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EDITORIAL

To screen or not to screen patients with an idiopathic venous thrombosis for an occult cancer: Netherlands versus the World: 1-0?

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Ever since Armand Trousseau reported the association between venous thromboembolism and cancer, we have been speculating whether screening patients with an idiopathic venous thrombosis for an occult cancer is useful. It is only worthwhile to do that when the cancer that we want to discover is limited and can be treated with curative intent. In the Netherlands, our Calvinistic approach has always been to do a thorough medical history and physical examination. When no alarming symptoms or abnormalities are found, we have always been taught that screening for a hidden cancer is not justified. In many other countries the same patient would have been screened thoroughly with total body CT scans, endoscopy, urological and gynaecological examinations, mammography and extensive laboratory tests including all tumour markers that are currently known. It has never been established which approach is the best.[1,2]

Until recently, only one randomised trial had been done to try to answer this question: to screen or not to screen patients with an idiopathic venous thrombosis for an occult cancer. Unfortunately this study failed and was stopped prematurely. The main reason for stopping the trial was that in the group with limited screening, patients and doctors requested more screening tests than previously agreed in the protocol. Therefore, the patient group with limited screening was in fact not very different from the group with extensive screening. Moreover, patient accrual was difficult because patients wanted to be screened in the extensive and not the limited way. No differences were found.[3]

It has been the merit of the Dutch Trousseau investigators that they have again tried to answer this question. Of course, the Netherlands was the ideal country to investigate the limited approach with only medical history, physical examination, chest X-ray and routine laboratory tests. This approach was compared with an extensive (or as the rest of the world would call it: less limited) approach, including an additional CT scan of the thorax and abdomen and mammography in women. Extensive screening detected slightly more cancers than the limited approach of which half were not curable. There was no difference in overall survival. It was definitely concluded that routine screening with CT scans and mammography in patients with an idiopathic venous thrombosis is not justified.[4]

In this Journal the same group (Kleinjan *et al.*) reports that the extensive screening with CT scans and mammography in the Trousseau study leads to additional costs due to a high percentage of false-positive findings.[5] In an era in which the costs in healthcare are extensively debated all over the world it is important to investigate whether a screening approach is cost-effective. Moreover, screening strategies resulting in false-positive findings leading to costly and invasive procedures potentially harming patients should be avoided. New approaches with FDG-PET/CT as screening strategy are currently under investigation, but the first reports do not show improvement in the cancer detection rate and costs.[6]

Hence, screening patients with an idiopathic venous thrombosis for an occult cancer with (PET) CT scans should **not** be implemented. It leads to extra costs, does not lead to the detection of curable cancers and does not lead to a better overall survival. The Trousseau study even raises the question whether the limited approach with medical history, physical examination, chest X-ray and routine laboratory testing is too extensive. There is no evidence that this approach is any better than a very limited approach with a precise medical history, a complete physical examination and only additional tests when abnormalities are found. Therefore, in patients with an idiopathic venous thrombosis screening for an occult cancer should be limited. The old Calvinistic Dutch approach does not seem to be that bad at all and this (very) limited approach should be adopted by the rest of the world.

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REVIEW

Comorbidity complicates cardiovascular treatment: is diabetes the exception?

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ABSTRACT

Background: Many patients with cardiovascular disease do not attain the targets for health-related lifestyle and preventive treatment recommended in practice guidelines. The aim of this study was to assess the impact of diabetes (DM) and chronic obstructive pulmonary disease (COPD) on the quality of cardiovascular risk management in patients with established cardiovascular diseases (CVD).

Methods and Results: Patients with established CVD were randomly selected in primary care practices using recorded diagnoses. Structured case forms were used to review data on 20 performance indicators concerning CVD from medical records. Descriptive and multilevel regression analyses were conducted.

In 45 primary care practices with 106 physicians in the Netherlands, 1614 medical records of patients with CVD (37.9% women) were reviewed. A total of 1076 (66.7%) patients had recorded CVD only (reference group); 7.8% had CVD and COPD; 22.4% had CVD and DM; 3.1% patients had CVD, COPD and DM. Compared with the reference group, patients with CVD and DM yielded higher scores on 17 of 20 indicators; patients with CVD, DM and COPD on 14 indicators; and patients with CVD and COPD on three indicators. Of the patients with CVD and DM, fewer patients had LDL-cholesterol levels over 2.5 mmol/l (OR=0.36; 95% CI 0.26-0.50), more had antiplatelet drugs prescribed (OR=1.72; 95% CI 1.17-2.54), and more had systolic blood pressure measurement (OR=4.12; 95% CI 2.80-6.06).

Conclusions: This study showed that DM but not COPD was associated with more comprehensive cardiovascular risk management. This finding adds to cumulating evidence that presence of DM is associated with better preventive treatment of cardiovascular risk.

KEYWORDS

Cardiovascular diseases, comorbidity, disease management, primary health care, quality of care

INTRODUCTION

Cardiovascular disease (CVD) remains an important cause of death and disability in the world. In the United States, 33.6% of all deaths are caused by CVD.[1] Similar numbers were found in the Netherlands where one in three individuals dies of CVD (Netherlands Heart Foundation).[2] Many activities have been developed to prevent CVD in public health and in primary care.[3,4] Despite these activities and a range of practice guidelines,[5,6] many individuals receive suboptimal cardiovascular risk management. Many cardiovascular disease patients do not attain the lifestyle, risk factor and therapeutic targets that are recommended.[6,7] One reason may be the presence of comorbidity in CVD patients, which can complicate treatment.[8-10] The prevalence of comorbidity in patients with cardiovascular risk is high, especially in patients over the age of 65 years.[11] Practice guidelines tend to ignore comorbidity, although adherence to a guideline for one disease may have a negative effect in treatment of a co-existing disease.[10] Nevertheless, studies on guideline adherence concerning patients with comorbidity have remained inconclusive and whether higher guideline adherence results in better health outcomes in patients with comorbidity is as yet unclear. On the one hand, many multi-morbid patients receive multiple drugs which may compromise adherence and safety of treatment.[12] Research has also suggested that these patients have a poorer functional status or quality of life, a higher

mortality risk and greater use of health services.[13] On the other hand, some studies have in fact shown a positive association between the number of medical conditions and guideline adherence.[14-17] For instance, a Dutch survey demonstrated that patients with chronic heart failure and diabetes mellitus (DM) received treatment that was more consistent with guideline recommendations than patients with chronic heart failure but no DM.[18] Furthermore, type of comorbid conditions may also be of influence on guideline adherence.[9,19]

The aim of this study was to assess the impact of DM and chronic obstructive pulmonary disease (COPD) on measures of cardiovascular risk management in patients with established CVD. Given the commonalities in the preventive treatment of the three conditions, which is illustrated by overlapping quality indicators, we expected comorbidity to be associated with higher scores on these measures.

MATERIALS AND METHODS

Design

This study was based on the baseline measurement in a cluster randomised trial no. NCT00791362, which was executed from September 2008 until February 2011. The trial aimed to determine the effectiveness and efficiency of a national accreditation and improvement program (NHG-Praktijkaccreditering) for primary care practice, focusing on patients with established CVD. The national accreditation and improvement program was a new strategy for quality improvement in Dutch primary care. It consists of a set of implementation interventions including: audit and feedback, outreach visits by trained facilitators and planning improvements according to the quality management principles. The Arnhem-Nijmegen ethics committee waived approval for this trial. Data were collected by audit of electronic medical records of primary care patients in the Netherlands.

Study population

We recruited patients with established CVD, namely angina pectoris, acute myocardial infarction, transient ischaemic attack (TIA), ischaemic stroke, peripheral arterial disease, aortic aneurysm and other chronic ischaemic heart diseases. Selection of patients with these conditions was based on corresponding diagnostic codes (ICPC K74, K75, K89, K90.3, K92.1, K99.1 and K76). Patients were classified as having DM or COPD if the corresponding diagnostic codes (T90 for DM, R95 for COPD) were recorded in their medical record. Patients were recruited from 45 primary care practices involving 106 family physicians in the Netherlands who agreed to participate in the study. All primary care practices which voluntarily enrolled in the Dutch national accreditation program (NHG-Praktijkaccreditering) from December 2008 until March 2010 were invited by letter to participate in the study. All primary care practices used electronic medical records, which is common in the Netherlands, and International Classification of Primary Care codes (ICPC codes), a worldwide system to label conditions in primary care.[20]

Measurements

In each practice 40 patients with established CVD were randomly sampled from the practice register. Data collection, related to the last 12 months, was based on quality indicators for established CVD[21] (developed by the Dutch College of Family Physicians), which included: systolic blood pressure in mmHg measured in the practice, LDL cholesterol in mmol/l, prescription of statin and antiplatelet drugs, smoking status, stop smoking advice, body mass index in kg/m^2, waist circumference ever measured, fasting glucose measurement measured in the past five years, influenza vaccination, registration of alcohol intake and control and advice on exercise and diet. This set of 20 indicators was complemented by information on age, sex and the presence of comorbidity (COPD and DM). Paper-based abstraction forms were used to collect data. Data were manually abstracted out of electronic medical records from January 2009 until May 2010. The starting point in this study was indicators related to established CVD[21] but when considering indicators for all three chronic illnesses,[21-23] seven indicators were commonly shared. These indicators were: exercise control, influenza vaccination, measurement of BMI, BMI <25 kg/m^2, smoking status, patient is a smoker and stop smoking advice. Eight indicators concerned both established CVD and DM. These indicators were: systolic blood pressure measurement, systolic blood pressure <140 mmHg, LDL-cholesterol measurement, LDL cholesterol <2.5 mmol/l, advice on physical activity, diet control, counselling about diet and registration of alcohol intake. Five indicators related to established CVD only (measurement of waist circumference, prescription of antiplatelet drugs, fasting glucose measurement, patients with LDL cholesterol ≥2.5 mmol/l with statin prescription and comprehensive risk assessment).

Statistical analysis

Data were analysed using the SPSS 16.0 software package (Chicago, Illinois, USA). Outcome measures were all indicators as described above. All indicators (all dichotomous outcomes) were included in a two-level logistic regression, taking into account the hierarchical structure of our study (patients nested within practices). Multilevel analysis was performed in the SAS 9.2 package with procedure PROC GLIMMIX. We performed a logistic

model (with a binomial distribution and a logit link function) with a random intercept and all other variables (group, age and sex) fixed. Only patient variables were included in the model. In the multilevel regression analysis four groups were taken into account. The first group, the reference group, consisted of patients with CVD only, the second group were patients with CVD and COPD, the third group were patients with CVD and DM, the fourth group were patients with CVD, DM and COPD.

RESULTS

Of the 336 practices invited to participate in this study, 45 entered the study, representing 106 family physicians. In 45 practices a random sample of 1614 patients with established CVD and possibly DM and/or COPD as comorbidity was recruited.

Table 1 presents characteristics of the study population. More men (62.1%) were included in the sample. The mean age was 69.5 years (SD 11.8). A total of 1076 (66.7%) patients had CVD only; 126 (7.8%) had CVD and COPD; 362 (22.4%) had CVD and DM; and 50 (3.1%) patients had CVD, COPD and DM. *Table 2* describes the cardiovascular diseases. The most common cardiovascular history was angina pectoris (37.4% of patients) followed by myocardial infarction (30%). Of patients with multiple cardiovascular disorders (n=247) 37.2% had coronary heart disease only (K74, K75, K76), 31.6% had coronary heart disease and peripheral arterial disease or aortic aneurysm (K92.1, K99.1) and 22.3% had coronary heart disease and TIA or ischaemic stroke (K89, K90.3). *Table 3* shows that in audited records, recording was best for blood pressure measurement (75.9%), influenza vaccination (76.3%) and prescription of antiplatelet drugs (84.8%) and worst for risk assessment (4.8%). Goals for outcome measurement BMI (<25 kg/m^2) were achieved in 16.9% of patients whose BMI was measured. Systolic blood pressure was <140 mmHg in 60.2% of patients with a record of BP, and LDL-cholesterol levels were below 2.5 mmol/l in 46.8% of patients with a record of LDL cholesterol.

Indicator scores

Indicators shared across conditions

Of the seven indicators that are relevant for each of the conditions, three to five yielded higher scores in patients with DM and/or COPD in addition to CVD (*table 4*). Smoking status was better registered for all patients with comorbidity compared with patients with CVD only. In the group of patients with CVD and COPD and in patients with CVD, DM and COPD more smokers were present (odds ratio (OR)=4.13; 95% confidence interval (CI) 2.26-7.54; OR=2.61; 95% CI 1.23-5.54). Patients with CVD and DM and patients with CVD, DM and COPD had more recordings of BMI (OR=7.09; 95% CI 5.24-9.60; OR=7.97; 95% CI 4.16-15.30) and control of exercise (OR=6.26; 95% CI 4.69-8.35; OR=5.72; 95% CI 3.06-10.68). More patients with CVD and DM and patients with CVD and COPD received influenza vaccinations (OR=1.84; 95% CI 1.30-2.59; OR=1.99; 95% CI 1.15-3.44) than patients with CVD only. No differences between groups were identified regarding the process measurement 'stop smoking advice'.

Table 1. *Characteristics of the study population (n=1614)*

	CVD (%)	CVD+COPD (%)	CVD+DM (%)	CVD+DM+COPD (%)	Total scores (%)
Men	665 (61.8)	90 (71.4)	212 (58.6)	36 (72)	1003 (62.1)
Women	411 (38.2)	36 (28.6)	150 (41.4)	14 (28)	611 (37.9)
Total	1076 (66.7)	126 (7.8)	362 (22.4)	50 (3.1)	1614
Mean age in years (SD)	68.7 (12.2)	71.3 (9.6)	70.9 (10.9)	70.1 (11.4)	69.5 (11.8)

Table 2. *Type of cardiovascular disease*

	ICPC	CVD (%)	CVD+COPD (%)	CVD+DM (%)	CVD+DM+COPD (%)	Total scores (%)
AP	K74	401 (37.5)	51 (40.8)	123 (34.5)	23 (46)	598 (37.4)
MI	K75	324 (30.3)	44 (35.2)	98 (27.5)	15 (30)	481 (30)
Other chronic IHD	K76	108 (10.1)	8 (6.4)	47 (13.2)	6 (12)	169 (10.6)
TIA	K89	175 (16.4)	17 (13.6)	48 (13.4)	2 (4)	242 (15.1)
Ischaemic stroke	K90.3	77 (7.2)	4 (3.2)	23 (6.4)	3 (6)	107 (6.7)
PAD, intermittent claudication	K92.1	104 (9.7)	17 (13.6)	68 (19)	9 (18)	198 (12.4)
Aortic aneurysm	K99.1	56 (5.2)	13 (10.4)	10 (2.8)	3 (6)	82 (5.1)

AP = angina pectoris; IHD = ischaemic heart disease; MI = myocardial infarction; PAD = peripheral arterial disease; TIA = transient ischaemic attack.

Table 3. *Record of indicators for cardiovascular risk management in electronic medical records*

Type of indicator	Indicators commonly shared across CVD/COPD/DM	CVD (%)	CVD+COPD (%)	CVD+DM (%)	CVD+DM+ COPD (%)	Total (%)
Process	Smoking status	359 (33.4)	62 (49.2)	212 (58.6)	35 (70)	668 (41.5)
Outcome	Patient is a smoker	110 (30.6)	36 (58.1)	43 (20.2)	18 (51.4)	207 (41.6)
Process	Stop smoking advice	60 (54.5)	22 (61.1)	26 (60.5)	12 (66.7)	119 (54.8)
Process	BMI measured	191 (17.8)	29 (23)	189 (52.2)	29 (58)	438 (27.2)
Outcome	BMI <25 kg/m^2	38 (19.9)	6 (20.7)	26 (13.8)	4 (13.8)	74 (16.9)
Process	Influenza vaccination	784 (72.9)	106 (84.1)	301 (83.1)	39 (78)	1230 (76.3)
Process	Exercise control	209 (19.4)	25 (19.8)	191 (52.8)	25 (50)	450 (27.9)
	Indicators shared across CVD/DM					
Process	Systolic blood pressure measured	755 (70.2)	90 (71.4)	329 (90.9)	48 (96)	1222 (75.9)
Outcome	Systolic blood pressure <140 mmHg	464 (61.5)	50 (55.6)	196 (59.6)	26 (54.2)	736 (60.2)
Process	LDL cholesterol measured	446 (41.4)	54 (42.9)	267 (73.8)	38 (76)	805 (50)
Outcome	LDL cholesterol <2.5 mmol/l	170 (38.1)	20 (37.0)	166 (62.2)	21 (55.3)	377 (46.8)
Process	Advice physical activity	150 (13.9)	19 (15.1)	142 (39.2)	16 (32)	327 (20.3)
Process	Diet control	137 (12.7)	17 (13.5)	216 (59.7)	28 (56)	398 (24.7)
Process	Counselling about diet	158 (14.7)	14 (11.1)	197 (54.4)	26 (52)	395 (24.5)
Process	Registration of alcohol intake	245 (22.8)	31 (24.6)	183 (50.6)	27 (54)	486 (30.2)
	Indicators CVD only					
Process	Patients with LDL cholesterol ≥2.5 mmol/l with statin prescription	170 (61.6)	23 (67.6)	73 (72.3)	7 (41.2)	273 (63.8)
Process	Waist circumference measured	103 (9.6)	12 (9.5)	87 (24)	16 (32)	218 (13.7)
Process	Prescription antiplatelet drugs	896 (83.6)	101 (80.2)	325 (89.8)	44 (88)	1366 (84.8)
Process	Fasting glucose measured	644 (59.9)	76 (60.3)	328 (90.6)	46 (92)	1094 (68)
Process	Comprehensive risk assessment*	27 (2.5)	2 (1.6)	41 (11.3)	7 (14)	77 (4.8)

***positive score when there is a record of: blood pressure, BMI, waist circumference, fasting glucose measurement, LDL-cholesterol measurement, smoking behaviour, alcohol intake, advice and control of diet and physical exercise in the past 12 months.**

More patients with CVD and DM had a BMI over 25 kg/m^2 (OR=2.05; 95% CI 1.15-3.65). On the practice level, intra-class coefficient (ICC) scores ranged from 0.038 for 'patient is a smoker' to 0.261 for 'BMI measured'.

Indicators shared across CVD and DM

Of eight indicators shared across CVD and DM all but one (systolic blood pressure <140 mmHg) yielded higher scores in patients with DM (with or without COPD). In patients with CVD and COPD, indicator scores were the same as in patients with CVD only. Patients with CVD and DM and patients with CVD, DM and COPD were more likely to have blood pressure measurement (OR=4.12; 95% CI 2.80-6.06; OR=10.56; 95% CI 2.53-44.09), LDL-cholesterol measurement (OR=4.03; 95% CI 3.08-5.28; OR=4.82; 95% CI 2.47-9.39), advice (OR=8.26; 95% CI 6.20-11.00; OR=7.32; 95% CI 3.96-13.56) and control (OR=12.04; 95% CI 8.94-16.21; OR=10.92; 95% CI 5.86-20.35) on diet, advice about physical activity (OR=4.38; 95% CI, 3.29-5.84; OR=3.21; 95% CI 1.68-6.14) and registration of alcohol intake (OR=4.18; 95% CI 3.17-5.51; OR=5.32; 95% CI 2.85-9.93) compared with patients with CVD only. No differences were found between groups regarding systolic blood pressure ≤140 mmHg. Patients with CVD and DM and patients with CVD, DM and COPD were less likely to have a LDL-cholesterol level ≥2.5 mmol/l (OR=0.36; 95% CI 0.26-0.50; OR=0.49; 95% CI 0.25-0.96). On the practice level, ICC scores ranged from 0.021 for 'systolic blood pressure <140 mmHg' to 0.159 for 'registration of alcohol intake'.

Indicators for CVD only

Of five indicators that are only relevant for CVD, three to five yielded higher scores in patients with DM (with or without COPD). No such differences were found in patients with CVD and COPD. Patients with CVD and DM and patients with CVD, DM and COPD were more likely to have a record of waist circumference (OR=4.83; 95% CI 3.33-7.02; OR=6.07; 95% CI 2.93-12.56), fasting glucose measurement (OR=7.40; 95% CI 4.99-10.98; OR=9.41; 95% CI 3.30-26.84) and a comprehensive risk assessment (OR=6.99; 95% CI 3.98-12.27; OR=7.15; 95% CI 2.56-20.02) than patients with CVD only. Antiplatelet drugs were more often prescribed to patients with CVD and DM (OR=1.72; 95% CI 1.17-2.54) than to patients with CVD only. Patients with CVD and DM with

Table 4. *Impact of recorded diseases on scores for CVD indicators (odds ratios with 95% confidence intervals and CVD only as reference group)*

Indicators commonly shared across CVD/COPD/DM	Smoking status	Patient is a smoker	Stop smoking advice	BMI measured	BMI ≥25 kg/m²	Influenza vaccination	Exercise control
Fixed effect							
CVD & COPD	2.58* (1.73-3.85)	4.13* (2.26-7.54)	1.48 (0.65-3.39)	1.46 (0.90-2.37)	1.18 (0.44-3.20)	1.99* (1.15-3.44)	1.35 (0.83-2.21)
CVD & DM	3.64* (2.78-4.75)	0.67 (0.44-1.03)	1.09 (0.52-2.28)	7.09* (5.24-9.60)	2.05* (1.15-3.65)	1.84* (1.30-2.59)	6.26* (4.69-8.35)
CVD & DM & COPD	6.31* (3.29-12.10)	2.61* (1.23-5.54)	2.18 (0.71-6.69)	7.97* (4.16-15.30)	1.87 (0.59-5.95)	1.50 (0.70-3.20)	5.72* (3.06-10.68)
CVD (reference group)							
Age[1]	0.97* (0.96-0.98)	0.95* (0.93-0.96)	0.99 (0.97-1.02)	1.01 (0.99-1.02)	0.94* (0.91-0.96)	1.05* (1.04-1.06)	1.00 (0.99-1.01)
Sex[2]	1.15 (0.92-1.44)	0.97 (0.66-1.42)	0.75 (0.41-1.38)	1.31 (0.99-1.72)	1.13 (0.66-1.95)	1.01 (0.77-1.32)	1.05 (0.81-1.35)
Random effect	Variance component (SE)						
Level-two variance (practice)	0.47 (0.13)	0.13 (0.11)	0.45 (0.31)	1.16 (0.31)	0	0.84 (0.24)	0.74 (0.20)
ICC	0.125	0.038	0.120	0.261	0	0.203	0.184

Indicators shared across CVD/DM	Systolic blood pressure measured	Systolic blood pressure <140 mmHg	LDL cholesterol measured	LDL cholesterol ≥2.5 mmol/l	Advice physical activity	Diet control	Counselling about diet	Registration of alcohol intake
Fixed effect								
CVD & COPD	0.97 (0.63-1.47)	1.22 (0.78-1.92)	1.10 (0.76-1.62)	1.06 (0.58-1.92)	1.22 (0.72-2.09)	1.27 (0.72-2.21)	0.81 (0.45-1.47)	1.35 (0.86-2.13)
CVD & DM	4.12* (2.80-6.06)	1.02 (0.77-1.34)	4.03* (3.08-5.28)	0.36* (0.26-0.50)	4.38* (3.29-5.84)	12.04* (8.94-16.21)	8.26* (6.20-11.00)	4.18* (3.17-5.51)
CVD & DM & COPD	10.56* (2.53-44.09)	1.36 (0.74-2.49)	4.82* (2.47-9.39)	0.49* (0.25-0.96)	3.21* (1.68-6.14)	10.92* (5.86-20.35)	7.32* (3.96-13.56)	5.32* (2.85-9.93)
CVD (reference group)								
Age[1]	1.02* (1.01-1.03)	1.03* (1.02-1.04)	0.99 (0.98-1.00)	1.00 (0.99-1.01)	0.99* (0.97-1.00)	0.99* (0.98-1.00)	0.98* (0.97-0.99)	0.99 (0.98-1.00)
Sex[2]	0.92 (0.72-1.18)	0.83 (0.65-1.06)	0.93 (0.75-1.15)	0.80 (0.59-1.08)	1.02 (0.78-1.34)	1.01 (0.77-1.33)	1.11 (0.85-1.45)	1.49* (1.16-1.90)
Random effect	Variance component (SE)							
Level-two variance (practice)	0.16 (0.07)	0.07 (0.05)	0.09 (0.05)	0.09 (0.07)	0.35 (0.12)	0.39 (0.13)	0.31 (0.11)	0.62 (0.17)
ICC	0.046	0.021	0.027	0.027	0.096	0.106	0.086	0.159

Indicators CVD only	Patients with LDL ≥2.5 mmol/l with statin prescription	Waist circumference measured	Prescription anti-platelet drugs	Fasting glucose measured	Comprehensive risk assessment
Fixed effect					
CVD & COPD	1.54 (0.70-3.43)	1.14 (0.57-2.26)	0.68 (0.42-1.11)	1.12 (0.75-1.66)	0.77 (0.17-3.44)
CVD & DM	2.13* (1.24-3.67)	4.83* (3.33-7.02)	1.72* (1.17-2.54)	7.40* (4.99-10.98)	6.99* (3.98-12.27)
CVD & DM & COPD	0.50 (0.18-1.43)	6.07* (2.93-12.56)	1.37 (0.56-3.34)	9.41* (3.30-26.84)	7.15* (2.56-20.02)
CVD (reference group)					
Age[1]	0.96* (0.94-0.98)	0.98* (0.96-0.99)	1.03* (1.01-1.04)	1.00 (0.99-1.01)	0.98 (0.96-1.00)
Sex[2]	1.44 (0.94-2.21)	1.39 (0.99-1.96)	1.99* (1.49-2.64)	1.04 (0.82-1.31)	1.31 (0.76-2.27)
Random effect	Variance component (SE)				
Level-two variance (practice)	0.20 (0.16)	1.67 (0.47)	0.19 (0.09)	0.37 (0.12)	1.95 (0.62)
ICC	0.057	0.337	0.055	0.101	0.372

***p<0.05; [1]age increasing in one-year steps; [2]reference group is men.**

LDL-cholesterol levels above 2.5 mmol/l were more likely to receive a statin (OR=2.13; 95% CI 1.24-3.67).
Increasing patient age was positively correlated with prescribing antiplatelet drugs (OR=1.03; 95% CI 1.01-1.04) and receiving influenza vaccination (OR=1.05; 95% CI 1.04-1.06). Recording of blood pressure measurement was positively correlated with increasing age as well (OR=1.02; 95% CI 1.01-1.03); however, with increasing age blood pressure targets were less often achieved.
Increasing age was negatively correlated with a record of smoking behaviour (OR=0.97; 95% CI 0.96-0.98), advice on physical activity (OR=0.99; 95% CI 0.97-1.00), dietary advice (OR=0.98; 95% CI 0.97-0.99) and control (OR=0.99; 95% CI 0.98-1.00), record of waist circumference (OR=0.98; 95% CI 0.96-0.99) and statin prescription for patients with an LDL-cholesterol level ≥2.5 mmol/l (OR=0.96; 95% CI 0.94-0.98). With increasing age, more patients had a BMI below 25 kg/m^2 (OR=0.94; 95% CI 0.91-0.96) and of the patients whose smoking behaviour was registered, less patients smoked (OR=0.95; 95% CI 0.93-0.96). On the practice level, ICC scores ranged from 0.055 for 'prescription of antiplatelet drugs' to 0.372 for 'comprehensive risk assessment'. Female gender was positively correlated with prescription of antiplatelet drugs (OR=1.99; 95% CI 1.49-2.64) and the registration of alcohol intake (OR=1.49; 95% CI 1.16-1.90). No differences regarding gender were found for the remaining indicators.

DISCUSSION

In line with our expectations, we found evidence that comorbidity was associated with more comprehensive cardiovascular risk management. However, this only applied to DM and not to COPD. This trend applied to indicators that were shared across the conditions, but remarkably also to indicators that were only related to CVD. This study adds to the cumulating research evidence that the presence of DM is associated with better preventive treatment for other diseases.[17,18,24] Our findings should be interpreted in the context of the sample of primary care practices, which may be the early majority with respect to quality improvement as they had voluntarily joined an accreditation program.
A plausible explanation for our findings seems to be that disease management programs for diabetes care have been well established on a nationwide basis in Dutch primary care in recent years. Evidence found that these programs have positive effects on the quality of care.[25] We suggest that similar programs might explain similar findings from studies in other countries.[17,24] In the Netherlands, disease management programs are governed by so-called 'care groups'. This is an organisation of 50 to 100 primary care practices which is responsible for the coordination and provision of contracted care in a particular region. Since 2010 all care groups in the Netherlands have a bundled payment contract for the diabetes care program; so 100% national coverage has been achieved.[26] So far, few care groups have focused on COPD or CVD in the Netherlands. The impact of disease management is based on a number of mechanisms. One component of care in disease management programs is that clinical activities and clinical parameters are registered in electronic medical records, which use this information to provide computer generated reminders. This implies that more such activities can be found in a chart audit.
DM and CVD are concordant conditions while they represent parts of the same pathophysiological risk profile and are more likely to be the focus of the same disease management plan. Discordant conditions, in contrast, are not directly related in management or pathogenesis.[27] COPD and CVD are less concordant conditions than DM and CVD.[19,28] Our findings illustrate that the management of DM and CVD has more in common than the management of COPD and CVD. This could even apply to the indicators concerning CVD only. For instance, better prescription of antiplatelet drugs might be explained by the fact that the recommendation for antiplatelet drugs for diabetes patients with established CVD is mentioned in the diabetes guideline. This is not recommended for diabetes patients without established CVD.[29,30]
A third determinant of our findings is that CVD patients visiting the practice because of their structured DM care are being considered not just DM related but more broadly as cardiometabolic risk, which can be seen as an integral primary care approach. For instance, waist circumference and risk for developing DM are related.[29] Although not an indicator for DM in the Dutch national accreditation program (NHG-Praktijkaccreditering), in many DM care groups in the Netherlands waist circumference is measured routinely. The same applies to fasting glucose measurement, which is not defined as a quality indicator for DM, but is used to diagnose DM and to monitor glucose levels in patients with DM.[29] When considering comprehensive risk assessment, all items are recommended preventive care in diabetes patients.
While most performance indicators yielded higher scores in patients with comorbidity, no differences were found between patient groups for 'systolic blood pressure ≤140 mmHg', which is a proxy health outcome. More smokers were represented in the group of patients with CVD and COPD and patients with CVD, DM and COPD. While smoking is the most important cause of COPD, most COPD patients smoke or have a history of smoking.[31] The decreasing numbers of patients who smoke with increasing age could be the consequence of the fatal effects of smoking.

For the proxy outcome indicator 'LDL cholesterol <2.5 mmol/l' targets were more often attained in patients with CVD and DM and patients with CVD, DM and COPD than in patients with CVD only. Previous research shows that many patients with CVD do not attain therapeutic targets set in guidelines for CVD.[6,32,33] Higher target attainment for LDL-cholesterol levels in patients with CVD and DM may be related to better prescription of statins in this group of patients, which may be related to the sample of primary care practices included in this study.

Overall, the results of this study showed room for improvement in preventive care in patients with established CVD, even in this sample of primary care practices. This is in line with results from other studies.[6,7,34] Improvements can be made especially on lifestyle counselling in patients with established CVD with or without COPD, while results on these items are disappointing. Primary care has an important role to play in effective health promotion and disease prevention.[35]

This study had some limitations. Primary care practices participating in this study were enrolled in a national implementation and accreditation program. It seems likely that they were better organised and staffed than average. Primary care practices with a clear preference for a specific improvement plan could not participate in the study while participating practices were randomised to a group which started with an improvement plan on cardiovascular risk management or to a group that did not. This also accounted for practices that participated in ongoing improvement programs due to regional developments in disease management, which makes the assessment of the true participation rate of practices in this study unattainable. The sampling of patients in this study was based on ICPC codes allocated to patients by family physicians. However, some cardiovascular diseases, for example TIA, are more difficult to diagnose, while diagnosis is made based on the anamnesis.[36] This does not seem to be a large problem as 12% of the patients had only TIA as cardiovascular diagnosis. In this study we only assessed COPD and DM as comorbidities of influence on preventive cardiovascular care while these are common in patients with established CVD.[37,38] Furthermore we only considered patient characteristics in this study while practice characteristics could also be of influence on the outcomes. Further research should consider the influence of other concordant and discordant comorbidities and practice characteristics on cardiovascular risk management.

At the time of the study, disease management programs for DM were well established in primary care practices, unlike disease management programs for CVD and COPD. The results of this study illustrate the influence of these programs on the quality of care. Currently ongoing initiatives aim to implement disease management programs for CVD and COPD in primary care. It would be relevant to repeat this study when disease management programs for CVD and COPD are well established. As many components of preventive care for patients with CVD and DM are shared, it may be efficient to integrate these components in a comprehensive care program. This would reduce the burden for both caregivers and patients and open up time for other important clinical tasks.

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REVIEW

Effect of the factor V Leiden mutation on the incidence and outcome of severe infection and sepsis

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ABSTRACT

Activation of coagulation frequently occurs in severe infection and sepsis and may contribute to the development of multiple organ dysfunction. Factor V Leiden is a relatively common mutation resulting in a mild prohaemostatic state and consequently with an increased tendency to develop thrombosis. Hypothetically, patients with factor V Leiden may suffer from more severe coagulopathy in case of severe infection or sepsis. Aggravation of the procoagulant state in sepsis may subsequently result in more severe organ dysfunction and an increased risk of death. Here we discuss the experimental and clinical evidence regarding the relationship between the presence of a factor V Leiden mutation and the incidence and outcome of sepsis.

KEYWORDS

Factor V Leiden, thrombophilia, sepsis, infection, coagulation

INTRODUCTION

Virtually all patients with sepsis have coagulation abnormalities. These abnormalities range from subtle activation of the coagulation system that can only be detected by sensitive markers for coagulation factor activation to somewhat stronger coagulation activation detectable by a small decrease in the platelet count and subclinical prolongation of global clotting times to fulminant disseminated intravascular coagulation (DIC), which is characterised by simultaneous widespread microvascular thrombosis and profuse bleeding from various sites.[1] Septic patients with severe forms of DIC may present with manifest thromboembolic disease or clinically less apparent microvascular fibrin deposition, which predominantly presents as multiple organ dysfunction.[2-4] Clinically relevant coagulation abnormalities are present in 50 to 70% of patients with severe infection or sepsis, whereas about 35% of patients will actually meet the criteria for DIC.[5,6] There is ample evidence that activation of coagulation in concert with inflammatory activation can result in microvascular thrombosis and thereby contributes to multiple organ failure in patients with severe sepsis.[4,7,8] Firstly, there are several reports of post-mortem findings in septic patients with coagulation abnormalities and DIC.[9,10] These autopsy findings include diffuse bleeding at various sites, haemorrhagic necrosis of tissue, microthrombi in small blood vessels and thrombi in mid-size and larger arteries and veins.[11] The demonstration of ischaemia and necrosis has been associated with fibrin deposition in small and mid-size vessels of various organs.[12] Importantly, the presence of these intravascular thrombi appears to be clearly and specifically related to the development of organ dysfunction. Secondly, experimental animal studies of DIC show fibrin deposition in various organs. Experimental bacteraemia or endotoxaemia causes intra- and extravascular fibrin deposition in kidneys, lungs, liver, brain and various other organs.[13] Amelioration of the haemostatic defect by various interventions in these experimental models appears to improve organ failure and, in some but not all cases, mortality.[14-17] Interestingly, some studies indicate that amelioration of systemic coagulation activation will have a profound beneficial effect on resolution of local fibrin deposition and improvement of

organ failure.[18,19] Lastly, clinical studies support the notion of coagulation as an important determinant of clinical outcome. DIC has shown to be an independent predictor of organ failure and mortality.[2,20] In a consecutive series of patients with severe sepsis, the mortality of patients with DIC was 43%, as compared with 27% in those without DIC. In this study, mortality was also directly related to the severity of the coagulopathy in septic patients.[21]

Apart from microvascular thrombosis and organ dysfunction, coagulation abnormalities may also have other harmful consequences. For example, thrombocytopenia in patients with sepsis confers an increased risk of bleeding.[22] Indeed, in particular critically ill patients with a platelet count of <50 x 10^9/l have a four to fivefold higher risk for bleeding as compared with patients with a higher platelet count.[23,24] A low platelet count may be both the best indicator of thrombin generation and a sign of increased platelet-vessel wall interaction.[11]

Since the prohaemostatic state in severe infection and sepsis seems to be relevant for the pathogenesis of organ dysfunction and mortality, it may be hypothesised that even a mild pre-existent prothrombotic state in patients, such as that caused by thrombophilia for example due to a factor V Leiden mutation, would aggravate the coagulation derangement during infection and sepsis and thereby affect outcome. Interestingly, experimental and clinical studies point to an interaction between a factor V Leiden mutation and the outcome of severe infection or sepsis, although the results are sometimes conflicting. In this article, we will briefly review experimental and clinical evidence on the relationship between factor V Leiden and the outcome of severe infection and sepsis.

THROMBOPHILIA AND OUTCOME IN INFECTION AND SEPSIS

Congenital thrombophilia is usually due to a genetic variation in a gene encoding a coagulation factor or – in general clinically less relevant – a fibrinolytic protein.[25] Such gene polymorphisms have been described for the coagulation factors prothrombin, factor V, fibrinogen and factor XIII and for the coagulation inhibitors antithrombin, protein C and protein S. In the last-mentioned, these mutations cause a deficiency of these natural anticoagulant factors. In the fibrinolytic system the most relevant polymorphism is the 4G/5G variation in the gene encoding plasminogen activator inhibitor type I (PAI-1). This polymorphism results in mildly elevated levels of PAI-1 and is related to an increased risk of myocardial infarction and ischaemic stroke.

Anecdotal reports have indicated that the presence of congenital thrombophilia may exacerbate the coagulopathy associated with severe infection and may even result in purpura fulminans.[26-30] Indeed, various coagulation defects seem to be associated with an aggravated coagulation response to infectious agents or sepsis, although a systematic overview is missing.[31,32] Prospective studies on the incidence or outcome of severe infections and sepsis in patients with a prothrombotic polymorphism or coagulation inhibitor deficiency are not available. However, some case-control studies have reported on the prevalence of thrombophilic abnormalities in cohorts of patients with severe sepsis. Moreover, a substantial number of animal studies have been performed. These studies have particularly focussed on deficiencies in the protein C and antithrombin pathways, the factor V Leiden mutation and genetic polymorphisms in the fibrinolytic system.

Antithrombin is the cardinal inhibitor of thrombin and factor Xa activity and, like the protein C pathway, a central regulator of coagulation activation *in vivo*. There is ample evidence that antithrombin is unable to adequately regulate these coagulation proteases in case of sepsis. Clinical studies show mean levels of antithrombin as low as 30% of normal values in patients with severe sepsis, whereas in selected individuals these levels may be even lower.[20,33,34] Low levels of antithrombin have been shown to be associated with a higher mortality in septic patients in several prospective studies.[20] Restoration of antithrombin levels in experimental DIC in animals has been demonstrated to adequately block the systemic activation of coagulation and in these studies was also associated with improved outcome in terms of less organ failure and a reduction in mortality.[15,35] In mice a heterozygous deficiency of antithrombin endotoxaemia leads to much more deposition of fibrin in various organs, including the kidneys, liver and heart, as compared with endotoxaemic wild-type mice.[36] There are no clinical data that point to a role of antithrombin deficiency in the outcome of sepsis or severe infection in humans.

There are several indications that the protein C system plays an important role in sepsis and also that defects in the protein C system may influence the outcome in sepsis. An impaired function of the protein C system is directly related to the severity and outcome of sepsis.[37] The most compelling evidence comes from experimental studies showing that administration of activated protein C to septic animals resulted in amelioration of DIC and an improved survival.[17] Clinical studies confirm the beneficial effect of activated protein C in sepsis.[38] Severe (congenital) protein C deficiency in mice results in thrombophilia as well as a proinflammatory phenotype with higher total white blood cell counts and higher basal IL-6 levels as compared with wild-type mice.[39] Further protein C deficiency was shown to affect endotoxaemia in a mouse model. In these experiments mice with a one-allele targeted deletion of the protein C, resulting in heterozygous protein C

deficiency,[40] were subjected to endotoxaemia.[41] Mice with a heterozygous deficiency of protein C had more severe DIC, as evidenced by a greater decrease in fibrinogen level and a larger reduction in platelet count. Also thrombin-antithrombin complex levels were 3.4-fold higher in protein $C^{+/-}$ mice as compared with wild-type mice and histological examination showed more fibrin deposition in lungs and kidneys in these mice. Survival at 12 hours after the endotoxin injection was diminished in the protein $C^{+/-}$ group. Interestingly, protein $C^{+/-}$ mice had significantly higher levels of the pro-inflammatory cytokines TNF-α, IL-6 and IL-1β, indicating an interaction between the protein C system and the inflammatory response. This last observation is consistent with many other studies indicating cross-talk between effects of protein C on coagulation and inflammatory modulation.[42] Similar findings were reported in studies in mice genetically predisposed to a severe protein C deficiency.[43] Interestingly, reconstitution of protein C levels in these mice with recombinant human activated protein C resulted in less severe inflammatory responses and an improved survival. In a model of severe abdominal infection through caecal ligation and puncture mice with a heterozygous deficiency of protein C had more profound organ dysfunction and an enhanced mortality in comparison with wild-type mice.[44] Taken together, these data suggest that preexistent protein C deficiency aggravates the coagulopathic response to severe infection and sepsis and is related to a worse outcome. It is not clear whether this observation may be extended to the clinical situation, mostly due to the fact that deficiency of protein C in humans is relatively rare. Therefore it is hard to establish a relationship between this condition and the incidence or outcome of sepsis.

FACTOR V LEIDEN IN MODELS OF EXPERIMENTAL INFECTION AND SEPSIS

In view of the central role of the protein C pathway in sepsis, a lot of attention has been given to the presence of factor V Leiden mutation, which leads to resistance to activated protein C, and the severity and outcome of sepsis or severe infection. In a clinical study in 259 children with meningococcal sepsis, factor V Leiden carriers had more profound coagulopathy and purpura fulminans, but their carrier status did not have a significant effect on survival.[45] Unfortunately, so far neither experimental or clinical studies in sepsis have shown unequivocal results regarding the presence of the factor V Leiden mutation. In one study, endotoxaemic mice carrying a heterozygous factor V Leiden mutation had a surprisingly lower mortality (19%) compared with their wild-type controls (57%).[46] In these experiments, factor V Leiden mice produced more thrombin than normal controls, indicating a more profound activation of coagulation. In contrast, in another study of experimental pneumococcal pneumonia in mice no major protective effect of the factor V Leiden mutation was seen.[47] Also, markers of coagulation activation, both systemically and in the bronchoalveolar compartment, were not different between factor V Leiden mice and wild-type littermates. Remarkably, homozygosity for the factor V Leiden mutation protected against lethality in mice that were treated with ceftriaxone. Also, factor V Leiden mice did not differ significantly in their response compared with wild-type mice in a model of septic peritonitis, as reflected by similar degrees of activation of coagulation, inflammation, organ dysfunction and survival.[48] In another experimental study the effect of the presence of one or two alleles of the factor V Leiden mutation was investigated in lethal H1N1 influenza.[49] Factor V Leiden mutation did not influence the procoagulant response, lung histopathology, or survival in this study. Lastly, however, in a more subtle model of endotoxin-induced coagulation activation in humans it was demonstrated that heterozygous carriers of factor V Leiden had a more pronounced increase in markers of thrombin generation and fibrinogen to fibrin conversion.[50] The authors also found an increase in fibrinolytic activity in factor V Leiden affected individuals, which they attributed to the facilitating role of soluble fibrin for endogenous fibrinolysis.

Taken together, it seems that factor V Leiden may have some effect on the coagulopathy associated with sepsis; however, the effect is so subtle that it does not seem to be relevant against the background of the profound derangement of coagulation that is seen in severe sepsis or overwhelming infection.

FACTOR V LEIDEN IN CLINICAL SEPSIS STUDIES

Clinical studies on the role of factor V Leiden in sepsis also show variable results. The presence of the factor V Leiden mutation was analysed in large cohorts of patients with severe sepsis that had been included in intervention studies with recombinant human activated protein C.[38,51] In this cohort of 3894 patients, the prevalence of factor V Leiden heterozygosity was 3.9%, which is slightly higher than the predicted allelic frequency of 2.5%.[52] The 28-day mortality in those with factor V Leiden was not significantly different from the control population (19.3 *vs* 26.2%, respectively; risk ratio 0.74; 95% confidence interval (CI) 0.53-1.03). Moreover there were no differences in the incidence of serious bleeding or thrombotic events between factor V Leiden carriers and non-factor V Leiden carriers. In another publication in which the data of only

one of these two studies were presented, patients with a heterozygous factor V Leiden mutation were shown to have a lower mortality (13.9%) than those without this mutation (27.9%; p=0.013).[46] The effect of treatment with recombinant human activated protein C did not differ between the two groups. In the Copenhagen City Heart study 9253 individuals were screened for the presence of the factor V Leiden mutation and followed for a period of more than seven years to establish the risk of hospitalisation for any infectious disease and the subsequent risk of progression of disease to death.[53] The relative risk of any infection in carriers of the factor V Leiden mutation was 1.08 (95% CI 0.87-1.35) as compared with noncarriers (after adjustment for age, sex, smoking, alcohol consumption, income and level of education). In contrast with the previously mentioned study, patients with the factor V Leiden mutation in this study had a higher risk of death from infection as compared with patients who did not have this mutation (adjusted relative risk 4.41; 95% CI 1.42-13.67). The same group of authors presented data from four case cohorts of patients with either Gram-negative sepsis, or invasive pneumococcal disease, or intensive care admission.[54] When they compared their 1249 patients with matched controls, they found in an adjusted logistic regression analysis that factor V Leiden carriers had a higher risk of intensive care admission (OR 1.62; 95% CI 1.08-2.42) and were at increased risk of death (relative risk 1.78; 95% CI 1.13-2.81) compared with controls. Factor V Leiden was not associated with susceptibility to or outcome from pneumococcal infection or sepsis. Similarly, in a prospective observational study in 73 patients admitted with severe sepsis, the presence of a factor V Leiden mutation had no effect on short- or long-term mortality or any other clinically significant outcome.[55] Lastly, and in contrast with previous studies, a small study in 106 patients with acute respiratory distress syndrome showed a survival benefit in factor V Leiden heterozygotes (30-day survival 7/7 = 100% compared with 57/99 = 58% in patients without the mutation).[56] Obviously, this observation needs confirmation in larger cohorts of patients.

CONCLUSION

Activation of coagulation seems to play a pivotal role in the pathogenesis and outcome of severe infection and sepsis. Hypothetically, a preexisting prohaemostatic state, as seen in congenital thrombophilia, may aggravate the severity of this coagulopathy and may thereby affect outcome. Both experimental and clinical studies show inconsistent results as to a difference in survival from sepsis or severe infection in carriers of the factor V Leiden mutation. Although it may be biologically plausible that the factor V Leiden mutation and the ensuing activated protein C resistance would aggravate the response to sepsis, the opposite may also be true as it has been speculated that a balanced and moderate increase in thrombin generation, as may be caused by a heterozygous factor V Leiden mutation, might be protective during severe infection and sepsis by means of generating slightly more activated protein C.[57] Additional analyses in larger cohorts of septic patients or long-term prospective studies in patients with a known factor V Leiden mutation will be required to clarify this issue.

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ORIGINAL ARTICLE

Limitations of screening for occult cancer in patients with idiopathic venous thromboembolism

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ABSTRACT

Background: Idiopathic venous thrombosis (IVT) is associated with occult malignancy in 10% of patients. The Trousseau study investigated whether extensive screening using abdominal and chest computed tomography (CT) scans and mammography in women would decrease mortality, compared with limited screening. Here, the costs and test characteristics of these screening strategies are presented, including true- and false-positive findings, sensitivity and specificity.

Methods: All investigations performed because of a suspicion of malignancy in the limited or extensive screening groups were collected. Costs were calculated using Dutch healthcare tariffs.

Results: A total of 342 and 288 patients with IVT were included in the extensive and the limited screening group, respectively. The prevalences of malignancy and mortality were comparable between these two groups, as were the abnormal findings during routine screening. In 30% of the extensively screened patients, the CT scans or mammography showed abnormalities necessitating further diagnostic work-up; this yielded six malignancies and resulted in a positive predictive value of 6.6%, sensitivity of 33% and specificity of 70%. Mean costs per patient were € 165.17 for the routine and € 530.92 for the extensive screening.

Conclusion: Screening using CT scans and mammography results in extra costs due to the high percentage of false-positive findings for which a further diagnostic work-up is indicated.

KEYWORDS

Whole body CT screening, costs, occult cancer, idiopathic venous thromboembolism

INTRODUCTION

In 1935, the first case of a patient presenting with an idiopathic venous thromboembolism (IVT) as a sign of an occult cancer was reported by Illtyd James and Matheson. The incidence of malignancy within the first years after an IVT is approximately 10%. The benefit of screening for cancer in patients with IVT is intensely debated.[1-5] In today's clinical practice, the approach to a patient with IVT varies widely, ranging from no screening to extensive screening using invasive tests. Only one randomised controlled trial has been performed.[6] In this prematurely terminated study 201 patients were included and were randomised to a limited screening strategy or an extensive screening strategy, consisting of a large number of imaging, invasive and laboratory tests. This trial suggested a beneficial effect of extensive screening, based on a less advanced cancer stage at the time of diagnosis. An additional analysis showed that the combination of computed tomography (CT) of the abdomen and a mammography in women had the potential to be the most cost-effective.[7] The design of the Trousseau study was based on these data. In this multicentre concurrently controlled cohort study a limited cancer screening strategy was compared with an extensive screening strategy consisting of CT of the chest and abdomen and additionally in women mammography. As reported recently, no difference in overall survival was observed between the two groups.[8]

The present study analyses the costs and test characteristics (i.e. false- and true-positive findings, sensitivity and specificity) associated with screening using CT scans and mammography in a population at high risk for cancer.

METHODS

Study population

The analysis is based on the previously reported Trousseau study, performed between 2002 and 2008 in the Netherlands after approval by the institutional review boards of all participating hospitals.[8] Briefly, patients with confirmed symptomatic deep venous thrombosis (compression ultrasound) and/or pulmonary embolism (high probability ventilation-perfusion scanning or CT angiography) who had no known risk factors for venous thromboembolism were potentially eligible. Informed consent was obtained prior to performing any study-related procedures.

Cancer screening strategies

In both the limited and extensive screening groups a history was taken and a physical examination was performed with a focus on signs and symptoms of malignancy with the use of a standardised data collection form. Furthermore, blood was drawn for determination of the erythrocyte sedimentation ratio, whole blood count with leucocyte differentiation, creatinine, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase and calcium; also a chest X-ray was routinely obtained. This screening, which was done in both groups, is referred to as the routine screening. In case of abnormal findings indicating a possible underlying malignant process, appropriate problem-targeted testing to detect the cancer was required. Patients in the extensive screening group underwent an additional CT of the chest and abdomen and a mammography was also performed in women, provided no cancer was identified at baseline screening. Follow-up visits were planned at 6, 12, 24 and 36 months. The last study visit was scheduled for April 2008. At each contact information regarding vital status and malignancy was obtained with a standardised questionnaire. In case of death or newly diagnosed malignancy all available relevant clinical information was collected and adjudicated by an independent and blinded adjudication committee.

All the extra tests to detect cancer, which were performed because of abnormalities at routine screening, extensive screening or follow-up, were recorded. Additionally, the medical records of all patients were searched for examinations additionally to the registered data.

Costs

Costs in euros were calculated using the data of the 2006 Committee of Tariffs for Healthcare; this committee regulates the fees to be charged by healthcare workers or institutions in the Netherlands. The 2006 tariffs were used because the study was conducted at that moment in time, and the declaration system in the Netherlands changed afterwards. One euro is currently approximately 1.30 dollar; in 2006 it varied between 1.20 and 1.32 dollar (average currencies per month). Costs were multiplied by the specific surcharge percentage of the specialist involved in the diagnostic procedure. Costs per procedure were multiplied by the frequency by which this specific test was done in a certain patient. Finally, all costs were added up to arrive at the total costs per individual patient. The total costs were calculated excluding and including costs for the screening X-ray, laboratory measures, CT scans and mammographies. Furthermore, a subdivision was made between costs made to evaluate abnormalities found by routine screening, extensive screening and during the follow-up period. Costs related to treatment for cancer or hospitalisations were excluded from these calculations. Statistical analyses were executed using SPSS 16. The Mann-Whitney test was used to evaluate whether costs were statistically significantly different between the two groups. Alternative diagnoses (i.e. diseases other than malignancy, found during the screening) and the tests used to evaluate these were scored and divided into alternative diagnoses for which treatment was initiated and those for which no treatment was needed. Also, alternative diagnoses which have an effect on prognosis or on future treatment were considered clinically relevant and taken into account.

Exploratory sensitivity analysis

Information on overall mortality and mortality among patients diagnosed with cancer was used to calculate the amount of life years gained (LYG) by the implementation of extensive screening.

A cost-efficacy limit of 50,000 US dollars or approximately € 30,000 per LYG is commonly used.[9] Using the costs for extensive screening and defining the hypothetical costs per LYG (€ 30,000), an exploratory fixed sensitivity analysis was performed. The observed costs were used to determine the minimum of LYG needed to remain within cost-efficacy limits.

RESULTS

Main results of Trousseau study

The results of the Trousseau study are presented in the original paper.[8] Briefly, 630 patients with IVT were included, 342 in the extensive screening and 288 in the limited screening arm. The baseline clinical characteristics were comparable between the two groups, except for smoking and the percentage of patients with pulmonary embolism. In both groups routine screening procedures were performed in 98% of the patients, with the exception of the chest X-ray which was performed in only 72% of the patients in the extensive screening group. In the extensive screening group an additional abdominal CT scan was performed in 299 of the 330 patients (91%) and a chest CT scan in 302 (92%). In 94 out of 119 women (79%)

mammography was done. The median time of follow-up was 2.6 years (IQR 1.6 to 3.7) in the routine screening group compared with 2.5 years (IQR 1.5 to 3.9) in the extensive screening group.

During the total study period a malignancy occurred in 21 of the 288 patients undergoing limited screening (7.3%), *vs* 30 out of 342 extensively screened patients (8.8%) (adjusted OR 1.25; 95% confidence interval (CI) 0.66-2.38). Overall, 50 patients died during follow-up, 24 (8.3%) in the limited screening group and 26 (7.6%) in the extensively screened group, for an adjusted hazard ratio of 1.22 (95% CI 0.69-2.22). The mortality rate among patients diagnosed with cancer during the study was 38% (8 out of 21) for the routine screening group and 57% (17 out of 30) in the extensively screening group (adjusted OR 2.22; 95% CI 0.63-8.33). The study was terminated prematurely at a planned interim analysis because of the low yield of extensive screening. Therefore, the effect of screening was expected to be very small, also after inclusion of the planned number of patients.

Diagnostic procedures performed after suspicion of malignancy

In the limited screening group, baseline routine screening prompted further investigations in 21.5% of the patients, which is not significantly different from the percentage of abnormalities after routine screening in the extensive screening group (16.7%, *table 1*). The routine screening performed in the limited as well as the extensive screening group identified 19 malignancies in 119 patients with a suspicion of malignancy at routine screening (positive predictive value (PPV) 16%, *table 2*).

Extensive screening resulted in 91 patients - 30% of all patients who underwent at least one extensive screening test – with an indication for further investigations. In six patients, cancer was confirmed, which yields a PPV of 6.6%. Abdominal CT findings prompted further tests in 16.7%, chest CT in 14.2% and mammography in 10.6% of all patients who underwent these tests. CT of the chest and abdomen together resulted in four identified malignancies, after 84 patients had to undergo further diagnostic procedures (PPV 4.8%). Screening using CT of the chest and abdomen only would have a sensitivity of 22% and a specificity of 72%. Mammography identified two malignancies in 94 women. Eight patients had abnormalities on mammography which ultimately turned out to be benign. This yields a sensitivity of 100%, a specificity of 91% and a PPV of 20%.

During the follow-up period further diagnostic tests were performed in 14.2% in the routine screening group and 17.3% in the extensive screening group (p=0.39).

The diagnostic procedures which were ordered because of abnormalities in routine or extensive screening are quite diverse and are listed in *tables 3* and *4*. From *table 3* it can be

Table 1. *Frequency of the suspicion of malignancy in the two study populations*

	Limited screening group (number of patients with abnormalities / total number of patients)	Extensive screening group (number of patients with abnormalities / total number of patients)	P value (Chi square)
Routine screening	62/288 (21.5%)	57/342 (16.7%)	0.42
History	22/288 (7.6%)	24/342 (7.0%)	
Physical examination	14/288 (4.9%)	18/342 (5.3%)	
Laboratory measures	26/288 (9.0%)	24/342 (7.0%)	
Chest X-ray	11/270 (4.1%)	5/260 (1.9%)	
Extensive screening		91/302 (30.1%)	NA
Chest CT		43/302 (14.2%)	
Abdominal CT		50/299 (16.7%)	
Mammography		10/94 (10.6%)	
Follow-up	40/281 (14.2%)	56/324 (17.3%)	0.39
Total study period	97/288 (33.7%)	171/342 (50%)	<0.05

Proportion of the patients, per part of the study and further subdivided in individual screening modalities, with abnormalities necessitating further diagnostics. Multiple abnormalities could be present in one patient.

Table 2. *Test characteristics of the screening methods*

	Sensitivity	Specificity	Positive predictive value
Routine screening	37% (19/51)	83% (479/579)	16% (19/119)
Extensive screening	33% (6/18)	70% (199/284)	6.6% (6/91)
Chest and abdominal CT scans	22% (4/18)	72% (204/284)	4.8% (4/84)
Mammography	100% (2/2)	91% (84/92)	20% (2/10)

Sensitivity, specificity and positive predictive values of the routine, extensive screening and subdivisions of the extensive screening, i.e. chest and abdominal CT and mammography. For the routine screening, the routine screening in the limited and the extensive screening group were combined.

Table 3. *Frequency and description of performed diagnostic procedures*

Diagnostic procedure	Limited screening group		Extensive screening group	
	Number of procedures	Number of patients	Number of procedures	Number of patients
Laboratory measurements	49	23	142	56
Imaging tests	157	77	282	134
Invasive techniques	60	40	131	85
Pathology	56	39	97	70
Consultation other specialist	25	17	106	53
Total	347	97*	758	171*

*** Multiple abnormalities could be found in one patient.**

Table 4. *Overview of diagnostic procedures*

Laboratory measures		**Imaging techniques**		**Invasive diagnostics**	
Tumour markers		*Nuclear*		*Scopy*	
Alpha-fetoprotein	10.69	Skeletal scintigraphy	90.70	Bronchoscopy	422.14
CA125/CEA	21.38	PET scan	1359.33	Broncho-alveolar lavage	422.14
Prostate specific antigen	10.69	Thyroid gland scintigraphy	135.82	Coloscopy	449.90
BetaHCG2	14.26			Cystoscopy	118.41
		Ultrasonography		Oesophageal endoscopic ultrasound	47.59
Clinical chemical lab		Abdomen	40.39	Endoscopic retrograde	245.14
Anaemia lab	53.34	Thyroid gland / neck	40.39	Cholangiopancreaticography	
Complete blood count	7.13	Vaginal	49.76	Gastroscopy	449.90
Calcium	7.13	Prostate	46.55	Hysteroscopy	171.69
Kidney function	7.13	Breast	52.67	Sigmoidoscopy	449.90
Parathyroid hormone	10.69				
Adrenal gland function	24.95	*Radiodiagnostics*		*Surgery*	
Liver function	8.91	CT brain	164.16	Exploratory surgery	941.87
LDH isoforms	1.19	CT thorax	200.77	Uterus extirpation	1596.13
Leucocyte differentiation	1.78	CT abdomen	164.16	Thoracotomy	1484.24
Thyroid function	19.25	CT neck	46.53	Mediastinoscopy	422.14
Prolactin	8.27	Mammography	66.14	Low anterior resection	2918.71
Albumin	1.78	X-ray rib detail	46.53		
		Chest X-ray	46.53	*Other*	
Other laboratory measures		Abdominal X-ray	46.53	Cervical smear	20.20
Protein spectrum	20.62	X-ray oesophagus	139.36	X-ray colon	155.74
Inhibin/oestrogen	51.92	X-ray small intestines	139.36		
Kahler measurements	21.38	X-ray spinal column	46.53		
Plasma/erythrocyte volume	883.39	Kahler series	325.72		
Plasma viscosity	7.13				
Punctures/biopsies		*MRI*		**Consultation specialists**	
Punctures		MRI pelvis	200.77	All consultations	185
CT-guided puncture	127.55	MRI leg	200.77		
Bone marrow puncture	115.28	MRI spinal column	455.20		
Pleura puncture	57.42	MRI neck	200.77	**Pathology**	
Ascites puncture	99.79	MRI brain	200.77	Pathology	38.34
Other puncture	99.79			Urine cytology	37.08
Ultrasound-guided puncture	66.53				
Biopsies					
Liver biopsy	139.36				
Skin biopsy	168.10				
Kidney biopsy	139.36				
Prostate biopsy	118.41				
Excision biopsy	909.02				
Breast biopsy	139.36				
Ultrasound-guided biopsy	66.53				
Wedge excision	2187.66				

Overview of all the different diagnostic procedures undertaken after abnormal findings in routine, extensive screening or during follow-up. Costs in euro per procedure, multiplied by surcharge for personal costs. Some laboratory measures (e.g. complete blood count) are a combination of different measures.

appreciated that the largest number (69%) of all diagnostic procedures were ordered in the extensive screening group. In this group, 758 diagnostic procedures were carried out in 171 patients, compared with 347 procedures in 97 patients in the routine screening group. None of the diagnostic procedures resulted in morbidity or mortality.

Mean costs per patient

The diagnostic procedures detailed above resulted in costs specified in *figure 1*. Costs for diagnostic procedures performed after suspicious findings following routine screening and during follow-up were comparable (p=0.77) between the two groups. Routine screening itself, i.e. chest

Figure 1. *Mean costs per patient in euros; of the resulting diagnostic procedures in case of abnormalities during screening, divided between the limited and the extensive screening group. The costs of performing the screening itself are excluded*

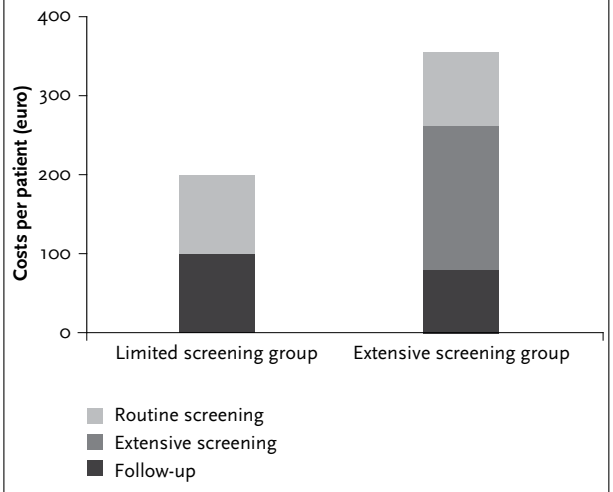

Table 5. *Alternative diagnoses*

Alternative diagnoses and frequencies			
Routine screening	***36***	***Extensive screening***	***24***
Renal insufficiency	6	*Abdominal CT*	*11*
Liver toxicity due to alcohol	4	Haemangiomas/cysts liver	5
Liver steatosis	1	Liver steatosis	1
Nodus thyroid gland	2	Neuroendocrinal pancreatic cyst	1
Anaemia due to myoma	4	Benign adrenal gland tumour	3
Aanemia of unknown origin	3	Asymptomatic retroperitoneal fibrosis	1
Pernicious anaemia	3	*Chest CT*	*12*
Hernia diaphragmatica causing anaemia	1	Nodus thyroid gland	8
Diverticle bleeding	1	Chronic obstructive pulmonary disease	1
Polycythemia vera	1	Tuberculosis	1
Uterus myoma	3	Aortic aneurysma	2
Intestinal polyp	1	*Mammography*	*1*
Haemorrhoids	1	Cyst breast	1
Asymptomatic gall stones	1		
Benign prostate hyperplasia	2		
Diabetes mellitus de novo	2		

Alternative diagnoses found by the routine screening (performed in the limited and extensive screening groups) and the extensive screening strategy.

X-ray plus laboratory tests, costs € 71.48 per patient. After the routine screening the additional tests ordered cost € 93.69 per patient in the limited group. In summary, costs for baseline screening itself and the tests subsequently ordered because of abnormalities were € 165.17 and comparable for the two strategies. From *table 4* it can be calculated that the costs for CTCA were € 364.93 and € 431.07 for CTCA plus mammography. In this study, the extensive screening itself costs € 349.37 per patient, due to the fact that mammography was not performed in all women and the CT scans were sometimes performed incompletely. Another € 181.55 (range 0-3710) per patient was spent on further tests, due to abnormalities seen on the CT scans and/or mammography. The sum of costs for extensive screening, including costs from the screening tests themselves and costs to exclude malignancy after observed abnormalities, was € 530.92 per patient.

Alternative diagnoses found

Routine screening resulted in the detection of 36 alternative diagnoses, of which 77% were considered relevant. In total, 24 alternative diagnoses were found after extensive screening, of which 25% were considered relevant (*table 5*).

Cost-efficacy

Total costs including the costs for the screening itself were € 47,659 for the routine screening (in the limited screening group) and € 181,574 for the extensive screening. The routine screening performed in the limited screening group found seven malignancies at the cost of € 6796 per malignancy (€ 47,659/7). Using the extensive screening strategy, six additional malignancies were discovered, at the cost of € 30,262 per malignancy (€ 181,574/6).

Extensive screening did not result in LYG for total mortality. The mortality rate among patients diagnosed with cancer during the study was 38% (8 out of 21) for the limited screening group and 57% (17 out of 30) in the extensive screening group. Hence, LYG for mortality due to cancer could not be computed. To exclude that the higher rate of mortality due to cancer in the extensive screening group was mainly caused by a difference in cancers found by routine screening, we excluded the malignancies diagnosed by routine screening in both groups. When the malignancies diagnosed by routine screening are excluded, 14 malignancies remain in the limited screening group (only follow-up) and 18 in the extensive screening group (i.e. malignancies identified by extensive screening and during follow-up). Mortality among these patients was 14% (2/14) in the limited screening group and 44% (8/18) in the extensive group.

Sensitivity analysis

The minimal mortality difference needed to stay within cost-efficacy limits was calculated, using the mean costs per patient of extensive screening using CT scans and

mammography (€ 530.92) divided by the commonly used upper cost-efficacy limit of € 30,000. We should have found a minimum mortality difference of 0.0177 LYG (€ 530.92/30,000) to remain within this limit. Extensive screening detected six of 18 malignancies, resulting in a sensitivity of 33.3%. In the power calculation, a sensitivity of 80% was assumed; in that case 14.4 malignancies would have been identified by extensive screening. Cost per malignancy would then shift from € 30,262 (€ 181,574/6) to € 12,609 (€ 181,574/14.4).

DISCUSSION

We compared the costs and test characteristics of extensive screening to routine screening for the detection of an underlying malignancy in patients with IVT. The extensive screening is three times more expensive compared with the routine screening. These additional expenses for the extensive screening did not save lives or costs spent in the follow-up period. When the costs for the extensive screening itself were not taken into account, costs resulting from extensive screening were still €181.55 on average per patient. These costs were mainly caused by the high proportion of patients with false-positive results. As a consequence, in a quarter of all patients in the extensive screening group invasive procedures were performed, which is twice as often as in the limited screening group. These invasive procedures did not result in additional morbidity or mortality. The minimal LYG that should have been reached by extensive screening to remain under the accepted limit of € 30,000 was 0.0177. The costs for screening would probably have been considered acceptable if there had only been an effect on mortality.

Several limitations of this study have to be acknowledged. Most important, due to the lack of effect of extensive screening, we could only perform a very limited and exploratory sensitivity analysis whereas a formal cost-effectiveness analysis was not possible. Although the study was terminated prematurely, it seems unlikely that continuation of recruitment would have resulted in a higher sensitivity. All costs were calculated using the 2006 Committee of Tariffs for Healthcare; these costs vary in time and could be different for other countries. Furthermore, the low sensitivity could be a result of the quality of the radiological assessment. However, the radiologists completed a standardised form with a predefined list of abnormalities suggestive for malignancy.

The low PPV is in line with that of CT of the chest in patients with a high risk for lung cancer. In two large lung cancer screening programs, more than 20% of all patients screened with one single CT scan had false-positive results.[10,11] This is comparable with the 27% of patients in our study with false-positive findings on a single CTCA. The sensitivity of screening using CT scans will deteriorate in low-risk populations, while the number of false-positive findings will probably be equal or higher in these individuals. Therefore the use of whole body CT scans as a screening modality in asymptomatic low-risk populations is likely to lead to a negative benefit-risk ratio.[12] This is important as there is a worldwide tendency to an increase in screening of asymptomatic patients, in some cases initiated by the 'patients' themselves. Alternative or non-cancer diagnoses were rarely (7.6%) found in our patient group. Furthermore, of these diagnoses, the majority did not lead to a change in treatment or prognosis. Therefore, screening for cancer using whole body CT scans in low-risk patients should be discouraged as long as no randomised or otherwise comparative trials have proved beneficial effects on mortality or morbidity. Also, further study of psychosocial effects of these false-positive findings is needed, as current literature suggests that false-positive findings strongly influence people's well being.[13]

In summary, although the prevalence of occult cancer in patients with idiopathic venous thrombosis is sufficiently high to justify screening and at least the costs of the screening strategy used in this analysis do not seem to be very high, screening for cancer using CT scans should not be implemented due to the low sensitivity and specificity and the high number of false-positive findings.

ACKNOWLEDGEMENTS

We would like to thank all participating centres in the Trousseau study for their help with this planned cost-efficacy analysis. The authors have no conflict of interest with respect to the present study.

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CASE REPORT

Hypogonadism in a patient with mild hereditary haemochromatosis

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ABSTRACT

Hypogonadism is a potential complication of haemochromatosis, usually seen in patients with severe iron overload and liver cirrhosis. We describe the diagnostic workup of a patient with an early stage of hereditary haemochromatosis, presenting with only mildly elevated liver enzymes and central hypogonadism in the absence of cirrhosis or diabetes, but with concurrent sarcoidosis.

KEYWORDS

Hereditary haemochromatosis, hypogonadism, sarcoidosis, iron overload.

What was known on this topic?
Hereditary haemochromatosis is usually suspected in patients with a combination of diabetes mellitus, hepatomegaly or cirrhosis, hyperpigmentation, and arthralgias. Male patients with haemochromatosis may also suffer from hypogonadism, particularly patients with cirrhosis or severe iron accumulation.

What does this case add?
Patients with hereditary haemochromatosis without overt cirrhosis or other signs of advanced iron accumulation may still have hypogonadism. In the case of hypogonadotropic hypogonadism, MRI of the brain is able confirm the presence of iron in the pituitary gland, and differentiate iron accumulation from other causes of pituitary dysfunction.

INTRODUCTION

The classic presentation of (advanced) HFE-related hereditary haemochromatosis is a combination of diabetes mellitus, hepatomegaly or liver cirrhosis, skin hyperpigmentation, and arthralgias.[1,2] In the face of iron accumulation in several organs, patients usually present with normal haemoglobin levels.[3] We report a case of haemochromatosis presenting with anaemia and endocrine abnormalities, but without diabetes mellitus or cirrhosis. The patient was finally diagnosed with hereditary haemochromatosis and sarcoidosis, a combination that has only been described in a few cases in the literature.[1,4,5] Using magnetic resonance imaging (MRI), we were able to confirm that pituitary iron deposition caused the endocrine deficiencies. We conclude that hormonal deficiencies may also be present in patients with an early stage of haemochromatosis without signs of advanced iron accumulation, such as cirrhosis, diabetes, hyperpigmentation, or arthralgias.

CASE REPORT

A 57-year-old male with an unremarkable medical history was admitted with a six week-history of decreased appetite, nausea, and continuous abdominal pain. In addition, he reported fatigue and 10 kg weight loss. He did not smoke and consumed about two units of alcohol daily. On physical examination, his blood pressure was 107/65 mmHg with a pulse rate of 102 beats/min and a temperature of 36.7 °C. Examination of the heart, lungs and abdomen was unremarkable except for mild tenderness in the epigastric region. A few lymph nodes of up to 1 cm diameter were palpable in the cervical region, and both lower legs revealed palpable purpura. Initial laboratory investigation showed a haemoglobin of 7.8 mmol/l with an MCV of 98fl,

leucocytes 6.8 x 10^9/l, and thrombocytes of 440 x 10^9/l. C-reactive protein was 35 mg/l, aspartate aminotransferase 100 U/l, alanine aminotransferase 65 U/l, alkaline phosphatase 103 IU/l, gamma-glutamyltransferase 130 U/l, and liver and kidney function were normal. Urine analysis and a chest X-ray revealed no abnormalities.

The combination of anorexia, weight loss, lymphadenopathy, anaemia and elevated liver enzymes raised suspicion of either a metastasised malignancy or a systemic inflammatory disease. However, abdominal ultrasound and oesophagogastroduodenoscopy revealed no abnormalities, autoimmune serology (antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulins, rheumatoid factor) turned out to be negative, and the vasculitis was found to be caused by a course of oral amoxicillin, and spontaneously disappeared. Surprisingly, additional laboratory tests revealed a transferrin oversaturation (>100%) with a serum ferritin of 2282 ng/ml, and an erythrocyte sedimentation rate of 96 mm/h. MRI showed extensive iron deposition in the liver (*figure 1*), and also some iron deposition in the pancreas. Eventually, the patient was found to be homozygous for the Cys282Tyr mutation, compatible with hereditary haemochromatosis type 1.

Simultaneously, 18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG PET/CT) showed tracer-positive mediastinal and hilar lymph nodes in the thorax, and a 2 x 3 cm lymph node in the liver hilus. Subsequent blood and stool cultures did not show an infectious agent, an interferon-gamma release assay was negative for tuberculosis antigens, and serology for syphilis, viral hepatitis B and C, and HIV was negative. Cytological examination of a fine needle aspirate of the mediastinal lymph node showed noncaseating granulomas without the presence of mycobacteria. Moreover, bilateral anterior uveitis was diagnosed by a consulting ophthalmologist. The combination of these findings was compatible with a diagnosis of sarcoidosis.

In addition, hormonal tests revealed a thyroid-stimulating hormone level of 1.7 mIU/l with fT4 12.3 pmol/l, follicle-stimulating hormone 0.47 U/l, luteinising hormone 0.38 U/l, testosterone 0.55 nmol/l, insulin-like growth factor-1 45 µg/l (-2.5 SD), fasting cortisol 550 nmol/l, and an HbA1C 42 of mmol/mol. The combination of hypogonadotropic hypogonadism and growth-hormone deficiency indicated a problem in the pituitary gland, but both iron accumulation and sarcoidosis could be considered causes of pituitary dysfunction. To differentiate between these two causes, we performed an MRI of the pituitary gland, which showed the presence of pituitary iron deposition (*figure 2*), but no signs of granulomas. Finally, bone densitometry showed severe osteoporosis (T score -4.3).

The patient was discharged and started treatment with phlebotomies, which were limited due to the present anaemia. No specific treatment for the sarcoidosis was started at this stage. Testosterone suppletion was initiated, but additional testing for growth hormone deficiency was withheld, as the patient was not candidate for growth hormone suppletion. Currently, the patient's ferritin is 1269 ng/ml with haemoglobin of 8.2 mmol/l and erythrocyte sedimentation rate of 21 mm/h.

Figure 1. *Decreased signal intensity of the liver on MRI, compatible with iron deposition (>350 µmol/g liver tissue according to Yves Gandon formula)*

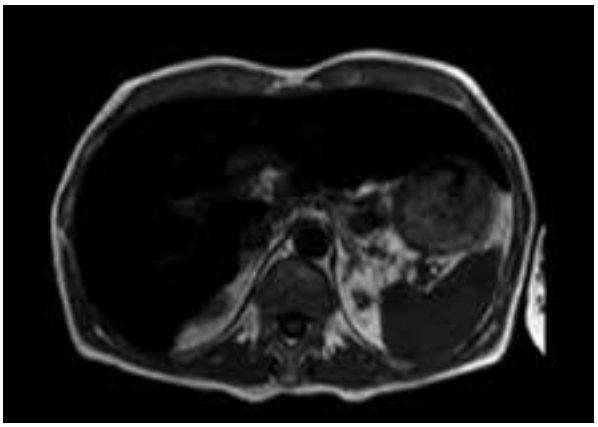
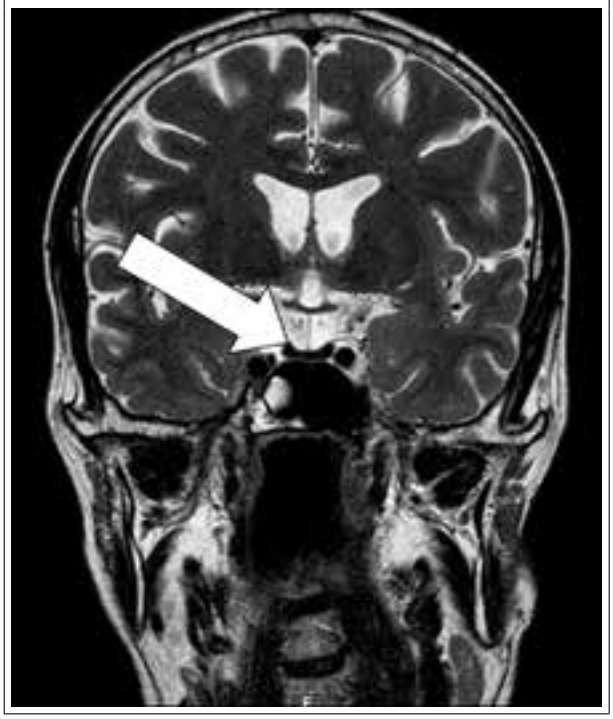


Figure 2. *Decreased signal intensity of the pituitary gland on T2-weighted MRI, compatible with iron deposition*



DISCUSSION

The present case clearly shows how the combination of three presumably independent pathophysiological processes (haemochromatosis, sarcoidosis and drug-induced vasculitis) may put the clinician on the wrong track, looking for malignancies and autoimmune diseases. Although, retrospectively, most signs of sarcoidosis are obvious in this patient, the patient's presentation of haemochromatosis is unusual, with only mild liver enzyme abnormalities, hypogonadotropic hypogonadism, and growth hormone deficiency. The co-existence of hereditary haemochromatosis and sarcoidosis has been described in a few sporadic cases,[1,5] and only once in a family: a mother and son with both haemochromatosis and hepatic sarcoidosis.[4] These studies have not shown any genetic predisposition (yet), and indicate that the co-existence of haemochromatosis and (hepatic) sarcoidosis is probably coincidental, but that this combination may increase susceptibility to cirrhosis.

Hypogonadism is the most frequent endocrine abnormality in hereditary haemochromatosis and is reported in up to 6.4% of male patients in the largest case series.[6] Although other causes such as Klinefelter's syndrome or use of androgenic anabolic steroids have also been reported,[7] hypogonadism is usually caused by iron accumulation in the pituitary gland, or sometimes in the testes. Other pituitary axes were normal in this large case series, indicating some preference of iron for gonadotropic cells.[6] Usually, patients with (central) hypogonadism also have severe (hepatic) iron accumulation and cirrhosis.

Localisation of granulomas in the central nervous system may also occur in about 10% of patients with sarcoidosis, and some case series have described granulomas in the hypothalamus and pituitary gland.[8] These lesions usually cause hypogonadotropic hypogonadism, but also failure of other pituitary axes and manifest diabetes insipidus. Most patients have multivisceral localisations and sinonasal involvement.

Our patient showed an atypical presentation with failure of two pituitary axes, without cirrhosis or diabetes, but also without severe (neurological) manifestations of sarcoidosis. Therefore, pituitary iron deposition and central granulomas were both considered possible causes of pituitary dysfunction, along with a pituitary adenoma or tumour. Eventually, MRI confirmed the presence of iron deposition in the pituitary gland and ruled out other causes. Despite its low prevalence, hypogonadism is an important complication of haemochromatosis. Testosterone replacement therapy together with phlebotomies can considerably improve the quality of life of these patients by restoring sexual function.[1,6] In addition, testosterone deficiency may have detrimental effects on bone mass and may cause mild anaemia, as shown in our case. In conclusion, we have shown that hypogonadism in haemochromatosis is an important complication that is not only confined to patients with overt signs of advanced iron accumulation. When laboratory investigations have indicated a central cause of hypogonadism, MRI may provide definitive proof of pituitary iron deposition.

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PHOTO QUIZ

A 'chigsaw' puzzle after a vacation in Brazil

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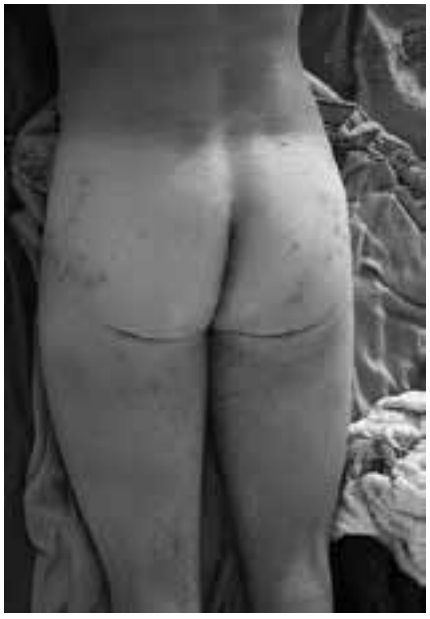
CASE REPORT

A 59-year-old, otherwise healthy, Dutch male consulted the Institute for Tropical Diseases of the Havenziekenhuis in Rotterdam for the diagnosis of itching skin eruptions during a vacation in Brazil. He developed intensely pruritic red papules on his hips, buttocks and upper legs after walking in the jungle and spending the night on towels on the beach at the Tapajós River (a branch of the Amazon river) near Jamaraquá.

At clinical examination, there were some small crustae and skin wounds distributed around the waist, probably due to scratching. However, he presented photographs taken from the skin eruptions during his holiday. These showed symmetrical, papular erythematous and oedematous eruptions over the hips, buttocks and upper legs (*figure 1*). The diameter of the lesions varied between 1 and 5 mm.

Figure 1. *Symmetrical, papular erythematous and oedematous eruption over the hips, buttocks and upper legs in our patient*



WHAT IS YOUR DIAGNOSIS?

See page 325 for the answer to this photo quiz.

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PHOTO QUIZ

A strange looking face in the stomach

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CASE REPORT

A previously healthy 45-year-old male presented to our hospital with a 24-hour history of passing black stools. Physical examination revealed a low blood pressure (100/70 mmHg) and tachycardia (120 beats/min). Abdominal examination was normal. Patient said that he had lost 5 kg in the last six months. The haemoglobin concentration was 7.5 g/dl. On oesophagogastroduodenoscopy a mass with two separate ulcer craters was detected in the anterior wall of the gastric corpus (*figure 1*). After that an endosonographic examination (EUS) was performed to determine the nature of the lesion (*figure 2*).

Figure 1. *Submucosal and ulcerous lesion in the stomach*

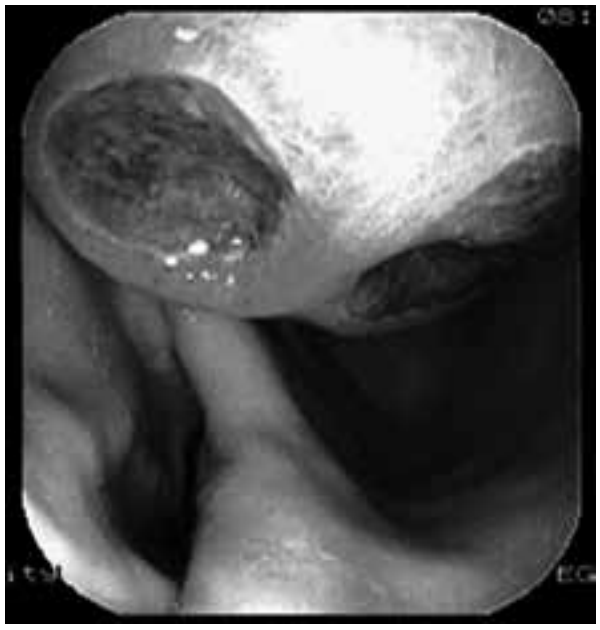
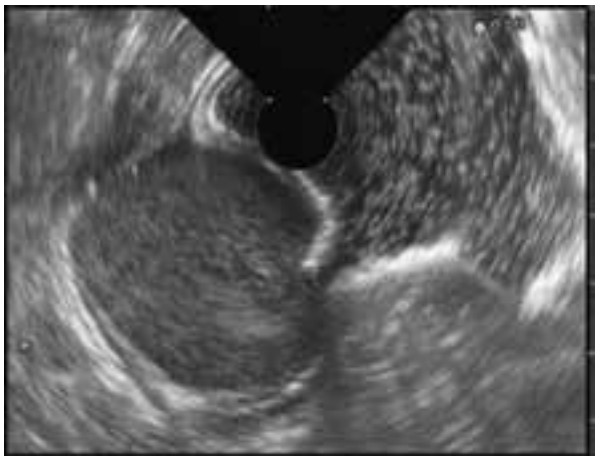


Figure 2. *Endosonography showing a hypoechoic and heterogenous lesion*



WHAT IS YOUR DIAGNOSIS?

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PHOTO QUIZ

A young man with odynophagia, nausea and vomiting

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A 22-year-old male was referred to our hospital with a two-day history of nausea and vomiting after drinking ten units of alcohol. He complained of odynophagia, shivering and fever. His medical history was unremarkable. He smoked ten cigarettes a day but did not use any drugs. On physical examination we saw a moderately ill man. Blood pressure was 120/80 mmHg, heart rate 116 beats/min. His respiratory rate was 20 breaths/min. The oxygen saturation was 98% without supplemental oxygen. His body temperature was 38.4 °C, height 173 cm and weight 60 kg. Examination of the heart, lungs and abdomen was normal. Laboratory results showed haemoglobin 13.0 mmol/l, haematocrit 0.56 l/l, white blood count 21.1 x 10^9/l, sodium 132 mmol/l, potassium 6.4 mmol/l, blood urea nitrogen 22.5 mmol/l, creatinine 532 µmol/l, C-reactive protein 165 mg/l, and glucose 7.6 mmol/l. Arterial blood gas analysis showed pH 7.39, pO2 11.4 kPa, pCO2 4.7, HCO_3^- 20.9 mmol/l, and a base excess of -3.4 mmol/l. Urinary sediment was normal. Electrocardiogram showed a sinus rhythm, rate 98 beats/min, right-axis deviation and high T waves. A chest X-ray was obtained (*figures 1 and 2*).

Figure 1. *Posteroanterior view of chest X-ray*

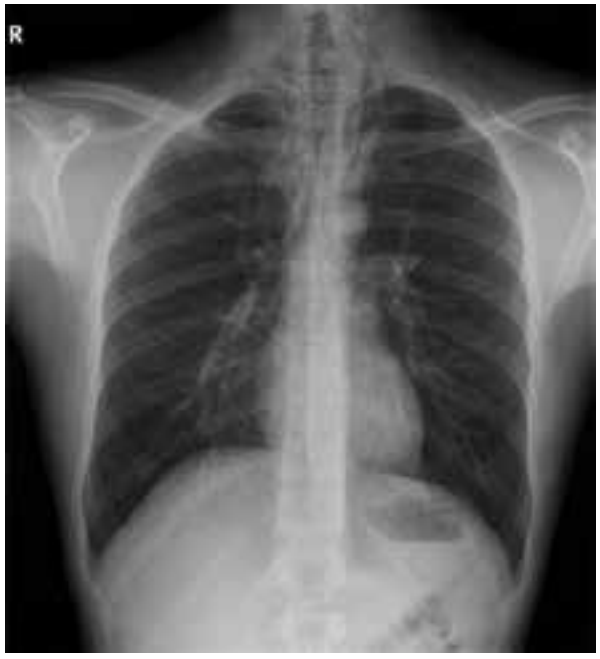
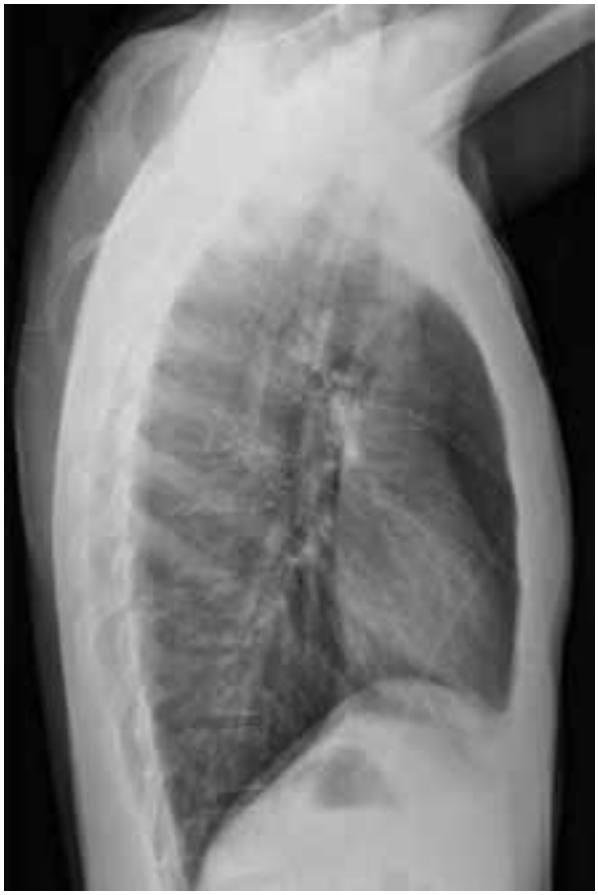


Figure 2. *Lateral view of chest X-ray*



WHAT IS YOUR DIAGNOSIS?

See page 327 for the answer to this photo quiz.

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PHOTO QUIZ

An odd looking man

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CASE REPORT

A 39-year-old man presented himself to the emergency department with confusion due to hepatic encephalopathy and hallucinations caused by alcoholic hepatitis. The patient had a history of alcohol abuse, which had been progressive in the last year. Laboratory blood analysis showed elevated liver enzymes and ammonia (130 µmol/l; reference value 10-45 µmol/l), renal insufficiency (eGFR 29 ml/min; reference value >60 ml/min) and elevated C-reactive protein (129 mg/l, reference value <5 mg/l). Ultrasonography of the abdomen showed an image suggestive for liver cirrhosis without ascites. The patient had a remarkable appearance with proximal adiposity (*figure 1*).

A few hours after admission the patient was transferred to the intensive care unit because of respiratory failure due to pneumonia. The patient was intubated and received inotropic medication. After extubation a symmetric paresis of both the forearms and the hand flexors became prominent.

Figure 1A. *Extreme accumulation of lipomatous tissue on the upper arms and thighs, with remarkable sparing of the shanks and forearms (figure 1B)*

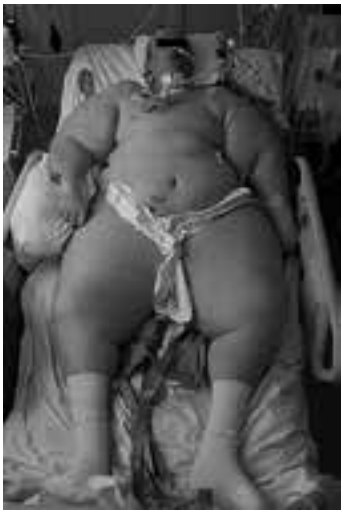
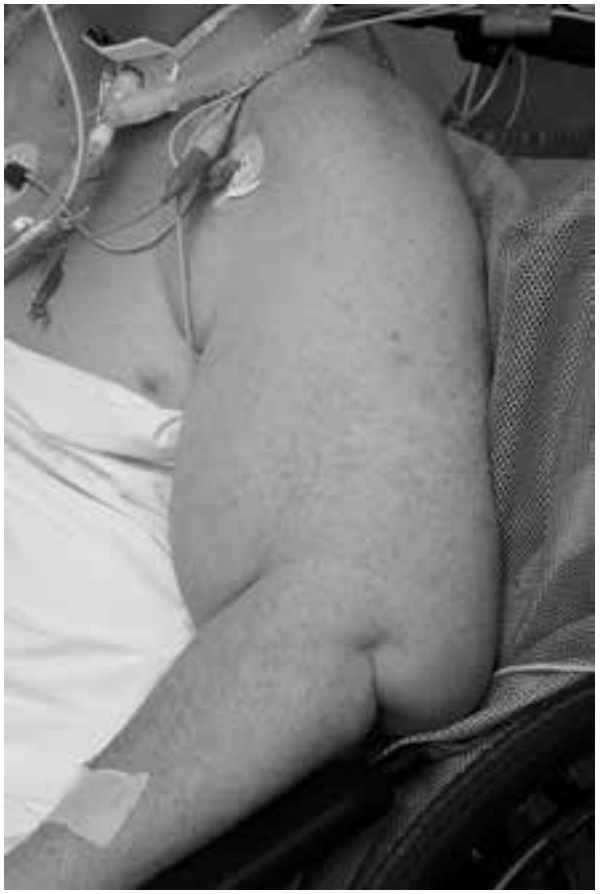


Figure 1B. *Proximal adiposity*



In addition, evident hyperesthesia of both shoulders and a paresis of the right hemidiaphragm were present. Magnetic resonance imaging of the head and neck showed no deviations. Computed tomography of the thorax and abdomen revealed diffuse atrophy of the muscles proximal in the thorax and abdomen and distal in the muscles of the legs, on the right-hand side more than the left.

WHAT IS YOUR DIAGNOSIS?

See page 328 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 321)

A 'CHIGSAW' PUZZLE AFTER A VACATION IN BRAZIL

DIAGNOSIS

A diagnosis of trombiculiasis, also known as chigger bites, was made.

DISCUSSION

Trombiculiasis or chiggers is a dermatosis caused by the biting larvae of trombiculid mites. Trombiculid mites live in soil in warm, humid areas of forests and scrub vegetation. Adult mites live on small insects and their eggs, while only the larvae are ectoparasites to mammals (accidentally humans).[1] The larvae crawl up the body of a host and seek thin skin or areas with tight clothing to settle. They then inject saliva containing lytic enzymes via chelicerae to feed on dissolved epithelial cells.[2] This digestive saliva is repeatedly injected and evokes an immune response that causes the typical severely itching papular skin lesions found mostly on the lower legs, around the waist, on the buttocks or in the armpits.[1,2]

Of the trombiculid mites found in different parts of the world, *Eutrombicula alfreddugesi* is the most common in the North and South of the Americas, and most likely to have been the causative species in our patient. *Neotrombicula autumnalis* is found mostly in Europe (including the Netherlands) whereas *Eutrombicula sarcina* is the most prevalent species in Asia.[1] While all trombiculid larvae cause similar local skin lesions, only the larvae of the *Leptotrombidium* species (Asian scrub typhus chigger mite) are able to transfer *Orientia tsutsugamushi*, the causative bacterial organism for scrub typhus.[1]

Although not often reported in the literature, this clinically typical dermatosis is prevalent all over the world, except for the arctic regions. Favouring a warm environment, chigger larvae are present all the year round in tropical climates and during the summer time in Europe and North America. In Europe and North America, the larvae and the associated skin lesions are particularly present in late summer and early autumn (hence the terms 'augustelingen' in Dutch and 'aoûtats' in French).[3] Normally transient and without systemic signs, trombiculiasis can be easily missed. In case of systemic signs in a traveller from Asia, scrub typhus has to be ruled out. The cutaneous lesions and the itching can be controlled by topical corticosteroids, whereas an *O. tsutsugamushi* infection needs to be treated with antibiotics.[4]

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ANSWER TO PHOTO QUIZ (PAGE 322)

A STRANGE LOOKING FACE IN THE STOMACH

DIAGNOSIS

On endoscopic examination (*figure 1*), a large submucosal lesion with ulcerations on it was observed. The appearance of this lesion reminded us of the head of the alien ET (Extra-Terrestrial) a movie character created by Steven Spielberg in 1982. Differential diagnosis of the lesion included tumours originating from the gastric wall (i.e. gastrointestinal stromal tumour (GIST), leiomyoma, lymphoma, neural tumours, lipoma or gastric metastasis). EUS examination revealed a large mass lesion (45 mm in diameter) originating from the muscularis propria (4th hypoechoic layer). It was hypoechoic and had a heterogenous echo pattern with cystic cavities. These findings were suggestive of a GIST with malignant degeneration.

After a surgical wedge resection, histopathological evaluation of the specimen showed that the tumour was composed of spindle cells exhibiting cytoplasmic positivity for c-KIT (CD117). The number of mitotic figures was 5 per 50 high power fields, suggesting a high-risk tumour.[1] There was no evidence of lymph node and distant metastasis.

Complete tumour resection is the definitive treatment for GIST if the tumour margins are negative and routine lymphadenectomy is not necessary since lymph node metastasis is very rare. Effective treatment of GISTs with activating mutations in the proto-oncogene c-KIT has been achieved with imatinib mesylate and published in recent studies.[2,3] KIT gene mutations are determined at a rate of 85 to 90% in GISTs and the presence of this mutation indicates a poor response to imatinib treatment.[4] In the current case, imatinib 400 mg was initiated as adjuvant therapy six weeks after the operation and patient was closely followed-up in terms of metastasis.

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ANSWER TO PHOTO QUIZ (PAGE 323)

A YOUNG MAN WITH ODYNOPHAGIA, NAUSEA AND VOMITING

DIAGNOSIS

The chest X-ray shows a pneumomediastinum: air tracking along the upper mediastinal structures and subcutaneous emphysema in the neck. On the lateral view, air around the aortic arch can be detected. No signs of pneumothorax are seen.

A pneumomediastinum can result from air escaping from the respiratory or gastrointestinal tract.[1] An underlying trigger can be identified in most cases of pneumomediastinum.

Acute asthma exacerbation is the most common trigger. Other causes include Valsava manoeuvre (intense sport activities, coughing), vomiting, respiratory infections, diabetic keto-acidosis, oesophageal rupture, inhalation of a foreign body, dental extraction and barotrauma (flying or diving).[2]

CT scan of the chest and upper abdomen with water soluble contrast media was obtained to search for the cause of the pneumomediastinum and to exclude Boerhaave's syndrome.[3] Extensive pneumomediastinum was seen with air extending into the neck. Air entering the retroperitoneum was not detected. A few sections showed a small air configuration eccentrically within the wall of the oesophagus suggesting an oesophageal perforation. However, no contrast media was seen in the soft tissues around the oesophagus. If this had been seen, it would confirm an oesophageal rupture, but its absence does not exclude rupture.

Oesophagogastroscopy was performed to confirm an oesophageal rupture with the option of positioning an expanding oesophageal stent.[4] During endoscopy, intraluminal contrast was given at a proximal and mid-oesophageal level. No signs of leakage were detected. However, a distal reflux oesophagitis grade D was confirmed.

A thorough examination of the oropharynx showed no abnormalities to explain the pneumomediastinum.

The patient was treated conservatively for a covered oesophagus perforation with parenteral infusion, antibiotics and proton pump inhibitors. The kidney function improved on parenteral infusion and the patient recovered uneventfully. Delayed diagnosis and treatment of an oesophageal perforation is associated with prolonged morbidity and high mortality.

Conclusion: In a patient presenting with odynophagia, nausea, vomiting and pneumomediastinum, an oesophageal rupture should be excluded.

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ANSWER TO PHOTO QUIZ (PAGE 324)

AN ODD LOOKING MAN

DIAGNOSIS

The remarkable appearance of our patient with proximal adiposity suggested the presence of Launois-Bensaude syndrome. Launois-Bensaude syndrome, also coined Madelung's disease or multiple symmetric lipomatosis, is a rare disease.[1]

The disease is characterised by accumulation of unencapsulated fat. In Launois-Bensaude, fat generally accumulates symmetrically around the neck, shoulders, trunk and proximal part of superior and inferior limbs. As a result, patients often have a pseudo athletic appearance. The face, forearms and shanks are usually unaffected.[1,2] The lipomatous tissue is able to infiltrate spaces between adjacent subcutaneous and muscular structures. As a result, neurological involvement is common, particularly peripheral neuropathy.[3] The neuropathy in our patient could be attributed to critical illness polyneuropathy and/or alcoholic neuropathy.

Although the aetiology of Launois-Bensaude syndrome remains unidentified, it is thought to be associated with mitochondrial respiratory chain dysfunction, which could not be demonstrated in our patient by means of an oral glucose tolerance test. Another suggested mechanism is a defect in the lipolytic pathway of the fat cell. Furthermore, most patients have or have had a history of alcohol abuse, as was the case in our patient who presented with alcohol-related hepatic encephalopathy, provoked by a community acquired pneumonia.[3,4]

Treatment is difficult and the chances of success are low. Dietetic interventions and cessation of alcohol consumption generally do not result in regression of lipomatosis. The standard treatment is surgical excision or liposuction, which has a high recurrence rate.[4]

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Netherlands
The Journal of Medicine

Therapeutic drug monitoring of free fraction valproic acid in patients with hypoalbuminaemia

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Dear Editor,

Valproic acid (VPA) is the most frequently reported anticonvulsant causing unintentional and intentional intoxications.[1] Symptoms of VPA toxicity include central nervous system dysfunction, ranging in severity from mild drowsiness to coma or fatal cerebral oedema. Long-term or high-dose VPA therapy may mediate hepatotoxicity.[2,3] We describe a patient with hypoalbuminaemia and a serious VPA intoxication due to high free fraction of VPA, with normal total blood VPA levels.

A 53-year-old man presented with weight loss (15 kg in 6 months), vomiting, and hyperglycaemia for two weeks. He had a history of epilepsy and chronic alcohol abuse, resulting in liver cirrhosis, and diabetes mellitus type 2. Physical examination was unremarkable. Laboratory results included hyponatraemia (120 mmol/l), hypokalaemia (3.0 mmol/l), hypocalcaemia (1.62 mmol/l), hyperglycaemia (18.3 mmol/l), hypoalbuminaemia (2.1 g/dl) and severe anaemia (haemoglobin 3.8 mmol/l). All other relevant laboratory tests were normal. At home he was treated with subcutaneous insulin once daily, VPA 600 mg four times a day and esomeprazole 40 mg. Based on his history, and spontaneously increased bleeding tendency (prothrombin time 27.3 sec), he was diagnosed with acute on chronic hepatic failure and was given blood transfusion, rehydration therapy, 10 mg vitamin K and thiamine 100 mg once daily. Gastroscopy showed severe oesophageal ulceration and grade II oesophageal varices, but no signs of active bleeding. On the second day of admission he developed respiratory distress and decline of consciousness (E1M5V1), without signs of cerebral bleeding. He was admitted to the intensive care unit for respiratory support and haemodynamic stabilisation. Laboratory results showed liver failure with an ammonium level of 165 mmol/l. Serum total VPA trough concentration was 62 mg/l (normal 50-100 mg/l), with an increased free fraction of 17 mg/l (normal 5-15 mg/l). VPA administration was stopped immediately, but that same day he developed multiorgan failure and died. The cause of death was attributed to a combination of acute on chronic hepatic failure and VPA toxicity.

Intoxication of VPA might be difficult to recognise in critically ill patients due to different pharmacokinetics, pharmacodynamics and their critical illness. This case report suggests that monitoring of unbound drug concentrations of VPA can be helpful in identifying unrecognised concentration-related adverse effects. Awareness of the pharmacokinetic relationship and adverse effects of VPA will aid clinicians to guarantee therapeutic action and prevent overdose. In parallel to the recommendations for phenytoin we would like to recommend routine measurement of VPA free fraction in patients with hypoalbuminaemia.

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Netherlands
The Journal of Medicine

A dialysis patient with a life-threatening hyperkalaemia due to the use of a low-salt spread

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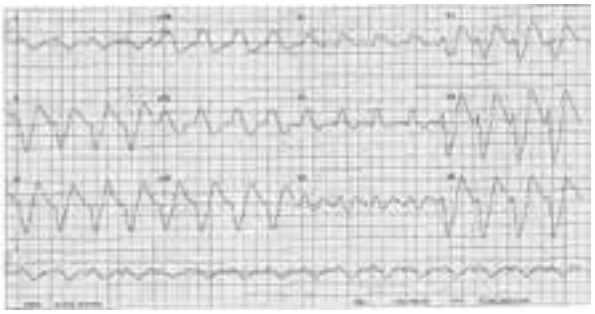
Dear Editor,

Dialysis patients and patients with end-stage renal disease are at risk for hyperkalaemia because renal potassium excretion is reduced or completely absent. Elevated potassium concentration leads to reduced myocardial conduction, and can cause acute death because of arrhythmia.[1]

A 67-year-old haemodialysis patient presented at the emergency room after a sudden collapse and paralysis of his legs. Electrocardiograms showed typical changes compatible with severe hyperkalaemia: peaking of the T wave, prolongation of the PR interval, loss of the P-wave amplitude and widening of the QRS complex (*figure 1*).[2] Laboratory analysis revealed severe hyperkalaemia. (K = 9.3 mmol/l; reference levels are 3.5-4.7 mmol/l). The patient was treated with calcium, insulin, glucose and sodium polystyrene sulphonate. Acute dialysis was arranged. Soon after treatment was initiated, the symptoms resolved and the electrocardiogram normalised.

A thorough analysis was performed to reveal the cause of this life-threatening hyperkalaemia. The patient was aware of potassium-rich products and adhered to his potassium-restricted diet. The only recent change in his diet was the addition of Becel pro.activ blood pressure spread®. His neighbour advised him to use the product to improve blood pressure regulation. Becel pro.activ blood pressure spread® is a low-sodium and potassium-enriched spread which helps maintain a healthy blood pressure.[3]

Figure 1. *Electrocardioagram at presentation showing changing characteristics for hyperkalaemia*



Without the consumption of the spread the patient had a potassium intake of 50 mmol per day. By measuring the weight of a slice of bread before and after addition of the spread we calculated an added potassium intake of 40 mmol a day. It seemed that this was the cause of the hyperkalaemia. No other cause of the sudden increase in potassium levels could be identified. After discontinuation of the Becel pro.activ spread, no excessive potassium levels were measured.

Some case reports in the past have been published in which hyperkalaemia was caused by salt substitutes.[4-6] Nowadays not only potassium-enriched salt substitutes are produced but low-sodium products also use potassium instead of salt. Severe hyperkalaemia requires emergency treatment. Management of this condition is based on small studies and expert opinions. Reports focus on the level of potassium and do not describe mortality or cardiac arrhythmia after the treatment. Despite this, treatment with calcium, insulin and a beta agonist are considered effective.[7-9]

Causes of hyperkalaemia in dialysis patients are pseudo-hyperkalaemia, extreme potassium intake, inadequate dialysis, drugs (in patients with considerable residual renal function), acidosis, cell lysis, fasting and constipation.[10] Excessive potassium intake is a very important preventable cause. Special attention should be given to low-salt and potassium-enriched products. These products are often recommended because they are assumed to lower cardiovascular risks. Indeed, effective dietary protocols for patients with hypertension include a low-salt and

high-potassium diet.[11] This can provoke excessive potassium intake and finally lead to life-threatening hyperkalaemia as in our patient.

This case report adds that even potassium-enriched spread can cause a life-threatening hyperkalaemia. It should create an awareness of this preventable cause of hyperkalaemia among doctors and dieticians. Furthermore this is the first case report to describe Becel pro.activ as a source of hyperkalaemia.

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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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