dichotomised according to severity (none-to-mild or moderate-to-severe). β = β *coefficient; p = p value.*

DISCUSSION

Main findings
In the present study, patients with paroxysmal AF were found to have on average a degree of neuroticism similar to age- and sex-matched controls. However, within the group of AF patients, impairment of QoL, in particular regarding social functioning and mental health, was related to a higher degree of neuroticism, independent of age and sex.

Atrial fibrillation and personality
The role of personality in patients with coronary artery disease is an issue of ongoing debate.[10,11] However, studies regarding personality and cardiac disorders other than coronary artery disease are scarce. In particular, to our knowledge no data are available on neuroticism in patients with AF, despite the fact that AF is rapidly becoming a major health problem associated with substantial morbidity and mortality. Perhaps based on clinical experience with individual patients one might intuitively surmise that patients with paroxysmal AF have on average a higher degree of neuroticism than other persons. However, the results of our study clearly indicate that this is not the case; although the EPQ scores on neuroticism differed among the individual patients, including some patients with high scores, mean score in the group as a whole was similar to the mean score in the group of age- and sex-matched controls. In other words, patients with paroxysmal AF would on average appear to have a 'normal' degree of neuroticism.

Quality of life and neuroticism
Notwithstanding the observation that patients with paroxysmal AF have on average a normal degree of neuroticism, it would be conceivable that patients with paroxysmal AF with a higher degree of neuroticism suffer from an even lower QoL than patients with a lower degree of neuroticism. Unlike the more physical domain of QoL, in the domains of social functioning and mental health a high degree of neuroticism was indeed found to be related to a low QoL. In more practical terms this finding implies that patients with a high degree of neuroticism experience poor social functioning and mental health, irrespective of the presence of the physical symptoms associated with their arrhythmia. In other words, whether or not the patient suffers from palpitations (or other symptoms), social functioning and mental health are likely to be poor if the patient has a high degree of neuroticism. Extending this concept even further, it may even be surmised that the presence or absence of AF as such is irrelevant, patients with a high degree of neuroticism experience poor social functioning and mental health anyway. Our study also provides a likely explanation for the finding in a previous study on QoL in patients with AF by Paquette *et al.*[12] By using the Barsky Somatosensory Amplification Scale, they investigated the tendency of AF patients to somatise, i.e. to amplify benign bodily sensations, and they showed that a high tendency to somatise predicted a poor QoL. Since the tendency to somatise is one of the established features of neuroticism,[5] it is readily conceivable that neuroticism was the actual underlying personality disorder in these patients.

Methodological considerations
In the present study we assessed the relation between neuroticism and QoL. The analysis was corrected for age and sex, but we did not incorporate measures on structural heart disease and arrhythmia burden. Also, medication (in particular antiarrhythmic agents) was not incorporated in the analysis. However, these factors have previously been shown to have only a minor effect (at the most) on QoL.[1,2] Another consideration concerns the possibility that personality was affected by paroxysmal AF. In particular, it is intuitively conceivable that the degree of neuroticism would increase over time, secondary to the illness. However, as a constitutional entity, personality is stable over time, and life events (including somatic disease) do not significantly affect personality.[13] Moreover, the fact that the degree of neuroticism in patients with AF was not higher than in controls argues against such an effect. Finally, this study was not designed to determine whether the patients were 'neurotic' in terms of a psychiatric disorder. Instead, the concept of neuroticism was used to describe a normal variant of human personality, and the results of our study merely indicate that the impairment of QoL in patients with paroxysmal AF is related to the relative degree of neuroticism, patients with a relatively high degree of neuroticism suffering from a lower QoL than patients with a lower degree of neuroticism.

Possible implications
Previous studies have shown that treatment of patients with paroxysmal AF, either with medication[14] or ablation techniques[15,16] leads to improvement of QoL. However, despite significant reduction of arrhythmia burden, not all patients obtained benefit from treatment in terms of QoL. Given the results of our study, it is conceivable that differences in the degree of neuroticism between the

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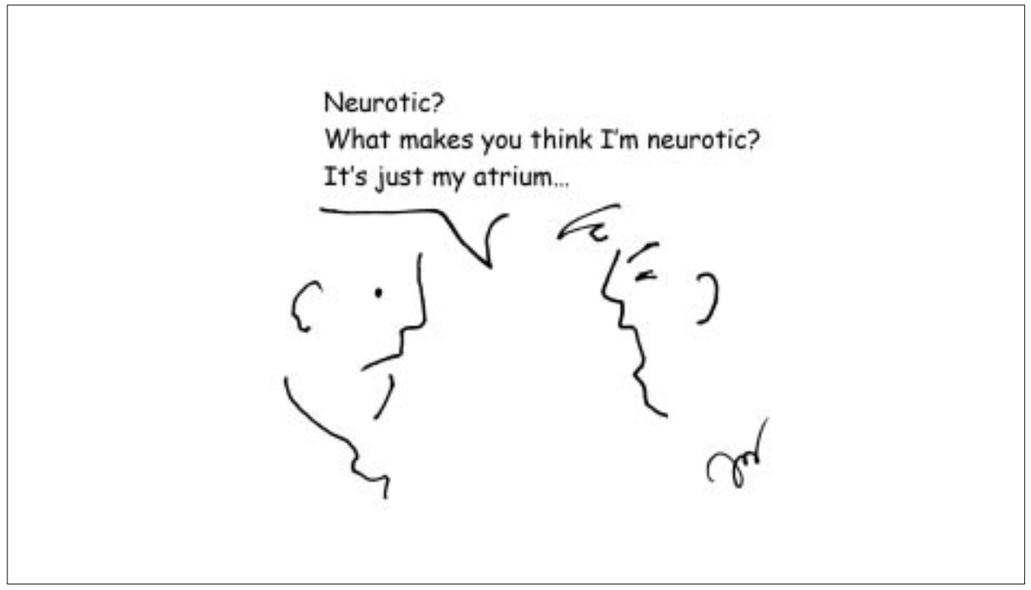
patients played a critical role in this connection, patients with a high degree of neuroticism benefiting less from treatment. As a practical implication, our findings suggest that when treating patients with paroxysmal AF one should take into consideration whether the patient has a high degree of neuroticism or not. If so, the goal of treatment in terms of improvement of QoL should probably be not too high, at least not regarding social functioning and mental health.

REFERENCES

1. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. J Am Coll Cardiol 2000;36:1303-9.
2. Van den Berg MP, Hassink RJ, Tuinenburg AE, et al. Quality of life in patients with atrial fibrillation and its predictors: importance of the autonomic nervous system. Eur Heart J 2001;22:247-53.
3. Savelieva I, Paquette M, Dorian P, Lüderitz B, Camm AJ. Quality of life in patients with silent atrial fibrillation. Heart 2001;85:216-7.
4. Ranchor AV, Sanderman R, Steptoe A, Wardle J, Miedema I, Ormel J. Pre-morbid predictors of psychological adjustment to cancer. Qual Life Res 2002;11:101-13.
5. Costa PT, McCrae RR. Neuroticism, somatic complaints and disease: is the bark worse than the bite? J Pers 1987;55:299-316.
6. Gallagher MM, Camm AJ. Classification of atrial fibrillation. Pacing Clin Electrophysiol 1997;20:1603-5.
7. McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247-63.
8. Eysenck SBG, Eysenck HJ, Barrett P. A revised version of the Psychoticism scale. Personal Individ Diff 1985;6:21-9.
9. Sanderman R, Arrindell WA, Ranchor AV, Eysenck HJ, Eysenck SBG. The assessment of personality traits with the Eysenck Personality Questionnaire (EPQ): a manual. Groningen: Northern Centre for Health Care Publishers, 1995.
10. Rosenman RH, Brand RJ, Jenkins CD, Friedman M, Straus R, Wurm M. Coronary heart disease in the Western Collaborative Group Study. Final follow-up experience of 81/2 years. JAMA 1975;233:872-7.
11. Denollet J, Sys SU, Stroobant N, Rombouts H, Gillebert TC, Brutsaert DL. Personality as independent predictor of long-term mortality in patients with coronary heart disease. Lancet 1996;347:417-21.
12. Paquette M, Roy D, Talajic M, et al. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. Am J Cardiol 2000;86:764-8.
13. McCrea R. Moderated analyses of longitudinal personality stability. J Pers Soc Psychol 1993;65:577-85.
14. Dorian P, Paquette M, Newman D, et al. for the CTAF Investigators. Quality of life improves with treatment in the Canadian Trial of Atrial Fibrillation. Am Heart J 2002;143:984-90.
15. Brignole M, Bianfranchi L, Menozzi C, et al. Influence of atrioventricular junction radiofrequency ablation in patients with chronic atrial fibrillation and flutter on quality of life and cardiac performance. Am J Cardiol 1994;74:242-6.
16. Bubien RS, Knotts-Dolson SM, Plumb VJ, Kay GN. Effect of radiofrequency catheter ablation on health-related quality of life and activities of daily living in patients with recurrent arrhythmias. Circulation 1996;94:1585-91.



Van den Berg. Atrial fibrillation and neuroticism.

ORIGINAL ARTICLE

Clinical experience with venlafaxine in the treatment of hot flushes in women with a history of breast cancer

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ABSTRACT

Objective: To obtain practical experience with venlafaxine for hot flushes in breast cancer patients and incorporate this in a treatment protocol.
Method: Twenty-two women with a history of breast cancer (mean age 49.2 years, range 35-65) were referred for consideration of treatment with venlafaxine for hot flushes. Patients received extensive information on treatment with venlafaxine and were advised to self-monitor the frequency of their hot flushes.
Results: Eight women did not start venlafaxine because they had no postmenopausal complaints, were lost to follow-up, had too low a frequency of hot flushes, or refused treatment. Eventually 14 women started venlafaxine. Two of them did not tolerate venlafaxine, four reported some effect but stopped because of side effects, two women had no effect whatsoever. Six women observed a clear (>50%) reduction in their hot flush frequency that was maintained at a median follow-up of 13 months.
Conclusion: The group of patients referred for treatment was more heterogeneous and more patients dropped out because of side effects than expected. Extensive patient education, patient selection and evaluation of the treatment effect (by self-monitoring of hot flush frequency) are mandatory to avoid useless (continuation of) treatment and to prepare patients for side effects. Under these conditions, a substantial minority of patients benefit from venlafaxine.

KEYWORDS

Antidepressants, breast cancer, hormonal therapy, hot flushes, venlafaxine

INTRODUCTION

Hot flushes can be very bothersome postmenopausal symptoms. In this phase of life, about 75% of women experience hot flushes.[1-3] Most prominent are attacks of intense feelings of warmth, ascending from the chest to the head and neck region. A hot flush lasts several minutes and is accompanied by (often heavy and visible) transpiration and reddening of the skin of the head and neck. Hot flushes can also be accompanied by palpitations, dizziness, anxiety and irritability.[1]
Some women have a couple of hot flushes a week, others experience dozens a day. Also the intensity of hot flushes can vary considerably. Hot flushes can easily lead to avoidance of social contacts. Nightly hot flushes are especially troublesome, resulting in awakening due to profuse transpiration and having to change nightclothes and bed sheets. The consequent interference with sleep easily leads to daytime fatigue and diminished functioning.
In women with breast cancer, menopause can occur as a physiological phenomenon, but also as a side effect of the (systemic) oncology treatment. Chemotherapy can induce premature ovarian dysfunction, and in addition, hormonal treatment with drugs such as tamoxifen and LH-RH-agonists ('chemical castration') in hormone-sensitive breast cancer can lead to frequent and annoying hot flushes.[4] Bilateral oophorectomy, if performed, equally results in an irreversible postmenopausal state.
Temporary treatment with oestrogens is the most effective treatment for hot flushes. In women without a history of breast cancer, oestrogens provide a 50 to 100% reduction in hot flush frequency.[1,5] However, in patients with a history of breast cancer, oestrogens are relatively contraindicated. This is certainly the case for patients with hormone-sensitive tumours, because oestrogens can stimulate the growth of

'microscopic' tumour cells that might still be present after surgery, radiotherapy and/or chemotherapy.[6,7] In addition, specifically in hormone-sensitive tumours, hormonal manipulations aim to knock out the production of oestrogens or to block the stimulatory effects of oestrogens on the tumour cell.

Until recently, only moderately effective alternatives for treatment of hot flushes were available for this patient group. With clonidine (Catapresan®, Dixarit®), for instance, a drug that affects the central noradrenergic neurotransmission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a modest effect, taking into account the possible side effects as sedation, sleep disturbance, gastrointestinal symptoms and hypotension.[4,8]

Over the past years, however, favourable results have been reported with several modern antidepressants in women with a history of breast cancer, at first with venlafaxine (Efexor®), later on with fluoxetine (Prozac®) and paroxetine (Seroxat®).[9-11] In a randomised, placebo-controlled trial in 221 women with either a history of breast cancer or reluctance to take hormones because of fear of breast cancer, venlafaxine 75 mg daily resulted in a 61% reduction in the hot flush scores (number of hot flushes/24 hours x intensity), a response that was twice as high as in the placebo group.[9] A daily dose of 37.5 mg was somewhat less effective, a dose of 150 mg was as effective as 75 mg but induced more side effects.[9] Recently, paroxetine was also reported to be effective against hot flushes in healthy women.[12] The effects on hot flushes of these serotonergic drugs are thought to be mediated by an influence on a complex interaction of serotonin, noradrenaline, gonadotropic hormones and sex hormones in the thermoregulatory centres of the brain.[12,13]

After the publication by Loprinzi *et al.* in 2000, the oncology staff of our hospital decided to refer breast cancer patients with troublesome hot flushes to the psychiatry service in order to concentrate the experience with venlafaxine for this indication. At that time, we were unsure of the generalisability of the findings. In addition, the psychiatrists were familiar with venlafaxine and its side effects. The aim was to incorporate this clinical experience, finally, in a protocol or checklist.

PATIENTS AND METHODS

From January 2001 until July 2003, 22 women (mean age 49.2 years, range 35-65, SD 7.8) with a history of breast cancer were referred to the psychiatry department for possible treatment with venlafaxine for hot flushes. No strict referral criteria were established: obviously, patients had to be burdened significantly by hot flushes.

Pretreatment with clonidine was advised. A semistructured history was taken and patient information was given according to *table 1*. For five days prior to starting venlafaxine, the patients monitored the frequency of troublesome hot flushes on a registration sheet (for each night, morning, afternoon, and evening). The decision to start venlafaxine was made by the patient and the psychiatrist together; a threshold frequency of hot flushes for starting venlafaxine was not required. Follow-up visits were arranged after two to three weeks, four to six weeks and four to six months. Before each follow-up visit, the women monitored the frequency of troublesome hot flushes for a period of two to three days. Some of these follow-up appointments took place by telephone, e-mail or fax. The starting daily dose of venlafaxine was 75 mg, after two or three weeks, the dose could be increased to 150 mg in case of insufficient effect. We did not use predetermined criteria for response: the decision to stop or to continue venlafaxine after four to six weeks (or earlier in case of side effects) was taken after the patient and psychiatrist had discussed the costs and benefits.

Table 1
Items to be addressed in breast cancer patients when prescribing venlafaxine for hot flushes

INFORMATION
No registration for this indication; few data on long-term efficacy
Most frequently occurring side effects: agitation, anxiety, gastric symptoms, constipation, dry mouth
May influence driving ability (warning on package)
Side effects manifest first, positive effects on hot flushes later
Venlafaxine only influences hot flushes, not other menopausal complaints as vaginal dryness or osteoporosis, nor does it have a direct positive effect on joint pains, fatigue, concentration difficulties
Effect to be expected is a reduction of 50% or more in hot flush frequency, according to literature data, intensity of flushes can also decrease
Explanation of rationale for self-monitoring of hot flush frequency: avoiding unnecessary treatment, enabling evaluation of the effect of therapy and of the ratio of benefits over side effects
INDICATION FOR PSYCHIATRIC REFERRAL, (RELATIVE) CONTRAINDICATIONS FOR VENLAFAXINE
Previous experience (side effects!) with serotonergic antidepressants (fluvoxamine-Fevarin®, fluoxetine-Prozac®, paroxetine-Seroxat®, sertraline-Zoloft®, citalopram-Cipram®)
Depressed now? Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks? In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time?
History of manic episode(s)? Have you ever had a period of time when you were feeling, 'up' or 'high' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? Do not count times when you were intoxicated by drugs or alcohol. Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or overreacted, compared with other people, even in situations that you felt were justified?
Anxiety disorder? Easily worried and tense? Sudden attacks of anxiety? Avoidance of places and situations in which you could become anxious or panicky? Compulsive behaviour as excessive checking or washing hands?

RESULTS

At the first visit to the psychiatrist (AVG), one woman had complaints which could not be regarded as hot flushes and not even as postmenopausal. She was not prescribed venlafaxine. Of the remaining 21 patients, the hot flushes were attributed to the physiological menopause in two women, and in 19 to previous or ongoing treatment for breast cancer. Fourteen women had previously been treated with clonidine for hot flushes. For one woman, no reliable self-monitoring could be obtained; she was lost to follow-up. At self-monitoring, the frequencies of hot flushes turned out to be rather variable. In six cases it was decided not to start with venlafaxine. In three of these six women, to their own surprise, the hot flush frequency at self-monitoring was considerably lower than previously perceived by them. After receiving information, three women declined treatment, mainly because of a reluctance to use more drugs than they were already taking and a reluctance to take a 'psychiatric' drug. One patient had a depressive syndrome, of mild intensity (score on the Zung self-rating scale for depression: 49). Problems at work and sleep disturbance because of nightly hot flushes (with resulting daytime fatigue and irritability) were thought to be causal factors in this depression.

Eventually, 14 women (mean age 48.5 years, range 42-59, SD 6.0) started venlafaxine. In one of these women the hot flushes were attributed to the physiological menopause, in the other 13 to previous or ongoing treatment for breast cancer (hormonal therapy in eight, chemotherapy in one, combination of hormonal and chemotherapy in four). The reported duration of annoying hot flushes was more than two years in eight women, between six months and two years in four, and less than six months in two.

On self-monitoring, ten women recorded between 10 and 25 hot flushes per 24 hours, while four women recorded more than 25. Ten women had been treated with clonidine. One patient insisted on continuing clonidine, and venlafaxine was added. Two women did not tolerate the starting dose of 75 mg venlafaxine because of severe agitation, anxiety and profound malaise occurring in the hours after taking the first dose. In four women, venlafaxine was effective to some extent (30 to 50% decrease in hot flush frequency), but they stopped taking venlafaxine because of troublesome side effects as constipation, weight gain and sleep disturbance. In two women, venlafaxine had no effect at all in doses of 75 and 150 mg respectively.

Six women took venlafaxine for three months or longer (four women in a daily dose of 75 mg, and two in a dose of 150 mg) and experienced a more than 50% reduction in hot flush frequency without significant side effects. In two of them, the hot flushes disappeared completely.

Two women reported a definite psychic alteration: in the above-mentioned depressive patient, the depression went into remission; the other woman reported feeling less irritable and more able to cope emotionally with her difficulties. In these six women, the effect was maintained in the long term: dose increase was not necessary during a median follow-up of 13 months (range: 5-36 months).

DISCUSSION

The group of breast cancer patients referred for treatment of hot flushes was more heterogeneous than expected in terms of the frequency (and in one patient even the presence) of hot flushes and in terms of subjective burden. After self-monitoring, some women turned out to have far less flushes than had thought beforehand. Others decided against treatment after receiving information. Presumably, aside from their reluctance to take more or 'psychiatric' drugs, knowing that a form of treatment would be available if the symptoms became more intense satisfied these patients. Patient selection by giving extensive patient information, a standardised history (*table 1*) and self-monitoring of the hot flush frequency appears to prevent unnecessary treatment in majority of patients.

Of the treated patients, quite a lot dropped out because of side effects. Two patients even became severely agitated after the first dose. Patient education, in this way, is obviously also useful to prepare patients for annoying or even frightening side effects. Furthermore, evaluation of the treatment effect by means of self-monitoring is mandatory to avoid useless continuation of treatment. We noticed in several patients that clonidine had been prescribed for longer periods without much evidence of a positive effect. Evaluation of the treatment turned out to also be useful in enabling the patients to weigh the beneficial effects on the hot flushes against the side effects and the necessity to take another medication. In a context of extensive patient education, standardised history taking and self-monitoring,

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more than one third of patients appear to derive a long-term benefit from venlafaxine.
The number of referrals was unexpectedly low. According to the oncology staff, women were mainly reluctant to take more drugs. In addition, a referral to a psychiatrist, for a possible treatment with a psychotropic drug, could have been an obstacle.
We realise that the procedure as presented here is relatively laborious. However, specialised oncology or psychiatry nurses could assist in patient education and self-monitoring. Moreover, as most oncologists will not be confronted frequently enough with this problem to build up experience, a standardised history as shown in *table 1* could be useful. In addition, it is important to obtain a short psychiatric history. For instance, in patients who went through a manic episode earlier in their life antidepressants might provoke a recurrent mania. Patients who had previously been treated with a serotonergic antidepressant should be asked about side effects: logically, they could experience the same side effects again. It is important to assess the presence of an ongoing mood or anxiety disorder. Questions on depression and a history of manic episodes can be asked directly or, as shown in *table 1*, with modules of the M.I.N.I.[14] Screening on depression and anxiety can also be done with self-report questionnaires as the Hospital Depression and Anxiety Scale.[15] If a mood or anxiety disorder is suspected, consulting with a psychiatrist or the general practitioner is self-evident.
Finally, we believe that our clinical experience in breast cancer patients is also relevant for the treatment of hot flushes in general (as part of the physiological menopause in otherwise healthy women), especially since long-term hormone replacement therapy in women with menopausal symptoms is under debate.[16]
According to the literature, venlafaxine is an effective therapy for hot flushes in breast cancer patients. Our experience indicates that matters are more complex and that the best results with this drug are obtained with extensive patient information, patient selection and repeated evaluation of the effects by self-monitoring of hot flush frequency.

REFERENCES

1. Stearns V, Ulmmer L, Lopez JF, Smith Y, Isaacs C, Hayes DF. Hot flushes. Lancet 2002;360:1851-61.
2. Bachmann GA. Vasomotor flushes in menopausal women. Am J Obstet Gynecol 1999;180:312-6.
3. Kronenberg F. Hot flashes: epidemiology and physiology. Ann N Y Acad Sci 1990;592:52-86.
4. Wymenga ANM, Sleijfer DT. Management of hot flushes in breast cancer patients. Acta Oncologica 2002;41:269-75.
5. McLennan A, Lester S, Moore V. Oral estrogen replacement therapy versus placebo for hot flushes (Cochrane Review). Cochrane Database Syst Rev 2001;1:CD002978.
6. Barton DL, Loprinzi C, Gostout B. Current management of menopausal symptoms in cancer patients. Oncology 2002;16:67-72.
7. Pritchard KI. Hormone replacement in women with a history of breast cancer. Oncologist 2001;6:353-62.
8. Clemons M, Clamp A, Anderson A. Management of the menopause in cancer survivors. Cancer Treat Rev 2002;28:321-33.
9. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059-63.
10. Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002;20:1578-83.
11. Weizner MA, Moncello J, Jacobsen PB, Minton S. A pilot trial of paroxetine for the treatment of hot flushes and associated symptoms in women with breast cancer. J Pain Symptom Manage 2002;23:337-45.
12. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes. A randomized controlled trial. JAMA 2003;289:2827-34.
13. Kouriefs C, Georgiou M, Ravi R. Hot flashes and prostate cancer: pathogenesis and treatment. BJU Int 2002;89:379-83.
14. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psych 1998 ;59(suppl 20):22-33.
15. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psych Scand 1983;67:361-70.
16. Vandenbroucke JP, van Leeuwen FE, Helmerhorst FM. Borstkanker en hormoongebruik rond de menopauze. Ned Tijdschr Geneeskd 2003;147:1829-34.

PHOTO QUIZ

A patient with abdominal distension

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KEYWORDS

Diagnostic imaging, intestinal obstruction, small bowel faeces sign

CASE REPORT

A 74-year-old woman was admitted to our hospital because of vomiting and abdominal pain. She had been well until 24 hours before admission, when she had had her last meal. She had not eaten anything unusual.
She developed pain in the left lower abdominal quadrant, and difficulties with her bowel movements. An enema was given unsuccessfully. There was progressive distension of the abdomen. The patient started to vomit gastric and later bilious contents. No history of abdominal symptoms or weight loss was reported. She currently takes oral antidiabetic agents and an angiotensin II blocker because of hypertension. On physical examination she was not in distress and was afebrile, blood pressure 130/100 mmHg, pulse rate 88 beats/min. On auscultation increased bowel sounds with rushes of high-pitched sounds were heard. Her abdomen was distended and a large tender mass filling the whole left lower quadrant without signs of peritoneal irritation was found. There were no faeces on rectal examination. The leucocyte count was 10.2 mmol/L, haemoglobin 7.2 mmol/L, C-reactive protein 36mg/l and lactate dehydrogenase 535 U/l.
Under suspicion of a mechanical bowel obstruction without signs of peritonitis, the patient was treated with a nasogastric tube, fasting and enemas on which she improved.
An abdominal X-ray in bed taken on day two showed no bowel distension (*figure 1*). After removing the nasogastric tube on day two the nausea returned. Abdominal examination was unchanged. An abdominal computed tomography (CT) scan after drinking oral contrast and intravenous contrast was performed (*figure 2*).

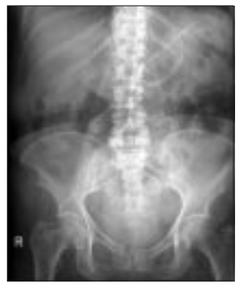

Figure 1
Abdominal X-ray on day 2

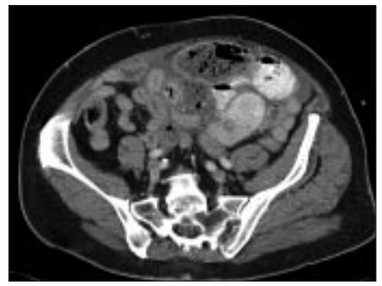

Figure 2
Abdominal CT after drinking oral contrast

WHAT IS YOUR DIAGNOSIS?

See page 187 for the answer to this photo quiz.

CASE REPORT

Neurological complications following *Plasmodium falciparum* infection

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ABSTRACT

Several neurological complications are associated with severe falciparum malaria. Cerebral malaria is one of the most life-threatening complications. A few patients may experience a neurological syndrome after complete recovery from *Plasmodium falciparum* infection. In the literature especially the postmalaria neurological syndrome (PMNS), acute disseminated encephalomyelitis (ADEM) and delayed cerebellar ataxia have been reported.

We describe a case of a 53-year-old woman who was re-admitted after an adequately treated *P. falciparum* infection with word-finding difficulties, confusion and tremor. Peripheral blood smears were repeatedly negative for malarial parasites. The clinical features best fitted a PMNS. Because of the severity of the syndrome she was treated with high-dose prednisone. She recovered completely. The possibility of ADEM is also discussed.

Aetiology of these syndromes is still unknown, but it could be mediated by an immunological mechanism. PMNS or ADEM must be considered when neurological signs and symptoms occur after recovery from a *P. falciparum* infection.

KEYWORDS

Malaria, neurological features, *Plasmodium falciparum*, postmalaria neurological syndrome

INTRODUCTION

Malaria affects 300 to 500 million cases worldwide with three million deaths each year.[1-3] In the Netherlands approximately 300 cases of malaria are reported annually.[4] True incidence is estimated to be three times higher. Increasing incidence has been related to growing mobility, resistance of the parasite to chemoprophylaxis, resistance of the *Anopheles* mosquito to insecticides, changes in the climate and failing of malaria reduction programmes.[1,2] *Plasmodium falciparum* is the most serious cause of malaria; it has a high mortality without treatment. *P. falciparum* invades erythrocytes of all ages, which can give parasitaemia levels of up to 50%.[2] Serious complications of *P. falciparum* infection include cerebral malaria, renal failure, pulmonary oedema, hypoglycaemia, anaemia, spontaneous bleeding and gastroenteritis. Cerebral malaria, an acute encephalopathy, is the most serious neurological disorder related to a *P. falciparum* infection. Symptoms are cerebral oedema and diffuse petechial bleedings with fever, severe headache, delirium and also stupor or coma with generalised seizures. Mortality is up to 20% and 10% of survivors still have neurological symptoms after discharge from the hospital. Malaria or quinine-induced hypoglycaemia can also lead to coma.[2,3]

A few patients may experience a neurological syndrome after complete recovery from *P. falciparum* infection. In the literature especially the postmalaria neurological syndrome (PMNS), acute disseminated encephalomyelitis (ADEM) and delayed cerebellar ataxia have been reported.[3,5-14]

We present a case of PMNS and will also discuss other possible causes of neurological complications following malaria, such as ADEM.

CASE REPORT

A 53-year-old woman was admitted to our hospital because of fever (body temperature up to 39°C), chills, headache and myalgia. She also mentioned severe tiredness, nausea, vomiting and nonbloody diarrhoea. Eleven days previously she had returned from a seven-day city tour in Kenya. She had not taken any chemoprophylaxis for malaria. Her fellow travellers were all healthy. A peripheral blood smear showed 6% parasitaemia with *P. falciparum*.

Physical examination revealed a seriously ill woman. Blood pressure was 105/70 mmHg, pulse rate 120 beats/minute and body temperature 41°C. Except for right upper abdominal pain, there were no other abnormalities, and in particular no hepatosplenomegaly. Neurological examination was normal. Immediately after admission, her blood pressure dropped to 85/50 mmHg with a good reaction to fluid challenge.

Laboratory investigations (*table 1*) showed raised liver enzymes, mild renal dysfunction which recovered within two days and diffuse intravasal coagulation. Electrocardiography revealed a sinus rhythm with right bundle branch block and negative T tops in leads III, AVF and V_3. Chest X-ray was normal. She was treated for seven days with quinine 600 mg three times a day by intravenous infusion. Peripheral blood smear became negative on day 4 and blood cultures were all negative. Because of consolidation of the middle and lower segment of the right lung on the chest X-ray cefazolin (1 g three times a day) and ciprofloxacin (200 mg twice daily) were given for seven days. Abdominal echography revealed splenomegaly and some pleural effusion on the right side.

On day 5 she became afebrile. After 13 days she was discharged from the hospital in a good clinical condition.

Five days later she was readmitted because of arthralgia and a body temperature of 38°C. She was tired, had diffuse pain in her body and a nonproductive cough. Physical examination revealed some crackles on inspiration, painful abdominal palpation and normal joints. Laboratory investigations (*table 1*) showed anaemia, mild transaminase elevations and negative peripheral blood smear for malaria. Chest X-ray was normal and she was readmitted for observation.

Table 1
Laboratory investigations

	DAY 1	DAY 18	DAY 21
Haemoglobin (mmol/l)	9.8	6.3	5.8
Leucocytes (10^9/l)	9.1	5.3	2.8
Thrombocytes (10^9/l)	22	276	166
CRP (mg/l)	184	6	6
Sodium (mmol/l)	128	139	137
Potassium (mmol/l)	4	4.8	4.5
Creatinine (µmol/l)	152	91	81
γ-GT (U/l)	141	88	52
Alkaline phosphatase (U/l)	110	138	101
ASAT (U/l)	160	68	55
ALAT (U/l)	75	93	65
LDH (U/l)	1412	919	932
glucose (mmol/l)	10.9	4.8	5.5
APTT (sec)	33	25	
D-dimer (mg/l)	25.3		
Blood smear (%)*	6	0	0

**Number of infected erythrocytes.*

Three days after readmittance, she became confused and had progressive difficulty in finding words. Her blood pressure was 90/60 mmHg, pulse rate 100 beats/minute and body temperature 37°C. Physical examination showed shortness of breath. The neurological examination revealed a mixed aphasia, a position tremor, general restlessness and wide open eyes with mydriasis; pupil reactions to light and convergence were normal. Neck stiffness, paresis or abnormal reflexes were absent. The differential diagnosis included a parasitic infection (malaria, borreliosis or trypanosomiasis), bacterial infection (enteric fever), viral encephalitis, acute disseminated encephalomyelitis (ADEM), a postmalaria neurological syndrome (PMNS) or a drug-related disorder (quinine or ciprofloxacin). Laboratory investigations showed normocytic anaemia, leucopenia and decreasing liver enzymes levels (*table 1*). Peripheral blood smears were repeatedly negative for parasites.

Examination of the cerebrospinal fluid (CSF) showed 5 x 10^6/l leucocytes (24% lymphocytes and 6% monocytes) and a protein level of 0.67 g/l. Results of extensive serological studies and cultures, both of serum and CSF, were negative except for *Rickettsia conorii* (IgM 1:128, IgG 1:64) and *Rickettsia tsutsugamushi* (IgM 1:32, IgG 1:128) in the serum. Brain computer tomography (CT) was normal. Magnetic resonance imaging (MRI) of the brain failed because of anxiety and dyspnoea. Electroencephalography showed diffuse slowing of the background activity with intermittent dysrhythmic discharges consistent with a diffuse encephalopathy.

On suspicion of severe PMNS prednisone was given intravenously (75 mg/24 hours for three days, and then tapered with 10 mg/day). We also started doxycycline 200 mg per day for a possible rickettsiosis, although clinical course, the absence of a rash or any other skin appearance and the long incubation period made this diagnosis improbable.[15] Rapid recovery was seen within 24 hours. On day 33 she left the hospital. One month later she had recovered completely.

DISCUSSION

Our patient had neurological signs and symptoms that seemed to be related to the prior *P. falciparum* infection. We excluded cerebral malaria by negative peripheral blood smear and also other causes of infectious meningoencephalitis as trypanosomiasis, viral or bacterial infections. Although *Salmonella typhi* infection can cause neuropsychiatric symptoms such as confusion, ataxia, meningitis, myelitis and acute psychosis,[16,17] this diagnosis was thought to be less likely because of the relatively long incubation period, and the negative investigation of CSF and negative cultures of blood and faeces.

We did find positive Rickettsial serology suggesting a possible infection with *R. conorii*. *R. conorii* infections are frequently reported from Africa and are known in Europe

as Mediterranean spotted fever and in Kenya as Kenya tick typhus. This rickettsial infection can cause cerebral symptoms and severe myalgia.[15] However, our patient developed her symptoms more than a month after returning from Kenya and did not show any signs of a rash or eschar. A rickettsial infection was therefore less likely to be the cause of the symptoms present during her second admission to the hospital.

Another explanation for the neurological symptoms of our patient could have been the earlier prescribed medication. Neurological symptoms induced by quinolones (such as ciprofloxacin) develop during the first days of treatment and disappear within 24 to 48 hours after discontinuation. So the time interval excludes a side effect of ciprofloxacin. A quinine intoxication was another option in our differential diagnosis. Calculated creatinine clearance on admission was 34 ml/min, which needed readjustment of the dosage of quinine. After rehydration creatinine clearance was 66 ml/min within two days, which justifies normal dosage. Quinine intoxication results in hypokalaemia, hypoglycaemia, cardiotoxicity, visual symptoms (also blindness) and neurological features as convulsions, coma and ataxia.[18-21] Except for the neurological symptoms our patient did not have any of the symptoms mentioned above. Normally these symptoms develop during or shortly after the usage of quinine. In our patient the symptoms developed 14 days after the last gift of quinine, and therefore a quinine intoxication was less likely.

It was most likely that she had PMNS or ADEM. Both syndromes have been reported following complete recovery of *P. falciparum* infection.[3,5-10,12]

In general, the inclusion criteria for PMNS are recent symptomatic malarial infection with parasites cleared from the blood, full recovery in cases of cerebral malaria and the development of new neurological or psychiatric symptoms within two months of acute illness.[7]

ADEM is an uncommon inflammatory demyelinating disease of the central nervous system with multifocal neurological symptoms, signs of an acute meningoencephalopathy, depressed level of consciousness, focal or generalised seizures, and psychosis. The disease is usually preceded by a viral or bacterial infection or a vaccination and has occasionally been reported in the literature following *P. falciparum* infection.[10,12]

PMNS was first described by Mai *et al.* in 1996. [7] They found 22 cases with PMNS in 18,124 patients treated for a *P. falciparum* infection from Vietnam and Thailand of whom 1176 had severe infections; 21 patients with PMNS had had a severe infection. Incidence in this population was estimated at 1.2 per 1000 patients (95% CI 0.7 to 1.8). The true incidence is probably higher, because people with mild neurological signs and symptoms do not visit a hospital and could have been treated at home. PMNS has been described only after *P. falciparum* infections, not after infections caused by other *Plasmodium* species.[7-9] At the time of the diagnosis all patients were aparasitaemic. The median time from parasite clearance to the onset of neurological symptoms was four days (range 6 hours to 60 days).[7] In our patient neurological symptoms were found 17 days after the first negative peripheral blood smear. In PMNS acute confusion or psychosis was seen in 13 cases, seizures in eight and a fine tremor of the extremities in one.[7] Serum and CSF investigations showed no other cause such as metabolic disorders or infections that explains these features. A minor increase in the CSF protein level was found in 13 patients described by Mai *et al.*,[7] both patients described by Schnorf *et al.*,[8] the case of Mohsen *et al.*[10] and in our patient. All patients described by Mai *et al.*[7] recovered spontaneously within ten days. They suggested a relation with the use of mefloquine.

Mefloquine may cause neuropsychiatric symptoms and seems to be a risk factor for developing PMNS, although five of 22 patients with PMNS were not taking mefloquine. In the randomised trial by Mai *et al.* ten patients out of 228 who were on mefloquine developed PMNS and one out of 210 treated with quinine developed PMNS.[7] Both patients reported by Schnorf *et al.* were taking quinine[8] as was our patient.

The clinical spectrum of PMNS was expanded by Schnorf *et al.*[8] They classify PMNS according to the severity of symptoms:

1. Mild or localised form characterised by isolated cerebellar ataxia or postural tremor.
2. Diffuse, but relatively mild self-limiting encephalopathy characterised by acute confusion or epileptic seizures.
3. Severe, progressive corticosteroid-responsive encephalopathy, characterised by motor aphasia, generalised myoclonus, postural tremor, and cerebellar ataxia.

This classification includes cerebellar ataxia occurring after *P. falciparum* infection, which was first described in Sri Lanka by Senanayake in 1984.[5,6] Senanayake and de Silva reported 74 patients with cerebellar ataxia after *P. falciparum* infection.[6] All these patients were fully conscious and alert without any signs of cerebral involvement. They all had gait ataxia. One third of these patients still had a parasitaemia at the time the ataxia occurred in contrast to the patients with PMNS. Ataxia started 3 to 41 days (median time 13 days) after the last febrile period and there was no response on antimalarial therapy, which suggests that the *P. falciparum* infection was not the cause of the cerebellar ataxia.[5,6]

Our patient with a progressive course of confusion, drowsiness, intention tremor and word-finding difficulties had a severe PMNS according to the classification by Schnorf *et al.*[8] Rapid recovery was seen after starting prednisone 75 mg/day for three days, followed by tapering by 10 mg/day.[6,8] Both patients described by Schnorf *et al.* were treated with prednisone 9 and 12 days respectively after development of the neurological features.[8] Treatment with prednisone (60 mg/day for seven days, than tapered) was given to three of 74 patients with cerebellar ataxia in the studies of Senanayake and de Silva. One patient recovered within seven days, while the symptoms of the others remained for two to 30 days.[5,6] In summary, treatment with prednisone is suggested when there is a severe and progressive course of PMNS.

Aetiology of PMNS remains unclear. As in cerebellar ataxia and ADEM, it seems to have an immunological origin.[3,5-8,10,11] The delay between the onset of the *P. falciparum* infection and the PMNS might also support an immunological mechanism, just as the rapid response to prednisone treatment.

Schnorf *et al.*[8] and Mohsen *et al.*[10] found normal brain CT scans, while MRI in two patients showed several discrete white matter lesions, which have also been described in mild ADEM. However, white matter lesions are far more prominent in most cases with ADEM including those with minor signs and symptoms.[10,11] The hallmark lesions of ADEM are perivenular inflammation and surrounding demyelination which may be minimal or widespread, with coalescence of the multiple lesions. ADEM is characterised by the presence of hyperintense lesions in brain MRI or diffuse or scattered low-density lesions in the white matter. Recovery can begin within days, with complete resolution occasionally noted within a few days, but more often over the course of weeks or months.[10-12] In postmalarial cerebellar ataxia demyelinating lesions have been described in the pons and cerebellar peduncles which disappeared after resolution of symptoms, but in two other cases MRI was normal.[12-14]

Unfortunately, in our patient MRI scanning was not possible. CT scanning did not show any abnormalities. From the evolution of signs and symptoms we concluded that our patient was suffering from PMNS, but a relation between PMNS and ADEM remains possible.

CONCLUSION

The aim of this case report was to draw attention to neurological syndromes after *P. falciparum* infection, especially the postmalaria neurological syndrome, which has not been described before in the Netherlands. Patients with a severe *P. falciparum* infection can develop a neurological syndrome which is related to a prior adequately treated *P. falciparum* infection after an initial good and rapid recovery. What is important is the fact that no parasites can be found in the blood when these symptoms emerge. It can be difficult to distinguish between PMNS and ADEM, which are possibly related. Most patients show spontaneous recovery. Treatment with steroids may be considered when the features are severe and the course is progressive.[8] Aetiology remains unclear, but an immune mechanism seems probable.[5-8,11]

REFERENCES

1. Sauerwein RW. Vaccins tegen malaria: nieuw perspectief. Ned Tijdschr Geneeskd 2000;2:64-9.
2. Leder K, Weller PF. Epidemiology, pathogenesis, clinical features, and diagnosis of malaria. Up to Date (11.1) 2003.
3. Garg RK, Karak B, Misra S. Neurological manifestations of malaria: an update. Neurol India 1999;47:85-91.
4. Richard E, Vreede WB, van Rosenstiel IA. Een gezin met malaria: van asymptomatisch tot levensbedreigend. Ned Tijdschr Geneeskd 2001;49:2361-3.
5. Senanayake N. Delayed cerebellar ataxia: a new complication of falciparum malaria? BMJ 1987;294:1253-4.
6. Senanayake N, de Silva HJ. Delayed cerebellar ataxia complicating falciparum malaria: a clinical study of 74 patients. J Neurol 1994;241:456-9.
7. Mai NTH, Day NPJ, Chuong LV, et al. Post-malaria neurological syndrome. Lancet 1996;348:917-21.
8. Schnorf H, Diserens K, Schnyder H, et al. Corticosteroid-responsive postmalaria encephalopathy characterized by motor aphasia, myoclonus, and postural tremor. Arch Neurol 1998;55:417-20.
9. Seneviratne U, Gamage R. Brainstem dysfunction: another manifestation of post-malaria neuroloical syndrome? Ann Trop Med Parasitol 2001;95:215-7.
10. Mohsen AH, McKendrick MW, Schmid ML, Green ST, Hadjivassiliou M, Romanowski C. Postmalaria neurological syndrome: a case of acute disseminated encephlomyeltis? J Neurol Neurosurg Psychiatry 2000;68(3):388-9.
11. Murthy JM. Acute disseminated encephalomyelitis. Neurol India 2002;50:238-43.
12. Dey AB, Trikha I, Banerjee M, Jain R, Nagarkar KM. Acute disseminated encephalomyelitis. Another cause of post malarial cerebellar ataxia. J Assoc Physicians India 2001;49:756-8.
13. Girard PM, de Broucker T, Fryer DG, Netter JM, Saimot AG, Coulaud JP. Cerebellar syndrome in mild Plasmodium falciparum malaria. Trans R Soc Trop Med Hyg 1988;82(2):204.
14. Chaine P, Woimant F, Corabianu O, Fayada C, Haguenau M. Isolated cerebellar syndrome: an atypical form of cerebral malaria. J Neurol Neurosurg Psychiatry 1991;54(7):655.
15. Cowan GO. Rickettsial infections. In: Cook GC, editor. Manson's tropical diseases. 20th edition. London, 1996. p.798-810.
16. Ali G, Rashid S, Kamli MA, Shah PA, Allaqaband GQ. Spectrum of neuropsychiatric complications in 791 cases of typhoid fever. Trop Med Int Health 1997;2(4):314-8.
17. Wadia RS, Ichaporia NR, Kiwalkar RS, Amin RB, Sardesai HV. Cerebellar ataxia in enteric fever. J Neurol Neurosurg Psychiatry 1985;48(7):695-7.
18. Bateman DN, Dyson EH. Quinine toxicity. Adverse Drug React Acute Poisoning Rev 1986;5(4):215-33.
19. Jeager A, Sauder P, Kopferschmitt J, Flesch F. Clinical features and management of poisoning due to antimalarial drugs. Med Toxicol Adverse Drug Exp 1987;2(4):242-73.
20. Boland ME, Roper SM, Henry JA. Complications of quinine poisoning. Lancet 1985;1:384-5.
21. White NJ. The treatment of malaria. N Engl J Med 1996;335:800-6.

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CASE REPORT

Treatment of postoperative bleeding after fondaparinux with rFVIIa and tranexamic acid

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ABSTRACT

Treatment of a haemorrhagic shock after just a single dose of fondaparinux in an orthopaedic patient with reduced renal clearance is presented. Since all routine haemostatic parameters were nearly normal, single doses of rFVIIa (90 µg/kg) and of tranexamic acid (15 mg/kg) were administered to improve thrombin generation and reduce fibrinolysis.
This case is the first showing the effectiveness of combining single doses of rFVIIa and tranexamic acid in controlling severe postoperative bleeding after fondaparinux.

KEYWORDS

Activated, clearance, factor VII, female, fibrinolysis, fondaparinux, haemorrhagic, orthopaedic, pentasaccharide, postoperative bleeding, recombinant, renal, shock, surgery, tranexamic acid

INTRODUCTION

Venous thromboembolism (VTE) develops in about 15% of orthopaedic patients after total hip replacement, despite the use of the current thromboprophylactic treatment, particularly low-molecular-weight heparins (LMWHs).[1] Recent studies suggest a superior efficacy of the new pentasaccharide fondaparinux over LMWHs in major orthopaedic surgery, resulting in no increase in the risk of fatal bleeding and need for reintervention, despite a higher nonfatal bleeding rate.[2] The present case is the first report of a patient developing severe postoperative bleeding after 2.5 mg of fondaparinux, which was successfully terminated after the administration of 6 mg recombinant activated factor VII (rFVIIa), combined with tranexamic acid.

CASE REPORT

A hip prosthesis was revised in a 79-year-old female patient. The patient had documented hypertension, and had previously undergone a subtotal thyroidectomy, and total hip replacement on both sides. There was no patient or family history of bleeding tendency. Perioperative medical treatment (aminocetophen as necessary, omeprazol 20 mg, calcium citrate 500 mg, raloxifene 60 mg, indapamine 2.5 mg, all once daily) was interrupted eight hours prior to surgery. During the surgical procedure the femur was exposed subtotally. Peroperative blood loss (1500 ml) was replaced by crystalloids. Postoperative blood management was according to the hospital's transfusion algorithm developed to reduce allogeneic red blood cell transfusions for major orthopaedic surgery, restricting red cell transfusion to patients over 60 years of age and with Hb levels <5.0 mmol/l, and to patients with cardiac disease and with Hb levels <5.5 mmol/l.[3] In order to prevent deep venous thrombosis the first dose of fondaparinux (2.5 mg) was administered subcutaneously six hours postoperatively (t=6 h). At that time the haemoglobin level was 6.5 mmol/l, blood pressure 135/60 mmHg, heart rate 60 beats/min, and blood loss per drain 75 ml/h. At t=17 hours the patient had received just one single dose of fondaparinux and haemorrhagic shock developed due to a severe bleed from the operative site as monitored by wound drains: haemoglobin (Hb) 3.7 mmol/l, blood pressure 90/40 mm Hg, heart rate 110 beats/min. Three units of red blood cell concentrates were transfused resulting in a clear rise in haemoglobin level (5.8 mmol/l) and blood pressure (130/50 mmHg). However, in the following hours blood loss persisted at an average drain rate of 75 ml/h, with deterioration of the anaemia (Hb 3.5 mmol/l), and development of atrial fibrillation. At t= 39 hours three additional units of red blood cell concentrates were transfused resulting in an increased Hb level (5.4 mmol/l). Coagulation parameters were checked as bleeding persisted 35 hours after a single dose of 2.5 mg fondaparinux. Since the platelet count was 69 x 10^9/l, and all routine coagulation parameters (INR 1.5, prothrombin time (PT) 15 seconds, activated partial thromboplastin time (APTT) 38 seconds, and Ca^{2+} 1.39 mmol/l) were nearly normal, plasma concentrates and platelets were not administered.

However, rFVIIa, being the only known antidote for severe bleeding after fondaparinux, was administered intravenously.[4-6] Simultaneously, intravenous tranexamic acid therapy (1 g three times a day) was started to stop fibrinolysis. Within one hour, blood loss diminished from 75 to an average of 2 ml/h by drain, which did not increase during the following 24 hours. Arterial blood pressure and Hb level rose after one final unit of red blood cell concentrate: RR 160/60 mmHg, heart rate 80 beats/min, Hb 5.9 mmol/l. The coagulation parameters (INR 0.9, PT 9 sec, APTT 38 sec) and platelet count (59*10^9/l) remained stable.

DISCUSSION

This case shows the risk of severe postoperative bleeding even after a single dose of fondaparinux in orthopaedic patients with reduced renal clearance. Furthermore, it is the first case showing the effectiveness of a single dose of rFVIIa in combination with tranexamic acid in controlling severe bleeding after postoperative thromboprophylactic treatment with fondaparinux in elective orthopaedic surgery. Fondaparinux, the first of a new class of synthetic pentasaccharides, binds to antithrombin (AT-III), thereby increasing its activity towards inactivation of factor Xa by about 300 times, and delaying tissue factor-induced clot formation. Furthermore, fondaparinux accelerates fibrinolysis due to downregulation of the activation of thrombin-activatable fibrinolysis inhibitor (TAFI).[6] However, it has no direct effect on thrombin, nor on platelets.[7]
Fondaparinux has improved antithrombotic effectiveness after both total knee and hip replacement in comparison with low-molecular-weight heparins.[2] In a meta-analysis of four trials, patients receiving fondaparinux had a >50% reduction in the relative risk of VTE at day 11 compared with LMWHs, but more postoperative bleeding.[2]
Fondaparinux is completely resorbed two hours after subcutaneous injection and has a variable half-life depending on kidney function and age: $T^1/_2$ is 17 hours in young healthy adults, 21 hours in the elderly, 29 hours at creatinine clearance 30 to 50 ml/min, and 72 hours when creatinine clearance <30 ml/min[7] and is registered for once-daily usage. Consequently, the drug must still be active after two half-lives. In this case report the patient's creatinine clearance was 45 ml/min according to the Cockroft formula, which resulted in an estimated fondaparinux $T^1/_2$ of 29 hours at minimum, suggesting the drug was effective for up to 58 hours.
Since the classical coagulation parameters (INR, APTT and PT) were (nearly) normal and the platelet count was adequate at the time of the haemorrhagic shock, administration of coagulation factors and suppletion of platelets was not necessary.[8] According to some studies severe bleeding after fondaparinux in the presence of sufficient coagulation factors is best stopped by recombinant FVIIa.[4-6] Factor VIIa activates factor X, which initiates the conversion of prothrombin into thrombin, also partially improves thrombin-activatable fibrinolysis inhibitor (TAFI)-mediated inhibition of fibrinolysis.[6] The potential clinical use of rFVIIa as haemostatic treatment of major bleedings related to fondaparinux has not been evaluated, but its *ex-vivo* effectiveness has been proven.[5,6] Furthermore, rFVIIa is capable of normalising coagulation times and thrombin generation during fondaparinux treatment in healthy subjects.[4] Accordingly, both 90 µg/kg rFVIIa and 15 mg/kg tranexamic acid, an antifibrinolytic agent with active serum plasma levels for seven to eight hours, were administered intravenously. Within one hour bleeding stopped and blood pressure normalised. Despite rFVIIa's short $T^1/_2$ no additional doses were needed, possibly because of the additional antifibrinolytic activity of the tranexamic acid. Since the direct cost of rFVIIa was € 3900 and of tranexamic acid was just € 21, it is suggested from the present case to use combined treatment of just a single dose of rFVIIa and an antifibrinolytic agent to resolve bleeding problems after the use of fondaparinux in orthopaedic surgery and in the presence of near-normal coagulation parameters. Otherwise, in case of a prolonged prothrombin time and APTT, the coagulation should be first normalised using human plasma.

REFERENCES

1. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. Chest 2001;119(1):S132-75.
2. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002;162(16):1833-40.

3. Slappendel R, Dirksen R, Weber EW, van der Schaaf DB. An algorithm to reduce allogenic red blood cell transfusions for major orthopedic surgery. Acta Orthop Scand 2003;74(5):569-75.
4. Bijsterveld NR, Moons AH, Boekholdt SM, et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. Circulation 2002;106(20):2550-4.
5. Gerotziafas GT, Depasse F, Chakroun T, Samama MM, Elalamy I. Recombinant factor VIIa partially reverses the inhibitory effect of fondaparinux on thrombin generation after tissue factor activation in platelet rich plasma and whole blood. Thromb Haemost 2004;91(3):531-7.
6. Lisman T, Bijsterveld NR, Adelmeijer J, et al. Recombinant factor VIIa reverses the in vitro and ex vivo anticoagulant and profibrinolytic effects of fondaparinux. J Thromb Haemost 2003;1(11):2368-73.
7. Samama MM, Gerotziafas GT. Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). Thromb Res 2003;109(1):1-11.
8. Kamphuisen PW, Levi M, van Kraaij MG, Kaasjager HA, Frolke JP. Diagnostic and pharmaco-therapeutic options in acute severe blood loss. Ned Tijdschr Geneeskd 2004;148(39):1907-11.

ABOUT THE COVER

'Untitled'

Carole Witteveen

This month's cover shows a graphic art, mixed technique/silk-screen printing by Carole Witteveen.
Carole works in Nijmegen, the Netherlands. She attended the Academy of Art in Arnhem and the Jan van Eijk Academy in Maastricht. She teaches at the Academy of Art in Arnhem, and has exhibited her work at numerous individual and group exhibitions in the Netherlands (Villa Sonsbeek and De Gele Rijder in Arnhem, Galerie Magenta in Nijmegen, Museum Waterland in Hoorn, Purmaryn Grafiek in Purmerend, Kunst in de AA Kerk in Groningen and Kunst Rai Amsterdam 2003) and abroad at Kunstverein in Basel, Switzerland, Zentrum Artoll in Bedburg-Hau, Germany, Centro La Luz in Santander, Spain, Les Images in Kasteel Brasschaat, Belgium, Kunstraum in Wuppertal, Germany, and Solas Sillas, Spain). She has served on a number of committees for advice and selection of art and participated in the Dutch television programme Kunst te Kijk (Viewing Art). In her work, she wants to depict beauty and desire, metamorphosis and changes, myth and reality; things around us that we see but do not observe.
A limited edition (5) of original print of this month's cover (size 30 x 40) is available at a price of € 275. You can order the print at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail to galerie-unita@planet.nl. Galerie Unita is online at www.galerie-unita.com.

ANSWER TO PHOTO QUIZ (ON PAGE 179)
A PATIENT WITH ABDOMINAL DISTENSION

DIAGNOSIS

Clinical presentation suggested mechanical bowel obstruction, although conventional radiographs did not support this. Because no signs of peritonitis were present, initially a more conservative treatment was started. We were surprised by the abdominal mass, which was also present on the CT, showing the small bowel faeces sign which is usually caused by partial mechanical obstruction of the small bowel.[1] The proximal part of the small intestine was filled with contrast, followed by distended loops filled with faecal-like material. More distally, no intraluminal contrast or fluids were seen.
Partial small bowel obstruction causes slow transit time leading to reabsorbing fluid. Once thickened only liquids will pass. Bacterial overgrowth causes gas bubbles as we normally see in the colon. An abdominal radiograph taken 12 hours after CT scanning showed contrast in the rectosigmoid (*figure 3*).

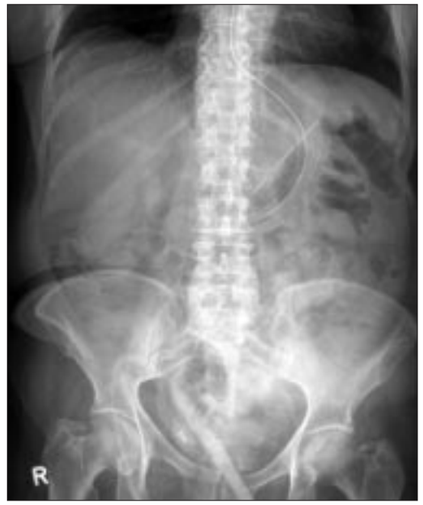

Figure 3
Abdominal X-ray 12 hours after drinking oral contrast

Based on the findings of the CT, the patient underwent abdominal surgery. The small intestine was partially fixated probably due to abdominal trauma during a car accident eight years before. Thickened faeces-like material was manually pushed towards the colon after adhesiolysis took place. There were no signs of peritonitis or malignancy.
The small bowel faeces sign suggests a slowly developing partial mechanical obstruction leading to a slow transit state, such as adhesions, hernias or tumours.
Once clinical presentation of small bowel obstruction is protracted, CT imaging can lead the clinician in making treatment decisions.

REFERENCE

1. Michael Fuchsjager. The small-bowel feces sign. Radiology 2002;225:378-9.

Bijsluiters

INFORMATION FOR AUTHORS

Aims and scope
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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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