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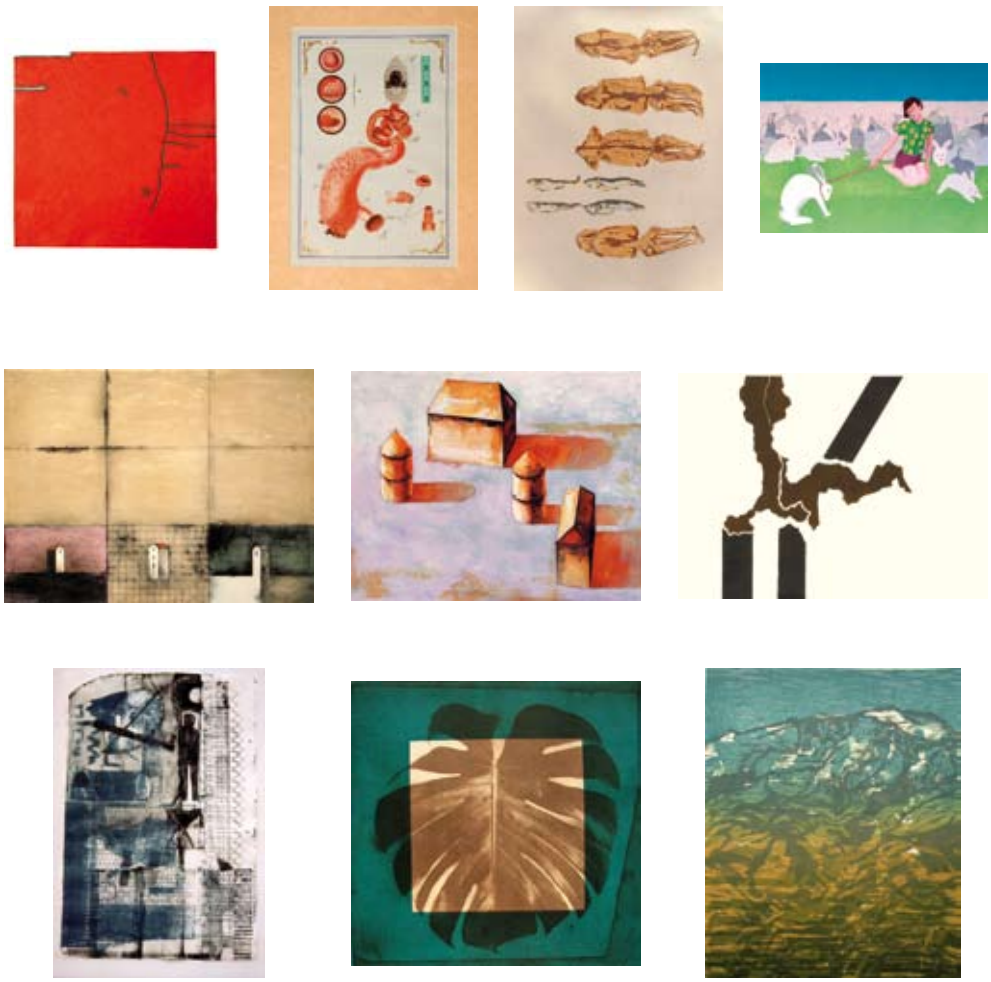

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EDITORIAL

Do we need new drugs for the treatment of type 2 diabetes mellitus?

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At this moment, approximately ten different classes of drugs are or soon will become available for the treatment of type 2 diabetes mellitus (*table 1*). Of the glucose-lowering agents, pramlintide has not been approved by the European Medicines Agency (EMEA) and two, a GLP (glucagon-like peptide)-1 and a DPP (dipeptidyl peptidase)-IV-inhibitor, have recently been approved but have not yet become available on the European market. The recent increase in available blood glucose-lowering drugs is remarkable, because after the introduction of insulin (at the beginning of the 20th century), the sulphonylureas and metformin (mid-1940s and 1950s) no innovative treatment modalities had been introduced until less than a decade ago.

The development of new classes of glucose-lowering medications has expanded the treatment options for type 2 diabetes, but has also introduced more uncertainty regarding which treatment option is the most appropriate. Recently, management guidelines have been published that provide a directive for the most appropriate intervention for treating patients with type 2 diabetes.[1,2] Nevertheless, except for the initial therapy, these reports acknowledge that in fact no definitive guidelines can be provided regarding subsequent treatment choices.

The primary goal is achieving glucose levels as close to normal as possible without imposing a high risk of (severe) hypoglycaemic attacks. An HbA1c ≥7% should serve as a call to act by initiating or changing therapy to ultimately reduce microvascular and most likely macrovascular complications in type 2 diabetes.[3]

Since durability and long-term safety have to be established in almost all new drugs, metformin is universally considered to be the drug of choice as it is cheap, safe and effective. Moreover, metformin is associated with either weight stability or weight loss.[2,4]

As type 2 diabetes is characterised by a progressive decline in β-cell function, treatment needs to be adjusted regularly and commonly results in combination therapy of metformin with sulphonylureas or insulin as second-line treatment; both are cheap and cause effective glucose lowering yet often at the expense of weight gain and a higher risk of hypoglycaemia. Some view the failure of clinicians and their patients to effectively implement available interventions as the main reason for insufficient glycaemic control, more so than the lack of available drugs.[5]

So, why do we need new drugs for the treatment of type 2 diabetes if the old ones are so effective?

Table 1. *Different therapeutic modalities for the treatment of type 2 diabetes mellitus and mode of action*

Agents	Mode of action
Insulin	Stimulation of insulin receptor and glucose uptake
Sulphonylureas	Stimulation of insulin secretion
Metformin	Inhibition of hepatic gluconeogenesis and increase in hepatic insulin sensitivity
Thiazolidinediones	Increase in muscle insulin sensitivity, decrease in lipotoxicity and modulation of adipocytokines
α-glucosidase inhibitors	Delay in glucose absorption
Meglitinides	Stimulation of insulin secretion
GLP-1 analogues	Stimulation of (glucose-dependent) insulin secretion and inhibition of glucagon release
DPP-IV inhibitors	Stimulation of (glucose-dependent) insulin secretion and inhibition of glucagon release via increase of endogenous GLP-1
Rimonabant	Weight reduction through blockade of the cannabinoid receptor-1; probably weight independent effects?
Pramlintide	Inhibition of glucagon release and gastric emptying

First of all, despite currently available treatment options, targets are not met in at least 50% of patients in clinical trials.[6,7] Keeping in mind that patients participating in clinical trials are most probably more motivated and interested, the percentage of patients reaching these targets will be even lower in daily clinical practice. It has been argued that lifestyle changes should always be part of everyday diabetes treatment. We acknowledge that lifestyle interventions flanked by diabetes education and dietary control are the cornerstone of treatment and have proven to be effective both during intervention and onwards.[8] Nevertheless, even then these measures alone are not sufficient to reach glycaemic targets and to sustain metabolic control. Secondly, even more stringent targets have been set recently with respect to HbA1c.[9,10] It is to be expected that these guidelines will be followed by other organisations and societies. Finally, as mentioned before, hypoglycaemia and especially weight gain are of particular concern with sulphonylureas and insulin.

The question arises whether combinations of new drugs, each specific with its pharmacological mechanism of action, can expand our ability to manage patients with diabetes.

Thiazolidinediones (or peroxisome-proliferator-activated receptor-gamma (PPAR-γ) agonists) represent a class of drugs with a new mechanism of action. In response to PPAR-γ activation the expression of different genes within the target cells changes. PPAR-γ is mainly expressed in fat cells and activation will lead to (pre)adipocyte differentiation. As such, fat cells take up triglycerides more easily while lipolysis is inhibited. Subsequently, the level of circulating free fatty acids decreases resulting in an increase in insulin sensitivity. Other mechanisms may also play a role in improving insulin sensitivity.[11]

The efficacy with respect to blood glucose lowering with thiazolidinediones is comparable with (but not better than) sulphonylureas and metformin. Recently two long-term trials were performed that investigated treatment with pioglitazone (PROactive trial) or rosiglitazone (ADOPT).[12,13] In the PROactive trial HbA1c levels were on average 0.5% lower in patients randomised to pioglitazone than to placebo, but no benefit was found with regard to its primary combined cardiovascular endpoint. A 16% decrease in its secondary endpoint (death, myocardial infarction and stroke) after three years was noted. However, this should be balanced against the main adverse effects, such as fluid retention, which are probably related to heart failure and weight gain. The trial outcome is therefore viewed controversial.[14]

In ADOPT, the study's primary endpoint was to compare glycaemic control achieved by rosiglitazone, metformin, and glyburide monotherapy. Rosiglitazone was found to be superior to glyburide (a sulphonylurea derivative) with respect to durability during five years of treatment. However, the differences between rosiglitazone and metformin were quite small and of questionable clinical relevance. Again weight gain and fluid retention were the main side effects in the rosiglitazone-treated group. Although insulin secretion (β-cell function) improved shortly after rosiglitazone treatment, this was unfortunately not sustained.

Recently, new side effects of the available thiazolidinediones (both rosiglitazone and pioglitazone) were reported.[15] The incidence of upper arm, hand, or foot fractures was significantly higher in women receiving rosiglitazone than in those receiving metformin or glyburide treatment. The company's clinical trial database also revealed that pioglitazone-treated women were more likely to have sustained a fracture than those receiving a comparator drug or placebo during a maximum period of 3.5 years. No increased risk for fracture was identified in men with either drug.

Because of weight gain, fluid retention and the increased risk of bone fractures in women, the thiazolidinediones do not appear to be the ideal drugs for intensification of combination therapy.

The α-glucosidase inhibitors and meglitinides are, certainly in the Netherlands, less widely prescribed. The α-glucosidase inhibitors have serious gastrointestinal side effects but are not associated with weight gain. The meglitinides are short acting so that optimal timing with meals is of crucial importance and they confer a risk of hypoglycaemia, although less than sulphonylureas. As such they can be used as an alternative for but should not be added to sulphonylureas.

All other new classes are characterised by a lack of sufficient data from long-term studies with 'hard' outcomes and limited experience, leaving us with questions about durability and especially side effects. In general the expectations with respect to glucose-lowering effects should not be that high in these new drugs. However, it would be of particular interest to find out what the effects will be, for example on weight gain, when these agents are combined with other drugs.

The glucagon-like peptide (GLP)-1 analogues stimulate insulin secretion, suppress glucagon and slow gastric emptying. The first results with these agents show that the effect on glycaemic control is moderate (decrease in HbA1c of 0.5 to 0.9%) but sustainable during 18 months of treatment.[16] They lower body weight, but serious gastrointestinal side effects occur and they need to be injected subcutaneously. Although it needs to be confirmed in humans, improvement of β-cell function was found in animal studies.[17]

As a natural gastrointestinal peptide, GLP-1 is rapidly inactivated by dipeptidyl peptidase IV (DPP-IV). Inhibitors of DPP-IV (gliptins) have been developed to increase levels of endogenous GLP-1. On top of metformin, sitagliptin

decreased HbA1c by 0.6% during a short follow-up of 24 weeks.[18] Distinct from GLP-1 analogues, DPP-IV inhibitors do not appear weight neutral and to lack gastrointestinal side effects.

Rimonabant is also an interesting option with respect to its effects on weight reduction. Nevertheless the glucose-lowering effects are limited.[19]

The amylin analogue pramlintide is currently not registered in the Netherlands. Its beneficial effect on weight is promising, but this drug also needs to be injected.

It can be concluded that at the moment the availability of new drugs should not preclude metformin and sulfonylureas (and insulin) as initial therapy since the 'oldies' are still very useful. For various reasons, a significant number of patients with type 2 diabetes will not reach the glycaemic target with these drugs. Therefore, we do need new drugs for the treatment of type 2 diabetes mellitus. These new drugs are promising but (long-term) comparative trials with different combinations focussing on glucose-lowering and disease-modifying effects, durability, as well as side effects (especially with respect to weight gain), are required. In short, we especially do need to know when and in whom to use the new drugs. We need to sort out which combination therapy should be given to a specific person with type 2 diabetes. Individualised medical therapy with different combinations of drugs has the future.

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REVIEW

Heterozygous alpha-1 antitrypsin deficiency as a co-factor in the development of chronic liver disease: a review

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ABSTRACT

Alpha-1 antitrypsin (A1AT) is an acute-phase protein that is produced in liver cells. A1AT deficiency is a hereditary disease which is defined by the hepatic production of an abnormal protein that can not be released into the plasma. This leads to deficiency of plasma A1AT and subsequently to an impaired protection against proteases, resulting in pulmonary disease. Accumulation of the abnormal protein in hepatocytes can lead to liver damage. Serum level measurement, phenotyping and liver biopsy can be used for establishing the diagnosis.

Homozygous A1AT deficiency can cause neonatal hepatitis; in adults end-stage liver disease, cirrhosis and hepatocellular carcinoma can develop. There are strong arguments to consider heterozygous A1AT deficiency as an important co-factor in the aetiology of chronic liver disease. Studies have shown that A1AT heterozygosity can be considered a modifier for hepatitis C virus, end-stage liver disease, cirrhosis and hepatocellular carcinoma. The accumulation of A1AT in the hepatocytes occurs more profoundly in a diseased liver, and as a consequence it affects the natural course of the liver disease. Therapeutic options include augmentation therapy (infusion of purified human plasma A1AT) in pulmonary disease; in end-stage liver disease liver transplantation is an option. For the future, other interventions such as gene therapy or strategies to inhibit polymerisation are promising.

KEYWORDS

Alpha-1-antitrypsin deficiency, hepatocellular carcinoma, heterozygosity, liver disease

INTRODUCTION

Alpha-1 antitrypsin (A1AT) is an acute-phase protein that is produced in liver cells. It is released into the plasma in response to an inflammatory stimulus. A1AT deficiency is a hereditary disease that is defined by the hepatic production of an abnormal protein that can not completely be released into the plasma. This leads to deficiency of plasma A1AT and subsequently to an impaired protection of the lungs against proteases. This results in pulmonary emphysema; hepatic accumulation of the abnormal protein can lead to chronic liver disease. This review gives an update of the present knowledge on partial A1AT deficiency in relation to various liver diseases.

GENETICS AND (PATHO)PHYSIOLOGY

The A1AT molecule is a serum glycoprotein acting as an acute-phase protein. It is released during inflammatory processes from the hepatocyte, which results in increased plasma concentrations. The major physiological function

J.P.H. Drenth was not involved in the handling and review process of this paper.

of this protein is the inhibition of destructive neutrophil elastase, thus protecting against pulmonary damage.[1]

The A1AT protein is encoded by the protease inhibitor (Pi) locus located on chromosome 14q32.1. The Pi locus is highly polymorphic, resulting in different A1AT isotypes that can be detected by electrophoresis.

The most common allele is the M allele that results in a functionally normal protein with normal serum A1AT levels. The normal A1AT protein has a tertiary structure based on a large central β-sheet, surrounded by two other sheets and a reactive centre loop. The reactive centre loop can move in and out of the large β-sheet. At higher temperatures polymerisation can occur between molecules due to insertion of the loop of one molecule into the large β-sheet of the other.

The point mutation, found in the Z variant, destabilises the loop-sheet polymerisation of the A1AT molecule, resulting in chains of polymers that are retained in the hepatocytes. These polymers accumulate in the endoplasmatic reticulum of the hepatocytes and may be recognised as PAS(+) inclusion bodies (*figure 1*). Only 15% of the Z variant of A1AT can be secreted into the plasma, the other 85% accumulates in the liver. In Pi ZZ homozygous subjects, this results in a severe deficiency of serum A1AT and in accumulation of the abnormal protein in the endoplasmatic reticulum of the hepatocyte, which can lead to chronic liver disease.

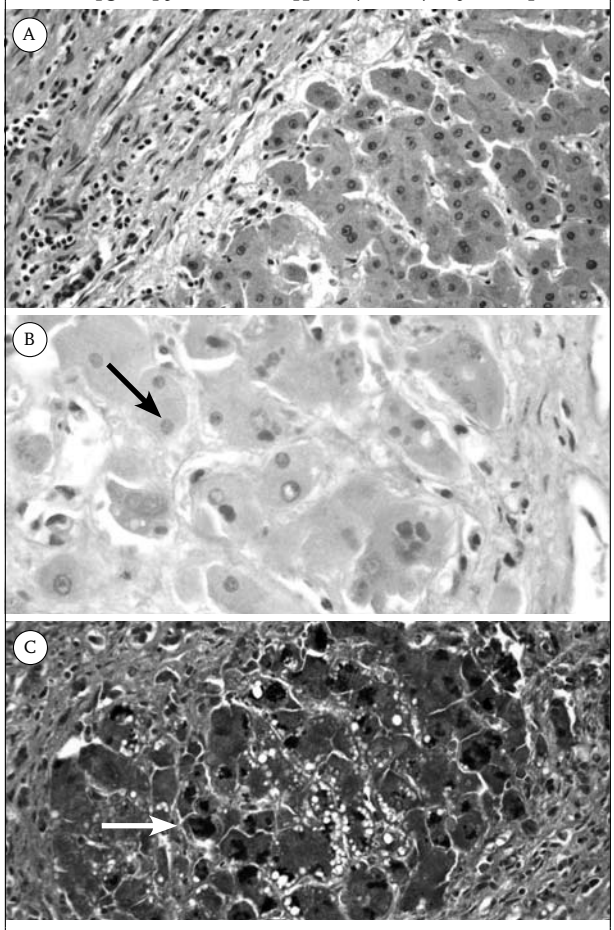
The S variant of the A1AT molecule has less effect on the loop-sheet polymerisation. Formation of S polymers is slower, resulting in less retention of protein in the hepatocytes compared with the Z variant. There is a mild reduction in serum A1AT levels. When an S and a Z variant are coinherited, the two interact with the formation of polymers within the hepatocytes; this can lead to reduction in the serum A1AT level, inclusion of the polymers, accumulation and subsequently development of cirrhosis.

Less frequently found variants are null alleles resulting in undetectable A1AT levels due to intracellular degradation or intracellular accumulation of the protein; this is usually associated with severe pulmonary disease, but not with liver disease (*table 1*).[2-7]

A1AT deficiency is characterised by an imbalance between the protease neutrophil elastase and the protease inhibitor A1AT. It has been suggested that neutrophil elastase might promote the development of cancer.[8] The exact carcinogenic mechanism or sequence is not known.

In a recent paper, the hypothesis was given that in A1AT deficiency, the hepatocytes in which A1AT is accumulated are inhibited in their growth, but they do express regenerative signals. Relatively normal cells, without A1AT deposits, are thereby stimulated and this chronic stimulation of regeneration may lead to the formation of neoplasmata.[9]

Figure 1. *Liver biopsy: cirrhosis due to alcohol abuse and heterozygosity for α1 antitrypsin (A1AT) deficiency*[33]



A. HE staining, 20x: micro nodular liver cirrhosis.
B. D-PAS staining, 40x: diastase resistant, Periodic-Schiff-Acid positive globuli, matching with A1AT accumulation.
C. A1AT antibodies, 40x: confirmation of A1AT accumulation.

DIAGNOSTIC ASPECTS

To establish the diagnosis, various methods are available. The A1AT serum level can be determined by clinical chemistry. In homozygous A1AT deficiency the level is very low. However, in the heterozygous variant the A1AT level can be within the normal range, especially during an acute-phase reaction. Therefore, electrophoresis should be performed in any case of suspected A1AT deficiency in order to determine the phenotype. Liver biopsy is the

Table 1. *Characteristics of the different A1AT alleles*

Allele	Mutation	Cellular defect	Enzymatic activity
M	-	-	Normal
S	Glu264Val	Intracellular degradation	Intermediate
Z	Glu342Lys	Intracellular accumulation	Low
Null	Different mutations	Most mutations no mRNA	Null

gold standard for establishing A1AT accumulation and PAS-positive, diastase-resistant inclusions can be found. A specific immunohistochemical staining can confirm the diagnosis. It is also possible to determine the phenotype on paraffin-embedded liver slides.

EPIDEMIOLOGY

Despite the fact that A1AT deficiency is a common disorder, it is poorly recognised in clinical practice. There are probably two main reasons for this; first in patients with liver disease, the diagnosis is not always considered and second not all subjects with a deficient phenotype develop liver disease, i.e. the penetrance is low.[10]

Given this well-known underdiagnosis, the real prevalence of A1AT deficiency has mainly been determined by epidemiological methods, either using a control cohort from an epidemiological study, or through neonatal screening. The Z allele is especially prevalent in Northern Europe, while the S allele is prevalent in Southern Europe (*table 2*).[11-15]

CLINICAL ASPECTS

Pulmonary disease

A1AT deficiency is associated with less inhibition of elastase resulting in pulmonary disease. A1AT homozygosity (Pi ZZ) results in a pulmonary phenotype with early onset of emphysema, asthma and bronchiectasia. A1AT deficiency results in panacinar pathology and disproportionate emphysematous involvement of the lung bases. Tobacco smoking is the most important additional risk factor for the development of pulmonary disease. Also subjects with the Pi MZ phenotype have an increased risk of developing pulmonary disease.[7]

Neonatal/paediatric liver disease

A1AT deficiency is the most common genetic cause of liver disease in early childhood. The most common presentation is by prolonged jaundice. The stools generally contain no yellow or green pigment, indicating cholestasis and mimicking biliary atresia. All patients have hepatomegaly and about 50% also have splenomegaly. Approximately 5% of the patients present with an increased bleeding tendency. This is due to vitamin K deficiency caused by the cholestasis-induced malabsorption. Less commonly children present later in childhood with hepatosplenomegaly or with cirrhosis.[16-19]

In Sweden, between 1972 and 1974, 200,000 neonates were screened for A1AT deficiency: 120 Pi ZZ (0.06%), 2 Pi Z-, 54 Pi SZ and 1 Pi S- children were found. Only 14 of the Pi ZZ children had prolonged jaundice, nine of those had severe liver disease. All infants appeared healthy at six months of age. Infants with a Pi SZ phenotype had no signs of liver disease.

At the age of 16 years, elevated liver enzymes were found in 17% of Pi ZZ adolescents and in 8% of Pi SZ adolescents. The adults with liver disease in infancy were clinically healthy. At the age of 26 years, the Pi ZZ subjects were compared with Pi MM individuals. The Pi ZZ subjects had normal lung function; 4 to 9% of them had mild liver test abnormalities.[11,20,21] In the Province of Bozen in Northern Italy, Pi phenotyping in umbilical cord blood was performed as a routine neonatal screening. About 5% of Pi SZ children were affected by liver involvement with elevated liver enzymes and 7% of 833 Pi MZ heterozygotes had elevated liver enzymes in early childhood. At the age of 5 and 10 years, none had liver disease. The serum levels of A1AT were similar in the groups with and without liver test abnormalities; however these values had a wide range.[22,23]

Although these studies suggest a good prognosis for neonatal cholestasis due to A1AT deficiency, other studies have described children who developed severe liver disease.[16,19]

Table 2. *Epidemiology*[10-15]

Country	Frequency			Method	Year
	Pi ZZ	Pi MZ	Pi SZ		
Sweden	0.06%	-	0.03%	Neonates, phenotyping when serum A1AT <40%	1976
The Netherlands	Z allele 0.03%	-	S allele 0.04%	Neonates, phenotyping when A1AT/transferrine <1,2	1980
France	0.01%	2%	0.15%	Control cohort epidemiological study	2003
Spain	0.01%	-	0.2%	Control cohort epidemiological study	2003
Italy	0.02%	2.4%	0.06%	Control cohort epidemiological study	2003
Portugal	0.02%	2.3%	0.3%	Control cohort epidemiological study	2003
Australia	0.02%	2.5%	0.12%	Control cohort epidemiological study	2003
USA	0.02%	2.7%	0.09%	Control cohort epidemiological study	2003
New Zealand	0.05%	4.3%	0.17%	Control cohort epidemiological study	2003
Canada	0.02%	2.7%	0.11%	Control cohort epidemiological study	2003

Liver disease in homozygous A1AT-deficient adults

Liver disease due to A1AT deficiency generally presents at adult age. One study reviewed adult patients with liver disease and A1AT deficiency; the mean age of the patients when liver disease became symptomatic was 58 years for the ZZ phenotype, 66 years for the SZ phenotype and 73 years for the MZ phenotype. At the time of diagnosis the liver disease was advanced, 42% of these patients died within two years.[24]

A review of autopsy data on 94 Pi ZZ homozygous A1AT deficient patients showed that cirrhotic patients survived longer compared with noncirrhotic patients. The noncirrhotic patients had more severe lung disease and died earlier.[25]

A cohort of patients who are registered in the Alpha-1 Foundation Registry (a USA foundation providing increased research and improved health for A1AT deficiency), and who had reported liver disease or jaundice (165 of the 2175 participants in the registry) completed a questionnaire. Of these patients 71% were Pi ZZ and 18% were Pi MZ, the remainder did not know what their phenotype was. Mean age at diagnosis of liver disease was 31 years (range 0 to 68 years), 30% had undergone liver transplant or were on the waiting list. Male gender and obesity were risk factors for advanced liver disease, while white race, Pi phenotype, infant jaundice, diabetes or hypercholesterolaemia were not.[26] Although this survey is the largest cohort of A1AT deficiency and liver disease in the literature, the self-selected cohort runs a risk of inclusion bias.

The natural history of the disease is not completely known. The risk of cirrhosis in adults is difficult to estimate because most available data are retrospective and derived from patients known to have A1AT-deficient lung disease or cirrhosis.[27,28]

Heterozygous A1AT deficiency and liver disease

Although the role of homozygous A1AT in liver disease is established, the association between heterozygous A1AT deficiency and chronic liver disease is still subject to ongoing investigation. Several studies, however, have shown an association between heterozygous A1AT deficiency and chronic liver disease.

In 1981 a study showed the association between Pi MZ and liver disease. About 1055 liver biopsies were screened for A1AT depositions in hepatocytes. A total of 34 patients with these inclusions were phenotyped; the prevalence of phenotype Pi MZ in the whole biopsy group was 2.4%. In liver cirrhosis, 9% had a Pi MZ phenotype. A percentage of 21% Pi MZ was found in cryptogenic cirrhosis and in chronic active hepatitis, this was significantly increased compared with other causes of cirrhosis. The prognosis of the Pi MZ cirrhotic patients was poor, most patients died within one year.[29]

More recently patients with end-stage liver disease, in work-up for liver transplantation, were investigated. Pi MZ was found in 7.3 to 8.2%, compared with 2.8% in the control population. A heterozygous phenotype was more prevalent in patients with hepatitis C, alcoholic liver disease, cryptogenic cirrhosis and hepatocellular carcinoma.[30,31]

In one study consecutive liver biopsies and autopsies were screened for Pi Z deposits. In the biopsy group 3.4% of cases were Pi MZ phenotyped, whereas in the autopsy group this was 1.8%. In biopsies from older people heterozygous for A1AT, more fibrosis and more Pi Z deposits were found; the liver involvement seems to be age-dependent. When there was another liver disease as well, the patients presented with more inflammation, more fibrosis and more Pi Z deposits than the biopsies without concomitant liver disease.[32]

We described three patients with alcoholic liver disease and a rapidly deteriorating clinical course, resulting in the patients' death. All three patients were found to be heterozygous for A1AT.[33]

To summarise, these studies showed that various liver diseases influence the A1AT accumulation and that the A1AT accumulation influences the course of the liver disease. The risk of developing liver cirrhosis is increased in patients with heterozygous A1AT deficiency, also without coexisting liver disease. The exact impact and involvement of liver disease by heterozygous A1AT deficiency are unknown. Further research is needed to give these data.

Heterozygous A1AT deficiency and coexisting hepatitis C virus infection

The role of A1AT deficiency in the severity and the course of liver disease in chronic hepatitis C virus (HCV) infection is not clear, despite the fact that several studies have analysed the association of HCV-induced liver disease and A1AT deficiency.

In Austria, 1865 patients referred for the evaluation of chronic liver disease were analysed, 9% had a deficient phenotype. From these patients with cirrhosis, 62% were HCV positive, 33% had evidence of HBV infection, 41% abuse of alcohol and 12% had features of autoimmune liver disease. Out of 53 cirrhotic A1AT-deficient patients, only five had no coexisting liver disease. These authors concluded that the risk for chronic liver disease is increased in patients with the Pi Z gene, because they may have increased susceptibility to viral infection or additional factors, necessary to induce chronic liver disease.[34]

The same authors investigated the prognosis of patients with A1AT deficiency. Some 54 patients with A1AT deficiency had evidence of chronic liver disease, 78% showed positive viral markers (hepatitis B or hepatitis C); this was compared with 106 patients with A1AT deficiency without chronic liver disease, without signs of additional viral infection. Life expectancy in A1AT-deficient patients was significantly lower in patients with chronic liver disease in comparison with patients without chronic liver disease.[35]

Patients with end-stage liver disease, in work-up for liver transplantation, were also investigated. In the HCV patients Pi MZ was found in 10 to 13%, compared with 2.8% in the control population. This suggests that an abnormal heterozygous phenotype is a co-factor in the development of chronic liver disease in HCV.[30,31]

In contrast, other studies showed no association between hepatitis C infection and A1AT deficiency.[36-38]
To conclude, the results of these studies are controversial. Some studies show a higher incidence of A1AT deficiency in HCV infection and an increased susceptibility to viral infections in A1AT deficiency and other studies do not. Different methods to determine the A1AT state were used. Further research on the influence of A1AT deficiency in the course of HCV infection and vice versa is necessary.

Heterozygous A1AT deficiency and hepatocellular carcinoma

Established risk factors for hepatocellular carcinoma include chronic hepatitis B, HCV infection and alcoholic liver cirrhosis. Several studies have investigated the correlation between A1AT deficiency and hepatocellular carcinoma.[39,40]
In 1986 it was suggested for the first time that men with A1AT deficiency may be at risk for cirrhosis and hepatocellular carcinoma (HCC). Autopsy was performed in 16 adult patients with A1AT deficiency. In five out of these 16 patients, an HCC was found.[41,42]
In 317 HCC patients, Pi Z deposits were found in 6% compared with 1.8% in the control group. In heterozygous A1AT deficiency, HCC had also developed in noncirrhotic livers and was frequently characterised by cholangiocellular differentiation. In patients with A1AT deficiency bile duct lesions were frequently found. This might reflect a predisposition for the liver tissue for developing tumours with cholangiolar differentiation in A1AT deficiency.[43,44]
In contrast to these studies, others did not show an association between A1AT deficiency and hepatocellular carcinoma, although carcinomas in noncirrhotic livers were Pi MZ associated.[45-48]
To summarise, several studies have been performed to investigate the relation between A1AT deficiency and hepatocellular carcinoma. The outcomes are not uniform. In our opinion studies with large cohorts of patients with hepatocellular carcinoma are the most reliable; these studies did find an association.

A1AT deficiency and associations with other diseases

A1AT deficiency is not only associated with liver and lung disease. Associations with panniculitis, nephrotic syndrome, intracranial aneurysm, hereditary haemochromatosis and celiac disease have been described.[49-62]

THERAPY

Most therapeutic strategies in the treatment of A1AT deficiency are directed towards the pulmonary disease. Infusion of purified pooled human plasma A1AT is known as augmentation therapy. The goal of this treatment is to raise and maintain serum A1AT concentrations above the protective threshold. Data from different studies suggest that intravenous augmentation therapy has a positive biochemical and clinical effect. The therapy is expensive (US $ 28,075 to 65,973 per year).[7] Different concepts have been studied to prevent the polymerisation and accumulation of the A1AT protein. New peptides that block the polymerisation of the Z protein have been developed.[63,64] Gene therapy by injecting adeno-associated virus carrying the human A1AT gene is another promising concept.[65] Liver transplantation is used in end-stage liver disease and results in acquisition of the donor phenotype, a rise in serum levels of A1AT and prevention of associated diseases.[66]

CONCLUSION

Alpha-1 antitrypsin deficiency is an autosomal recessive disorder that can lead to chronic pulmonary disease and liver disease. The liver disease is caused by accumulation of an abnormal, polymerised protein. Deficient phenotypes are present worldwide.
Homozygous A1AT deficiency in children can cause neonatal hepatitis. In adults homozygous patients are at risk for developing end-stage liver disease, cirrhosis and hepatocellular carcinoma. Heterozygous A1AT deficiency is probably an important co-factor in the aetiology of chronic liver disease, as several studies have shown associations with HCV, end-stage liver disease, cirrhosis and HCC.
Low-threshold screening for A1AT deficiency should therefore be carried out. A1AT serum levels may be used, but phenotyping is crucial, as serum levels may not reflect true deficiencies (as inflammation serum levels can be falsely normal). Especially in cryptogenic chronic liver disease and liver disease that deteriorates faster than may be expected, A1AT deficiency may be of clinical significance as a (co)-factor. Clinical research is needed in A1AT-related liver disease to investigate the association between heterozygous A1AT deficiency and the presentation and course of liver diseases.[67]
We believe that the current data are insufficient to decide on the pros and cons of screening on hepatocellular carcinoma in A1AT deficiency. Therapeutic options in A1AT deficiency include augmentation therapy in pulmonary disease; in end-stage liver disease liver transplantation is an option. For the future, gene therapy or strategies to inhibit polymerisation are promising.

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ORIGINAL ARTICLE

Non-evidence-based variables affecting physicians' test-ordering tendencies: a systematic review

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ABSTRACT

Background: The concept of evidence-based medicine (EBM) was introduced in 1992. Incorporation of EBM into physicians' practices, however, has been slow. Test-ordering tendencies are still based on variables that are not necessarily evidence-based.

Methods: The literature was reviewed to identify the non-EBM variables that affect physicians' practices of test ordering. Studies of interest were limited to original research on the determinants of physicians' test-ordering tendencies. The search strategy included queries in MEDLINE (1992-2006), Web of Science (1993-2006), EMBASE (1992-2006), and PsycINFO (1992-2006); checking of reference lists; hand searching relevant journals; and personal communication with experts. Two independent reviewers abstracted information on the design, quality, and limitations of the study. Review articles, letters, and editorials were excluded from analysis.

Results: 104 original studies reporting on the variables affecting test ordering were identified. Of these, 53 studies assessing physician variables affecting test ordering were identified. Some of the recognisable physician factors included age, sex, degree of specialisation, geographic location and practice setting, individual belief systems, experience, knowledge, fear of malpractice litigation, physician regret, financial incentives, awareness of costs of tests ordered, and provision of written feedback by peers or employers.

Conclusion: Despite considerable advances in our understanding of EBM and its application to patient care, several non-EBM physician variables influence physicians' test-ordering characteristics. Ongoing effort is needed to identify the modifiable non-EBM determinants of physicians' test ordering and to use appropriate tools and techniques to encourage evidence-based behaviours for test ordering.

KEYWORDS

Decision-making, diagnostic tests, evaluation studies, evidence-based medicine

INTRODUCTION

With technological advances creating newer diagnostic tests, along with easy accessibility of medical information on the World Wide Web, physicians and patients now have access to a larger amount of information. A critical understanding of newer medical information and incorporation of the data into everyday medical practice gradually evolved into the concept of evidence-based medicine (EBM), a term that was formally introduced in 1992.[1]

EBM includes an evidence-based approach toward therapeutic interventions and diagnostic processes. Diagnostic tests are an integral part of health care and contribute to a large percentage of health care costs. Ordering relevant laboratory and imaging tests is an essential component in the process of medical decision-making.

The process of medical decision-making usually starts with collection of relevant information, which then leads to the generation of a hypothesis. This hypothesis is then refined and its probability is increased or reduced based on the results of the diagnostic tests. Tests may be ordered in series (sequence of tests ordered in the future is based on the results of prior test) or in parallel (several tests ordered during one visit) depending on the urgency of making a diagnosis and the perceived risk (medical or legal) in a clinical situation. Understandably, several variables, involving the physicians, patients, and the health care environment, influence this multistep process.

Most medical schools in the United States and other countries have established curricula for teaching EBM in their undergraduate and postgraduate medical courses.[2] With increased focus on evidence-based practice, it was hoped that physicians would adopt a measured approach to test ordering and follow established algorithms, thereby reducing the variability in physician practice and subsequently the overall cost of health care. However, the health care environment is complex and rapidly changing. Thus, physicians experience changing expectations from the patients and the health care system and are unable to be algorithmic in their approach. Several determinants likely affect physicians' tendencies for test ordering.

In this study, we reviewed the literature on non-EBM physician determinants of test-ordering practices. Our goal was to delineate the factors that sway physicians away from evidence-based test ordering and identify possible targets of intervention for changing practice patterns.

METHODS

Data sources

The search was focused on studies performed since 1992. Data were abstracted from the following databases: MEDLINE (1992-2006) (National Library of Medicine, Bethesda, Maryland), Web of Science (1993-2006) (Thomson Scientific, Philadelphia, Pennsylvania), EMBASE (1992-2006) (Elsevier, Amsterdam), and PsycINFO (1992-2006) (American Psychological Association, Washington, DC). The searches were performed with the OVID search engine (Wolters Kluwer, New York).

Search strategy

A comprehensive retrieval of relevant articles was obtained by using different search strategies in different electronic databases. Searches were limited to human studies. In MEDLINE, EMBASE, and PsycINFO, the search terms used were laboratory techniques and procedures/utilisation or diagnostic tests, routine/ (also used laboratories, hospital/ utilisation) AND physician's practice patterns (also used unnecessary procedures/ or guideline adherence/ and attitude of health personnel/). Additionally, in EMBASE, the search terms used were diagnostic test/ or laboratory test/ AND professional practice/ or primary medical care/ or medical decision making/. In Web of Science, which uses only the key words, test order$ or (diagnostic test$ or laboratory test$ AND order$ or behavior$) were used to search for relevant articles. Two reviewers abstracted information on each study's eligibility for inclusion by screening its title, abstract, or full-text bibliographic citation.

We divided the factors affecting test ordering into three broad categories: physician factors, patient factors, and environmental factors. Original studies that addressed physician factors influencing test ordering were considered for inclusion. Several articles alluded to one or more of these factors as simultaneously affecting test ordering. These were included in all the relevant categories for the purpose of this review, with the recognition that these factors invariably interact in a clinical situation and, thereby, the exact contribution of a given variable is sometimes difficult to pinpoint. However, this simple categorisation still provided a useful starting point to understand the individual variables involved in test ordering. These factors were further subcategorised into potentially modifiable factors, that is, those that can be modified by a physician's own endeavour (belief system, experience, fear of malpractice, feedback, and education) *vs* nonmodifiable factors, over which physicians have no control (age and sex of physicians, practice settings, geographic location, and specialisation).

Disagreements regarding sorting out the factors affecting test ordering and classification under a subcategory were resolved by independent review by a third reviewer. If a study was considered appropriate for inclusion in our review, one reviewer assessed its design, quality, and limitations. In addition to searching of the electronic databases, other strategies included checking reference lists and educational websites, hand searching relevant journals, and personal communication with experts.

INCLUSION AND EXCLUSION CRITERIA

Studies of interest were limited to original research on the determinants of physicians' test-ordering tendencies. All studies using prospective study design, surveys (mailed and telephone), and chart reviews involving physicians and test-ordering characteristics were identified for review. We concentrated on articles published in the English literature since 1992, when the concept of evidence-based practice was well known to the medical community. A standard format was used to review data, including analysis of study design and study characteristics. Qualitative studies, review articles, letters, and editorials were excluded from the analysis.

Statistical analysis

Because the literature on test ordering is very heterogeneous, performing a meta-analysis was not considered appropriate. A narrative review of the topic is thus presented.

RESULTS

Search results

A total of 328 articles were retrieved. Of these, 104 articles were original studies and available in full text in English. A total of 53 articles that discussed the physician variables

comprised the final sample that was reviewed for this study. Fifty-one articles were excluded from the study because they dealt with patient factors, environmental factors, and physician uncertainty or disparities of medical care affecting test-ordering tendencies. All the studies reported were found in the Ovid databases. The non-evidence-based physician factors affecting test ordering tendencies are summarised in *tables 1* and *2*.

Nonmodifiable physician factors

Several nonmodifiable physician factors affected test ordering (*table 1*). These included practice location, practice setting, age and sex, and specialisation of the physician. Six studies evaluated the effect of geographic location on physicians' practices of test ordering.[3-8] In general, US physicians were reported to order more tests than physicians from the United Kingdom or Canada.[5,6] In Europe, there was considerable variation among countries, which was partly explained by the differences in the physician:population ratio.[7] Within the United States, physicians in the Northeast were reported to order more specialised tests than physicians in other geographic areas.[3] In Canada, according to a mail survey, bone densitometry was ordered more often by urban physicians than by their rural counterparts.[4] Finally, in a survey conducted in Norway, in areas that had a high turnover of physicians, such as municipalities, more tests were ordered, partly related to lack of continuity of care.[8]

Practice setting was evaluated in six studies.[9-14] Various practice settings were studied, including solo *vs* group practice, academic *vs* nonacademic practice, primary care *vs* tertiary care setting, and emergency *vs* outpatient setting. No clear pattern emerged from these studies, partly because of different study designs and difference in response rate between the different studies. Thus, a telephone survey of patients after physician visits (97% response rate) found that solo practitioners ordered more radiographic tests for acute low back pain,[11] but a mail-out survey of solo practitioners (56% response rate) showed that they tended to order fewer preventive services.[13] Hospital-based physicians ordered more tests than other practitioners,[9] academic physicians ordered more tests and nonacademic practice physicians had a higher threshold of test ordering,[14] the number of tests ordered by emergency room physicians did not differ from that by primary care physicians,[12] and a health-maintenance organisation setting did not affect test ordering.[10]

The effect of age and sex was reported in seven studies.[4,8,12,13,15-17] In general, across different settings, countries, and patient groups, female physicians tended to order more tests,[4,8,12] give more referrals,[16] and adhere better to guidelines than their male counterparts.[17] However, no attitudinal difference could be detected in this study to account for this difference.[17] Further, the older providers were reported to order tests more often,[8,15] and the younger providers adhered better to the guidelines.[13]

The degree of specialisation had a substantial impact on test ordering.[11,14,18-25] In general, a greater degree of specialisation was associated with more test ordering. Thus, gastroenterologists,[19] cardiologists,[20] orthopaedic surgeons,[11] vascular surgeons,[24] and infectious disease specialists,[14] all ordered more diagnostic tests or ordered tests earlier in the patient's illness than internal medicine physicians. The studies involving generalists specialising in hospital care (the hospitalists) showed variable results, ranging from ordering fewer tests with more evidence-based tests[18] to ordering more tests[25] than the community physicians. However, although specialists ordered more tests, they also ordered more focused tests and tests that were more likely to have positive results than internists.[23,24] In a chart-review study of patients with undifferentiated symptoms, family practitioners generated the lowest cost of all physicians.[21]

Modifiable physician factors

The modifiable physician factors (*table 2*) are among the most important because a better understanding of these variables can have a considerable impact on test ordering and health care costs. These variables include physician experience and knowledge, belief systems, fear of malpractice lawsuit and physician regret, financial incentives, awareness of the cost of testing, and education and feedback. Physician experience or knowledge was reported to affect test ordering in several studies; however, no consistent pattern emerged. Thus, increased physician knowledge or experience was reported to increase,[14,16] decrease,[25,26] or result in no change[12] in test ordering.

Physicians' personal beliefs that were not entirely evidence-based affected the frequency of test ordering.[27-34] Thus, physicians who doubted the effectiveness of mammography as a screening tool were, as expected, less likely to order the test,[33] whereas those who believed in its usefulness ordered it more often.[34] Physicians who believed that cancer screening reduced cancer-related mortality ordered the tests more often.[32] Physicians who believed strongly in doing routine baseline tests were more likely to perform them,[30] and physicians who doubted the interpretation of clinical trial results were less likely to adhere to guidelines.[29] Further, physicians' reasons for doing tests such as radiography of the lumbar spine for chronic back pain were related not only to medical necessity but also to a perception that radiography might provide psychological reassurance to the patient.[31]

Fear of malpractice consistently increased test ordering,[16,35-37] except in one study (54% response rate) in which physicians were asked to respond to hypothetical situations.[38] This finding was true for both specialists[35] and general practitioners.[16,36]

Table 1. *Nonmodifiable physician factors affecting test ordering*

Physician factors	Reference	Year	Study design	Results
Geographic location (n=6)	Wideroff *et al.*[3]	2003	National survey of 1251 physicians by mail, fax, Internet; response rate 71%	Physicians in Northeast ordered more testing for germline mutation than those in other locations
	Ridout and Hawker[4]	2000	Canadian mail survey of 711 FPs; response rate 64%	Urban physicians used bone densitometry more often than rural physicians
	Vickrey *et al.*[5]	1998	Mail survey involving 595 US and 210 UK neurologists; response rate, 92 and 63%, respectively	More tests ordered for each scenario by US neurologists
	Katz *et al.*[6]	1996	Chart review assessment of laboratory or x-ray utilisation in 7980 US and 6491 Canadian patients discharged from the hospital	Utilisation was higher in the US; explained by use of more expensive tests and more testing on elderly
	Leurquin *et al.*[7]	1995	European survey obtaining information from physicians and patients regarding ordered tests	Marked variations in test ordering were noticed between different countries; these were partly explained by the physician:population ratio
	Kristiansen and Hjortdahl[8]	1992	Chart review study in Norway involving 6848 surgery consultations from 128 GPs	Physicians in municipalities ordered more tests (high turnover of physicians)
Practice setting (n=6)	Bushnell *et al.*[9]	2001	Chart review involving 674 patients admitted for acute ischaemic stroke to assess for use of coagulation testing	Physicians practising at tertiary-care centres were more likely to order coagulation testing
	Landon *et al.*[10]	2001	Cross-sectional survey of national sample of 7423 primary-care physicians; response rate 65%	Solo practitioners ordered more tests, referrals, and treatments than physicians in academic setting. No effect of HMO setting *vs* non-HMO setting
	Carey and Garrett[11]	1996	Telephone serial survey of 1633 patients in a community setting after index visit; at 6 months, data for analysis were available for 97% of patients; a physician survey also was incorporated	Solo practitioners ordered more radiographic tests for acute low back pain than practitioners in group practices
	Scholer *et al.*[12]	1996	Chart review involving 1140 paediatric patients evaluated for acute abdominal pain in the emergency department or as an outpatient	The setting of evaluation did not affect the number of tests ordered
	Stange *et al.*[13]	1994	Mail survey of 480 FPs nationwide regarding adherence to USPSTF guidelines; response rate 56%	Solo practitioners ordered fewer preventive services
	Winkenwerder *et al.*[14]	1993	Mail survey about case scenarios of syphilis to 126 internal medicine and 31 infectious disease experts; response rates 35 and 62%, respectively	Nonacademic practice physicians had a higher threshold of doing serological tests
Age and sex (n=7)	Stafford and Misra[15]	2001	Chart review involving 190,238 visits in internal medicine group practices; assessed for variation in performance of ECG in patients with no heart disease	Older male providers were more likely to order ECG
	Franks *et al.*[16]	2000	A survey of 275 internal medicine and FPs along with analysis of claims database; response rate 66%	Being a female physician was associated with more referral rates
	Ridout and Hawker[4]	2000	Canadian mail survey of 711 FPs; response rate 64%	Female physicians were more likely to order bone mineral density tests
	Ferrier *et al.*[17]	1996	Canadian mail questionnaire involving 564 new FPs; response rate 70%	Female physicians adhered better to guidelines
	Scholer *et al.*[12]	1996	Chart review involving 1140 paediatric patients evaluated for acute abdominal pain in the emergency department or as an outpatient	Female physicians were more likely to order tests
	Stange *et al.*[13]	1994	Mail survey of 480 FPs nationwide regarding adherence to USPSTF guidelines; response rate 56%	Younger physicians adhered better to guidelines
	Kristiansen and Hjortdahl[8]	1992	Chart review study in Norway involving 6848 surgery consultations from 128 general practitioners	Female and older physicians ordered tests more often

Table 1. *Continued*

Physician factors	Reference	Year	Study design	Results
Specialisation (n=10)	Conway *et al.*[18]	2006	National survey of 213 hospitalist and random sample of 352 community paediatricians	Hospitalists reported greater adherence to evidence-based tests and less use of tests of unproven benefit
	Hilsden *et al.*[19]	2005	Questionnaire sent to gastroenterologists, internists, and surgeons in Alberta, Canada	Internists less likely to order for screening colonoscopy *vs* surgeons and gastroenterologists
	Cohen *et al.*[20]	1999	Analysis of national ambulatory medical care surveys involving 1.12 billion patient visits with 6.2 million exercise stress tests ordered	Cardiologists were 3.7 times more likely to order stress tests than internists (after adjusting for clinical and nonclinical variables associated with the office visit)
	Lin *et al.*[21]	1999	Retrospective chart review of 254 patients	FPs generated lower costs for undifferentiated problems such as unexplained weight loss than other specialists
	Collins *et al.*[22]	1997	Mail and telephone survey of a nationwide random sample of 444 primary-care providers and 394 urologists. Response rates were 51 and 68%, respectively	Primary-care physicians ordered routine creatinine measurement more often than urologists
	Glassman *et al.*[23]	1997	A survey of 318 cardiologists and 598 internists about three hypothetical non-life-threatening clinical scenarios	Cardiologists ordered more focused cardiac tests, whereas internists ordered broader tests; the overall cost of the two was the same
	Hill *et al.*[24]	1997	Chart review of 4764 scans for indications for carotid duplex scanning	Vascular surgeons were more likely to order carotid duplex scanning than internal medicine or FP; further, vascular surgeons were more likely to order scanning that had positive results
	Carey and Garrett[11]	1996	Telephone serial survey of 1633 patients in a community setting after index visit; at 6 months, data for analysis were available for 97% of patients; a physician survey also was incorporated	Orthopaedic surgeons and chiropractors ordered more radiography for acute low back pain evaluation than internists
	McGillivray *et al.*[25]	1993	Prospective chart review of 6191 visits of febrile children	Hospital-based subspecialists ordered more diagnostic tests than community physicians
	Winkenwerder *et al.*[14]	1993	Mail survey about case scenarios of syphilis to 126 internal medicine and 31 infectious disease experts; response rates were 35 and 62%, respectively	Infectious disease specialists tended to order serological testing and lumbar puncture sooner than internal medicine physicians

ECG = electrocardiography; FP = family practitioner; GP = general practitioner; HMO = health maintenance organisation; UK = United Kingdom; US = United States; USPSTF = US Preventive Services Task Force.

Table 2. *Modifiable physician factors affecting test ordering*

Physician factors	Reference	Year	Study design	Results
Experience/ knowledge (n=5)	Yuan *et al.*[26]	2005	Mail questionnaire survey of 1335 anaesthetists; response rate 46%	80% would order tests in asymptomatic low-risk individuals based on clinical indications, 15.1% to follow guidelines 44% had disagreement over need for routine preoperative ECG
	Franks *et al.*[16]	2000	A survey of 275 internists and FPs along with analysis of claims database; response rate 66%	More years in practice was associated with more referral rates
	Scholer *et al.*[12]	1996	Chart review involving 1140 paediatric patients evaluated for acute abdominal pain in the emergency department or as an outpatient	Level of training did not affect test ordering for the most part; students ordered fewer urinalyses, and paediatricians with more than 10 years of experience ordered fewer throat cultures
	McGillivray *et al.*[25]	1993	Prospective study involving 6191 visits of febrile children studied for test ordering	Physicians with more than 10 years of experience ordered fewer tests
	Winkenwerder *et al.*[14]	1993	Mail survey about case scenarios of syphilis to 126 internal medicine and 31 infectious disease experts; response rates were 35 and 62%, respectively	Infectious disease experts were more likely to obtain serological tests to diagnose syphilis and to do lumbar puncture to diagnose neurosyphilis
Belief system (n=8)	Prochazka *et al.*[27]	2005	Postal survey of attitudes and belief regarding annual physical examination of 1679 primary-care practice; response rate 47%	Despite lack of evidence, 88% of primary-care providers perform annual physical examination and order urinalysis (44%) and complete blood count (39%)
	Turner *et al.*[28]	2003	Mail survey of 413 primary-care practices affiliated with a managed care organisation; response rate 77%	Physicians with intermediate or high intentions to evaluate a positive haemoccult test were 2 times as likely to order diagnostic colon evaluation than physicians with low intention
	Rello *et al.*[29]	2002	Mail survey of 110 opinion leaders from 23 countries on reasons for nonadherence to EBM guidelines for ventilator-associated pneumonia; response rate 56%	Physicians disagreeing with interpretation of clinical trials did not adhere to guidelines
	Nakar *et al.*[30]	2002	A survey of 165 FPs in Israel; response rate 89%	Baseline screening laboratory tests were performed more often by physicians who believed that performing these tests results in more case finding
	Little *et al.*[31]	1998	A survey of 236 GPs in UK to determine the reasons for doing back radiography; response rate 70%	General practitioners ordered back radiography for both medical and psychosocial reasons, including patient satisfaction and reassurance
	Hicks *et al.*[32]	1995	Mail survey of 286 FPs in Oklahoma, asking them about reasons for ordering PSA test; response rate 53%	A belief that screening for prostate cancer reduces mortality and improves quality of life increased ordering of PSA test
	Taylor *et al.*[33]	1994	Mail survey of 129 internal medicine physicians; response rate 66%	Physicians doubting the effectiveness of mammography were less likely to order it
	Conry *et al.*[34]	1993	A study of 10 FPs involving 839 patient visits with 277 mammograms ordered	Physicians' belief in patient compliance and need for mammography was associated with increased ordering of mammography
Fear of malpractice lawsuit/physician regret (n=5)	Birbeck *et al.*[35]	2004	Survey of 595 US neurologists; response rate 92%	Higher malpractice concerns and reimbursement for testing were associated with more test ordering
	Sorum *et al.*[36]	2003	Survey of 32 US internal medicine physicians and 33 French generalists regarding cancer screening	Physicians ordered more tests because of high regret if cancer was missed
	Franks *et al.*[16]	2000	A survey of 275 internal medicine and FPs along with analysis of claims database; response rate 66%	Risk aversiveness and fear of malpractice were variables associated with higher referral rates
	Van Boven *et al.*[37]	1997	Prospective study of 16 Dutch FPs involving 31,343 patient visits and 8897 tests ordered	Of all the tests ordered, 27% were ordered as defensive testing
	Glassman *et al.*[38]	1996	Multispeciality survey of 1540 providers; response rate 54%	Malpractice experience and fear of malpractice had no substantial impact on test ordering in hypothetical clinical situations

Table 2. *Continued*

Physician factors	Reference	Year	Study design	Results
Financial incentives (n=3)	Birbeck *et al.*[35]	2004	Survey of 595 US neurologists; response rate 92%	Receiving reimbursement for testing was associated with a higher likelihood of ordering neuroimaging tests
	Stafford and Misra[15]	2001	Chart review involving 190,238 visits in internal medicine group practices; assessed for variation in performance of ECG in patients with no heart disease	Providers who billed for ECG interpretation ordered tests more often
	Carey and Garrett[11]	1996	Telephone serial survey of 1633 patients in a community setting after index visit; at 6 months, data for analysis were available for 97% of patients; a physician survey also was incorporated	More radiographic testing was done for low back pain evaluation by practitioners who owned these machines
Awareness of cost of testing (n=4)	Seguin *et al.*[39]	2002	Prospective observational and sequential study of all admitted patients over 4 months in a 21-bed ICU; 128 patients in period 1 and 159 in period 2	Almost all the tests, particularly blood gas analysis and urinalysis, were ordered less frequently when physicians were aware of the cost
	Rudy *et al.*[40]	2001	Hypothetical scenario study involving 23 internal medicine residents	Residents with charge data spent less on diagnostic tests
	Hampers *et al.*[41]	1999	A prospective study involving 5395 patients (90% of eligible patients) in a paediatric emergency department	Knowledge of the costs decreased test ordering by 27% in patients with acute illness not requiring admission
	Bates *et al.*[42]	1997	Two prospective randomised controlled trials involving 7090 (clinical laboratory tests) and 17,381 (radiological tests) in patients in which physicians were or were not shown charge of the test being ordered	Computerised display of charges had no effect on test ordering in hospitalised patients
Feedback/ education (n=13)	Bunting and Van Walraven[43]	2004	In a Canadian study involving 200 physicians who ordered the largest number of common laboratory tests, physicians were randomised to receive feedback or no intervention. Follow-up was up to 2 years after completion of the intervention that itself was carried out over 2 years	Utilisation decreased by 7.9% in the intervention group *vs* the control group, a difference that persisted until the end of study observation
	Baker *et al.*[44]	2003	Randomised controlled trial involving 46 general practitioners in UK. Physicians received guidelines and then feedback about ordering of specific tests	The intervention had no impact on test ordering
	Stafford[45]	2003	Nonrandomised design involving 117 primary care physicians. Study tested the effect of feedback on ordering screening ECG	A considerable decrease in ordering ECG was shown during the interventions and up to 9 months after the intervention (duration of the study)
	Verstappen *et al.*[46]	2003	In a randomised controlled trial in the Netherlands, 26 primary care physician groups received education in specific medical conditions. These physicians were divided into two arms that acted as a control for the other	Test ordering was modestly reduced as a result of these interventions
	Barazzoni *et al.*[47]	2002	Health professions from six practices in Switzerland were educated about appropriate preoperative testing. This was followed by observation of using preoperative testing in 17,978 patients admitted for elective surgery	Adoption of recommendations was associated with substantial reductions in utilisation of coagulation, glucose, and renal function tests, chest radiography, and ECG
	Beaulieu *et al.*[48]	2002	87 FPs in Canada randomised to receive a 90-minute workshop or no training in the Canadian Task Force Preventive service recommendations	At 6 months, physicians randomised to workshop group showed a substantial decrease in ordering of unnecessary screening tests
	Eccles *et al.*[49]	2001	Pragmatic cluster randomised trial with a factorial design in UK involving 6 radiology departments and 244 general practices served by them	Educational reminder messages substantially reduced number of radiography requests per 1000 patients per year, whereas 6-monthly feedback of audit data was ineffective
	Goodwin *et al.*[50]	2001	A group randomised trial involving 77 practices in Ohio. Physicians were given individualised tools and services to increase preventive services	Intervention group showed a considerable increase in use of preventive services recommended by USPSTF *vs* the control group at 1-year follow-up

Table 2. *Continued*

Physician factors	Reference	Year	Study design	Results
	Plapp *et al.*[51]	2000	Administrative changes and physician education initiatives were introduced in a hospital to reduce utilisation of tests that were of high volume, difficult to perform, or expensive or had questionable medical benefit	After 5 years of intervention, average number of tests per patient dismissed decreased from 44 at baseline to 29
	Sucov *et al.*[52]	1999	Standards for diagnostic tests were developed for all the staff members at an emergency room. Frequency of test ordering was compared before and after the education programme was introduced	The number of tests ordered per 100 patients substantially decreased after introducing the intervention
	Ramoska[53]	1998	Interventional study involving emergency room physicians; physicians' use of laboratory tests was presented at monthly meetings, and the effect of this intervention was observed on testing tendencies	Test ordering as a result of the intervention decreased by 17.8% with no adverse changes in quality of care
	Winkens *et al.*[54]	1996	The effect of 9 years of twice-a-year feedback was studied on test ordering by general practitioners in the UK *vs* a control region (Netherlands). The trends in use of tests were compared	Compared with the control region, the intervention group showed a considerable reduction in the number of tests ordered during the period studied. Repeated feedback had the greatest impact
	Winkens, *et al.*[55]	1995	A randomised controlled trial involving 79 physicians in the UK. Physicians were divided into 2 groups and received feedback on different tests ordered, thus acting as their own controls	Volume of tests ordered substantially decreased in the intervention group. Further, a greater decrease was found in the number of non-rational tests that were ordered in the intervention group

EBM = evidence-based medicine; ECG = electrocardiography; FP = family practitioner; GP = general practitioner; ICU = intensive care unit; PSA = prostate-specific antigen; UK = United Kingdom; US = United States; USPSTF = US Preventive Services Task Force.

Financial incentives, as expected, increased test ordering, as found in three different studies designed as patient survey,[11] chart review,[15] and physician survey.[35] An awareness of the cost of testing, in general, decreased test ordering.[39-41] However, in the largest and most rigorously designed study to test this variable, physicians in two prospective randomised controlled trials were either shown the cost of the test or were not. The intervention had no substantial impact on test ordering.[42]

The best-studied modifiable variable is the impact of feedback on test ordering. A total of 13 interventional studies have been reported,[43-55] seven of them randomised controlled trials.[43,44,46,48-50,55] In all but one of these studies,[44] provision of education or feedback or both considerably reduced the number of tests ordered.

Other physician variables affecting test ordering included individual risk-taking attitudes of the physicians,[56] endorsement of a professional organisation,[33] influence of peer practices,[57] and source of payment by private insurance compared with Medicare.[20]

DISCUSSION

The study shows that several physician variables that are not evidence-based affect test ordering. This issue is important because appropriate test ordering is central to cost-effective and quality patient care. Recognition of the modifiable physician variables is particularly important because a system-wide multicomponent intervention that addresses these variables might successfully optimise test ordering. As an example, a randomised trial from the Netherlands compared the effect of a multi-intervention strategy in one group compared with feedback only in the other group.[58] The intervention group received a multi-intervention strategy involving evaluation of personal test-ordering data compared with that of other colleagues, group education on national and evidence-based guidelines, and attendance at quality improvement meetings. Although the initial cost of development and running the intervention arm was expensive, the mean cost reduction per physician due to avoidance of unnecessary tests was larger in the intervention group (€ 144 per physician per six months). Admittedly, the long-term effects of implementing this strategy remain unclear.

Our study has several limitations. First, articles published before 1992 were not included. Thus, we are not able to determine time trends or any differences in physicians' tendencies to order tests before and after introduction of the concept of EBM. Second, the approach in this survey was inclusive; thus, studies included are very heterogeneous in their structure and quality. This feature may explain different conclusions from some of the studies. The heterogeneity of the studies precludes a quantitative pooling of the results to produce any statistical inference, our study is thus essentially descriptive. Third, most of the studies included used questionnaires that were not well validated. Finally, the review does not include description of designs and biases of the individual studies that were included.

Our study also has several strengths. Our literature search is exhaustive and gives a very good overview of the subject matter. The studies included are from multiple practice situations and geographic locations; thereby, the inferences of the review are generalisable to a large population.

Non-EBM test ordering does not always mean inappropriate test ordering. An exploration of the reasons why physicians deviate from EBM test ordering might be instructive. For example, family practitioners ordered fewer tests in routine practice and in situations of uncertainty. Several reasons may include a different training background, community-based practice that allows long-term relationships with families, a greater use of support and reassurance compared with specialists, less aversion to risk, and possibly less anxiety in the midst of uncertainty.[59] Similarly, Northeast US physicians ordered more germline mutation testing than physicians in other geographic locations, likely because of the geographic concentration of population at higher risk and also because of physicians' knowledge of and attitude toward the disease.[3] Rural family practitioners in Canada ordered bone densitometry less often because of nonavailability of this test locally or within reasonable distance.[4] Solo practitioners order more testing, at least partly related to the relative nonavailability of peers for informal consultation.[60] Primary-care physicians in health-maintenance-organisation settings ordered more tests for social and symbolic reasons and to resolve tensions and conflicts related to time constraints and access problems.[61]

Recent studies including interventions such as telephonic peer coaching sessions integrated with education resources for general practitioners,[62] use of preventive care checklist forms,[63] and hands-on supervision of resident test ordering behaviour by senior physicians[64] have all found a decrease in unnecessary test-ordering tendencies. However, despite the benefits of these interventions, it is unclear from these studies whether the beneficial effects could be sustained in the long term.

In general, test ordering is a skill that changes with time and is related to several complex interacting variables. Nevertheless, most clinical trials showed a sustained effect of education and feedback for improving test-ordering tendencies. Further, an optimised test ordering, although cost-effective, does not increase the risk of adverse events, including hospitalisation.[65]

In summary, the study found that several modifiable and nonmodifiable physician variables affect test ordering. Ongoing effort is needed to identify the modifiable

non-EBM determinants of physicians' test ordering and to use appropriate tools and techniques to encourage evidence-based behaviours for test ordering. Further studies are indicated to identify whether system-wide multicomponent strategies would be consistently useful for reducing physician variability in ordering tests.

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ORIGINAL ARTICLE

Single-centre experience with nonmyeloablative allogeneic stem cell transplantation in patients with multiple myeloma: prolonged remissions induced

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ABSTRACT

Background: The role of allogeneic stem cell transplantation in multiple myeloma is not yet established.

Methods: We retrospectively evaluated the outcome of nonmyeloablative allogeneic stem cell transplantation (NMA) in patients with multiple myeloma treated at the Department of Haematology of the University Medical Centre Utrecht. Thirty-six patients received NMA as part of the first-line treatment; 23 patients as part of salvage therapy. Conditioning regimen was low-dose total body irradiation (TBI, 2 Grays) only; fludarabine was added in patients without previous autologous stem cell transplantation and patients with matched unrelated donors received antithymocyte globulin in addition to fludarabine and TBI.

Results: Following NMA overall response increased from 84 to 90%, complete remission rate from 15 to 32%. As part of first-line treatment NMA induced complete remission in 50% of patients *vs* one patient (4%) treated for relapsed multiple myeloma. Median progression-free survival was 26 months (13 months for the salvage group, 38 months for the 'upfront' patients). Median overall survival has not been reached yet. The achievement of complete remission following NMA as part of first-line treatment was associated with prolonged progression-free and overall survival. Major toxicities were acute and chronic graft-*vs*-host disease occurring in 64% (23% grade 3-4) and in 54% (49% extensive) patients, respectively. Seven patients (12%) died from nonrelapse mortality, five patients (9%) directly related to toxicity of NMA.

Conclusion: NMA in multiple myeloma is feasible, is associated with acceptable nonrelapse mortality and may induce prolonged complete remission. In pretreated patients the result of NMA is disappointing which urges new strategies.

KEYWORDS

Myeloma, nonmyeloablative allogeneic stem cell transplantation

INTRODUCTION

Allogeneic stem cell transplantation (ASCT) is probably the only treatment with a curative potential for multiple myeloma. This is due to the graft-*vs*-myeloma effect, mediated by immune competent donor lymphocytes, best illustrated by the induction of sustained remissions following donor lymphocyte infusions after ASCT.[1-3] However, the necessity of performing ASCT in multiple myeloma is disputed as no survival advantage has been obtained compared with autologous SCT, in particular when myeloablative conditioning for the ASCT is applied.[4] An important factor for this is the high nonrelapse mortality associated with myeloablative conditioning.[4,5]

In an attempt to lower nonrelapse mortality and make ASCT available to more patients, nonmyeloablative conditioning was introduced. Nonmyeloablative ASCT (NMA) is associated with reduced acute toxicity, while antitumour activity is probably maintained.[6-9] In this

retrospective single centre study we show that NMA is feasible in multiple myeloma, with acceptable nonrelapse mortality and that prolonged remissions may be induced in patients who received NMA as part of first-line treatment and achieved a complete remission following SCT.

PATIENTS AND METHODS

Selection of patients

Patients with multiple myeloma who received an NMA at the University Medical Centre Utrecht, the Netherlands, between September 2001 and September 2005 were included in this retrospective study. During this period, the human leucocyte antigens (HLA) class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DP, HLA-DQ) were typed in the first three months after diagnosis in all newly diagnosed patients younger than 66 years and their siblings. If an HLA-matched sibling donor was available (1 factor class I or class II mismatch was allowed), patients could proceed to NMA between two and six months after high-dose melphalan (HDM) 200 mg/m^2 and autologous stem cell rescue, which followed three courses of induction therapy with vincristine, adriamycin, dexamethasone (VAD) or thalidomide, adriamycin, dexamethasone (TAD).[10] Also patients with a relapse after the preceding treatment but responsive to salvage therapy and with an HLA-matched related or unrelated donor were eligible for subsequent NMA.

Conditioning

The conditioning regimen before allogeneic stem infusion for the patients with completely matched HLA-identical sibling donors consisted of one course of low-dose total body irradiation (TBI) (2 Grays) only, if they had received HDM 200 mg/m^2 within the preceding two and six months (tandem auto-NMA). Fludarabine 30 mg/m^2 intravenously for three days was added if no preceding autologous SCT had been performed. The conditioning regimen before allogeneic stem infusion for the patients with an HLA-mismatched or unrelated donor consisted of antithymocyte globulin (ATG; 2 mg/kg/day for 4 days) followed by fludarabine 30 mg/m^2 intravenously for three days and one course of low-dose TBI (2 Grays).

Immunosuppression

In the post-transplantation period all patients were treated with the immunosuppressive drugs cyclosporine A (CSP) and mycophenolate mofetil (MMF). Patients received 30 mg/kg/day MMF for 60 to 90 days and 2 x 4.5 mg/kg/day CSP for three to six months according to the Seattle regimen.[8]

GVHD grading and treatment

For diagnosing and grading acute graft-*vs*-host disease (GvHD) the Gluckberg criteria[10] were used. Chronic GvHD was graded according to the Seattle classification.[11] Time of onset of acute and chronic GvHD and grade of GvHD were monitored. Acute GvHD > grade I was treated with prednisone 1-2 mg/kg/day and when necessary topical prednisone treatment was applied. In these cases the doses of CSP and/or MMF were increased or continued. In case of steroid-refractory acute GvHD other drugs were used, such as sirolimus, tacrolimus, rituximab or more experimental drugs, such as alemtuzumab and dacluzimab.

Chronic GvHD of the skin was treated with topical prednisone. In severe cases of extensive chronic GvHD prednisone 1 mg/kg/day was given.

Definitions

Response and progression were determined according to the European Group for Blood and Marrow Transplantation (EBMT) criteria.[12] In short, a partial response was defined as ≥50% reduction of serum M-protein or ≥90% reduction in 24-hour excretion of Bence Jones proteinuria in case of light chain disease (LCD). A complete response was defined as complete disappearance of serum and urine M-protein as determined by immune fixation of serum and tenfold concentrated urine. In addition monoclonal myeloma cells as determined by immune phenotyping had to be absent in a representative bone marrow aspirate or biopsy. Nonrelapse mortality was defined as any death not related to progressive or relapsed myeloma.

Statistical analysis

For the statistical analysis SPSS 12.0.1 for Windows (SPSS Inc., IL, and USA) was used. Overall survival was measured in months and defined as the time from the date of transplantation until the date of death or last follow-up. Progression-free survival was measured in months and defined as the time from the date of transplantation until the date of progression or death from any cause or last follow-up. Time to acute or chronic GvHD was calculated from the date of transplantation until occurrence of acute or chronic GvHD.

Probabilities of overall survival, progression-free survival, and nonrelapse mortality were calculated using the Kaplan-Meier method. Kaplan-Meier curves were generated to illustrate survival and the log-rank test was used to compare survival curves between subgroups.

Univariate Cox regression analysis was used to determine the prognostic value of various variables for overall survival and progression-free survival. The predictive value of acute and chronic GvHD for overall and progression-free survival was calculated using a time-dependent univariate Cox regression analysis.

RESULTS

Patient characteristics

Fifty-nine patients were included in this study. The median age was 55 (range 35 to 67). There were 42 males (71%) and 17 females (28%). The median follow-up duration of survivors was 25.2 months (range 6.8 to 54.6) (*table 1*). In 36 patients (61%), NMA was part of first-line treatment and in 23 patients (39%) it was part of salvage treatment. At the time of transplant, nine patients (15%) were in complete remission and 40 patients (68%) were in partial remission.

Forty-four patients (74%) had a matched related donor, four patients (7%) had a partially matched related donor and six patients (10%) had a matched unrelated donor, and five patients (9%) had a partially matched unrelated donor. In 16 cases (27%) there was a female donor and a male recipient. Thirty-five patients (59%) were conditioned with TBI only (2 Gy) and 24 (41%) with TBI and fludarabine (30 mg/m^2/day for 3 days).[7] Fifteen patients (25%) received ATG as *in vivo* T-cell depletion. At the time of diagnosis 21 out of 50 patients (42%) had chromosome 13 abnormalities in FISH analysis and 20 out of 44 patients (46%) had an elevated β_2-microglobulin (≥3.0 mg/l).

Table 1. *Patient characteristics (n=59)*

	No. of patients (%)
Sex	
Male	42 (71.2)
Female	17 (28.8)
Age (years)	
Median	55
Range	35-67
Median follow-up[1] (months)	
Median	25.2
Range	6.8-54.6
Extent of prior therapy	
First-line treatment	36 (61.0)
Relapse treatment	23 (39.0)
Donor	
MRD	44 (74.6)
PMRD	4 (6.8)
MUD	6 (10.2)
PMUD	5 (8.5)
Conditioning regimen	
TBI	35 (59.3)
TBI and fludarabine	24 (40.7)
Donor sex match	
Female to male	16 (27.1)
Other	43 (72.9)
Deletion of chromosome 13[2]	
Presence of deletion of chromosome 13	21 (42.0)
Absence of deletion of chromosome 13	29 (58.0)
β2-microglobulin[3]	
<3 mg/l	24 (54.5)
>3 mg/l	20 (45.5)
Status at the time of ASCT	
CR	9 (15.3)
No CR	50 (84.7)

ASCT = allogeneic stem cell transplantation; CR = complete response; MRD = matched related donor; MUD = matched unrelated donor; PMRD = partially matched related donor; PMUD = partially matched unrelated donor; TBI = total body irradiation.
[1]Follow-up duration of survivors; [2]determined in 50 patients (84.7%); [3]determined in 44 patients (74.6%).

Response and survival

Total response rate following NMA increased from 83% (n=49) to 92% (n=54); complete response rate increased from 15 to 32%. NMA as part of first-line treatment induced a complete remission in 50% of patients, as compared with achievement of a complete remission in one patient (4%) treated for relapsed multiple myeloma. An ongoing response, defined as improvement of partial to complete response and from no response to partial or complete response occurred in 24% of patients; 28% in patients who received NMA as part of first-line treatment and 17% in patients who received NMA as part of relapse treatment (*table 2*).

Twenty-five patients (42%) relapsed or progressed after NMA, two from complete remission and 23 from partial remission. At the time of analysis 48 patients were alive. Eleven patients (19%) had died, four from progressive disease and seven (12%) from nonrelapse mortality. The estimated overall survival of the whole group of patients at two years was 84% (*figure 1*). Median progression-free survival was 23.5 months (range 1.0 to 38.0 months; *figure 2*). In patients who received NMA as part of first-line therapy, overall and progression-free survival at two years were 88.9 and 68.9%, respectively (*figures 3A* and *B*). The achievement of complete remission after NMA in this group of patients was associated with superior overall survival and progression-free survival (*figures 4A* and *B*). Also the presence of complete remission before NMA was associated with prolonged progression-free survival (p=0.037), but not with prolonged overall survival (p=0.234). The occurrence of chronic GvHD was associated with prolonged overall

Table 2. *Response rates to nonmyeloablative ASCT in first-line and relapse treatment*

	Total no. of patients (%)	First-line treatment n (%)	Relapse treatment n (%)	P
Remission state before ASCT				
CR	9 (15.3)	9 (25)	0 (0)	0.007
PR	40 (67.8)	24 (66.7)	16 (69.6)	
NR	10 (16.9)	3 (8.3)	7 (30.4)	
Remission state after ASCT				
CR	19 (32.2)	18 (50)	1 (4.3)	<0.001
PR	35 (59.3)	17 (47.2)	18 (78.3)	
NR	5 (8.5)	1 (2.8)	4 (17.4)	

ASCT = allogeneic stem cell transplantation; CR = complete response; PR = partial response; NR = no response. Differences in categorical variables were determined with the Pearson χ^2 test.

Figure 1. *Overall survival following nonmyeloablative allogeneic stem cell transplantation*

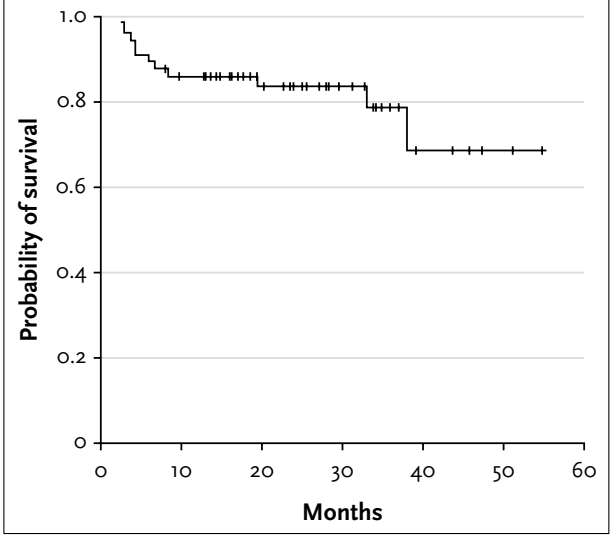


Figure 2. *Progression-free survival following nonmyeloablative allogeneic stem cell transplantation*

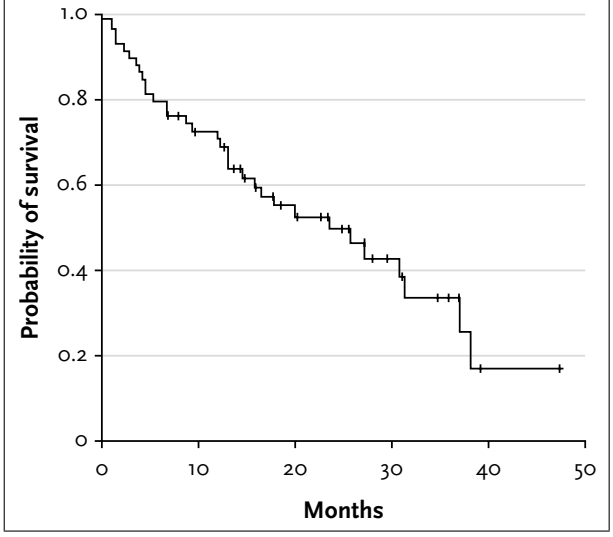
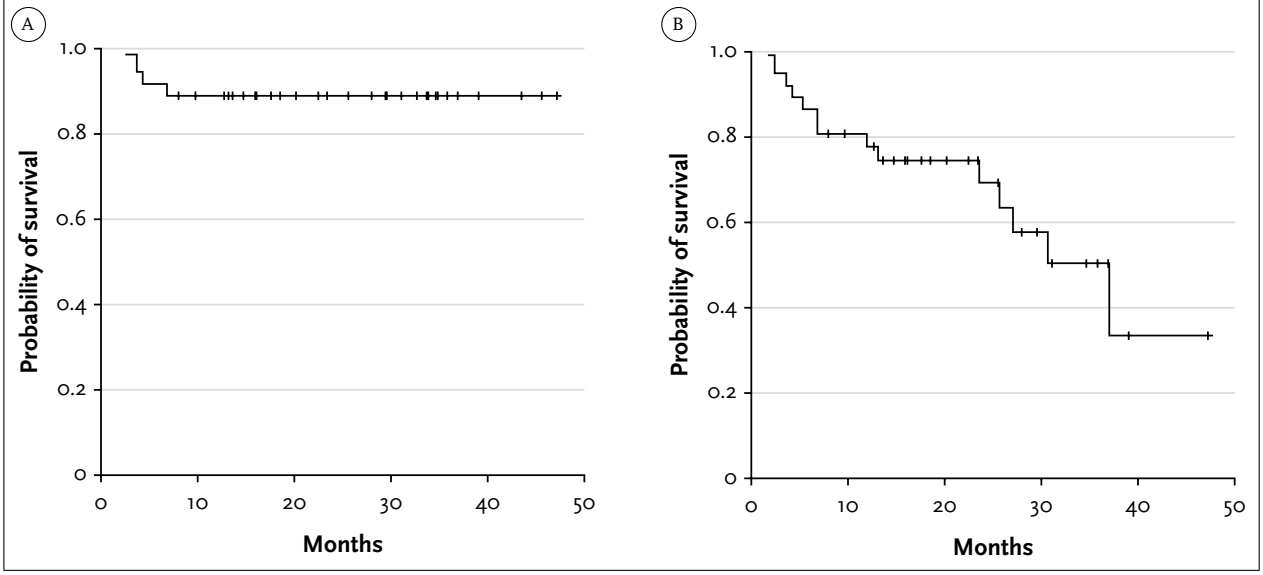


Figure 3. *A: Overall survival in patients who received NMA as first-line treatment. B: Progression-free survival in patients who received NMA as first-line treatment*



survival (p=0.012) but not with progression-free survival (p=0.3). The 11 patients with acute GvHD grade III and IV had inferior overall survival due to fatal outcome of this complication in five patients (p=0.001). No fatal deaths were observed in the patients with acute GvHD grade 0 to II. None of all other factors tested including age, gender of recipient or donor, conditioning regimen, use of ATG, family or a matched unrelated donor, deletion of chromosome 13 (FISH), β2 microglobulin ≥3 mg/ml, had an impact on overall or progression-free survival. In the patients who received NMA as part of the treatment for relapsed myeloma overall survival and progression-free survival at two years were 77.5 and 23.9%, respectively (*figure 5*). None of the factors tested including age, gender as described above had an impact on progression-free and overall survival. It should be mentioned, however, that the statistical analysis must be interpreted with caution due to the small number of patients.

Toxicity

Nonrelapse mortality at 12 months was 12% (*figure 6*). Five patients (9%) died from acute GvHD grade III to IV. One patient died from complications occurring after heart catheterisation and one relapsed patient refused further treatment, including a stem cell boost for secondary aplasia and ultimately died from overwhelming septicaemia. Acute

Figure 4. *A: Overall survival in patients who received NMA as first-line treatment and did reach complete remission afterwards and patients who did not reach complete remission. B: Progression-free survival in patients who received NMA as first-line treatment and did reach complete remission afterwards*

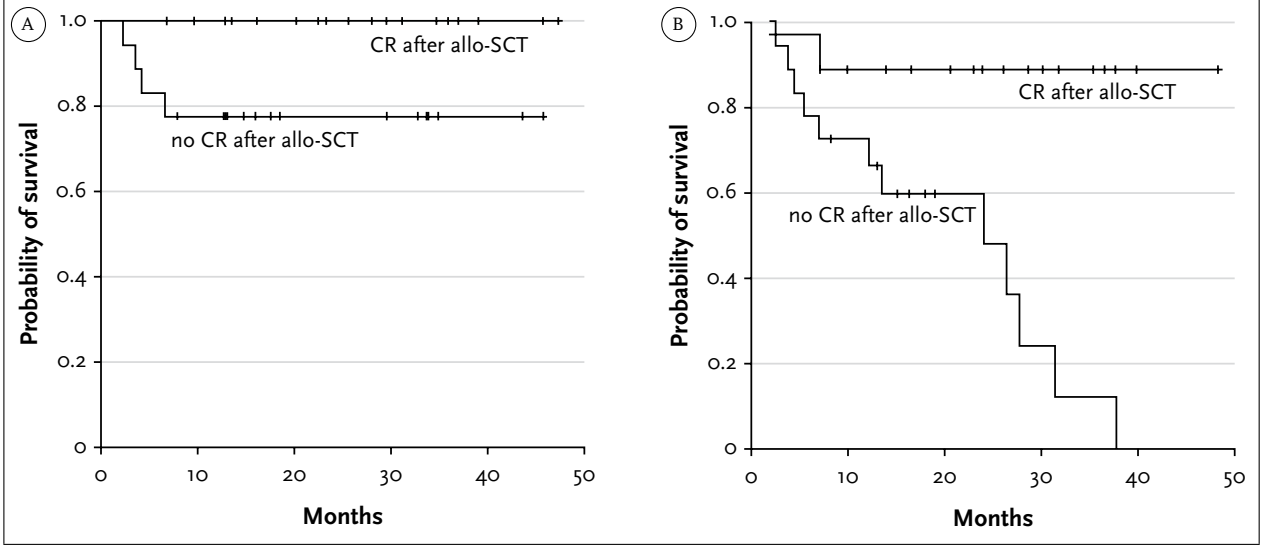
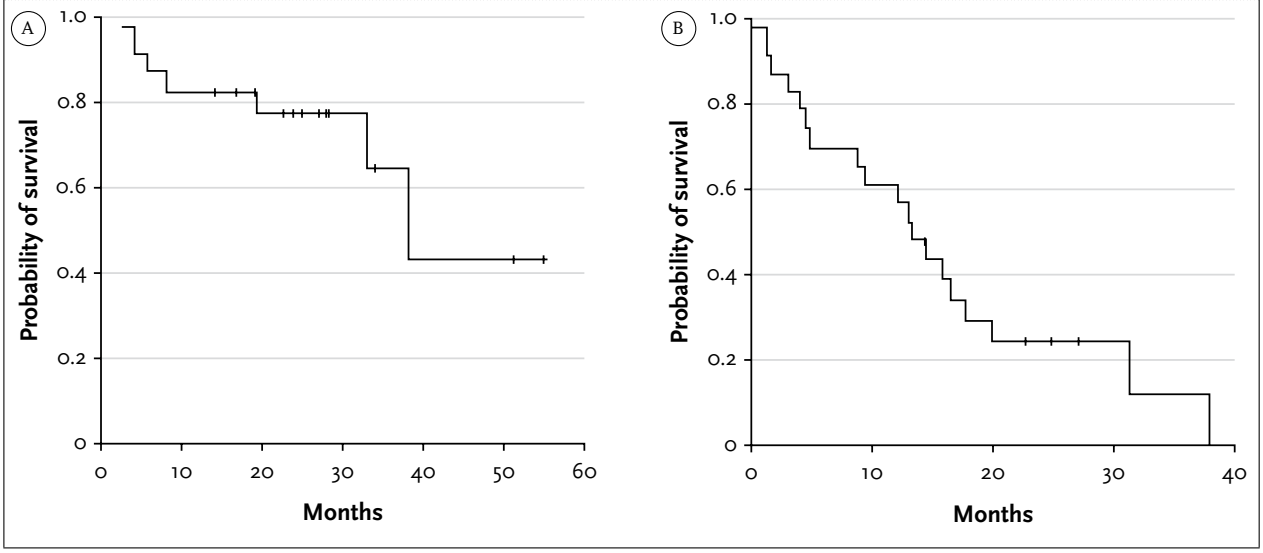


Figure 5. *A: Overall survival in patients who received NMA as treatment for relapsed myeloma. B: Progression-free survival in patients who received NMA as treatment for relapsed myeloma*

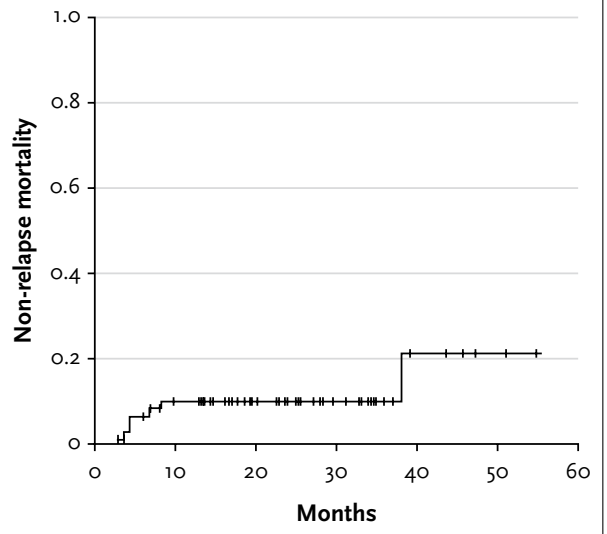


GvHD following NMA occurred in 38 patients (64%): grade I in 12 (20%), grade II in 12 (20%), and grade III or IV in 14 patients (24%). Chronic GvHD following NMA occurred in 32 patients (54%), with three patients (5%) experiencing limited disease and 29 patients (49%) extensive disease. NMA as first-line treatment was associated with a higher incidence of grades II to IV acute GvHD, when compared with NMA as relapse treatment (56 *vs* 26%; p=0.034). The use of ATG significantly reduced the incidence of chronic GvHD (20 *vs* 66%; p=0.003). This may explain the lower incidence of chronic GvHD in patients with an unrelated or mismatched donor. All other factors tested were not associated with occurrence of chronic or acute GvHD.

DISCUSSION

Several conclusions can be drawn from this retrospective study. The first one is that NMA is feasible in multiple myeloma, even in heavily pretreated patients. Nonrelapse mortality after NMA compares very favourably with nonrelapse mortality after myeloablative ASCT.[4,5] What is remarkable is the absence of nonrelapse mortality in the patients receiving a transplant from a matched unrelated donor, probably due to the administration of ATG. The second observation is that NMA as part of first-line therapy results in a high percentage of complete responses which seems to be predictive for prolonged progression-free and

Figure 6. *Nonrelapse mortality*



overall survival, while all patients not achieving a complete response, including the vast majority of the relapsed patients, have remissions of short duration. Longer observation, however, is needed to determine the quality and durability of these complete remissions. Late relapses from complete remissions are not uncommon after ASCT for multiple myeloma.[13] The third conclusion is that overall survival is remarkably good even in the pretreated patients. This may be due to the efficacy of novel agents such as thalidomide, bortezomib and DLI given to the patients who relapsed after NMA.[14,15] Acute and chronic GvHD were the most important toxicities and responsible for the fatal outcome in five patients (9%). Nonrelapse mortality percentage may still increase due to the considerable number of patients with chronic extensive GvHD. Chronic GvHD, the most important negative factor for quality of life after NMA with full stem cell grafts, is however a significant factor for prolonged progression-free and overall survival.

Although our results and results from other studies are encouraging, the role of NMA for myeloma is not yet established.[8,16] In the recently published prospective study by the French IFM, high-risk myeloma patients with an HLA-identical family donor and treated with tandem autologous/NMA-ASCT had comparable progression-free and overall survival to the patients with no donor who were treated with double autologous SCT.[18] In this study *in vivo* T-cell depletion was performed with high-dose ATG as part of the nonmyeloablative conditioning regimen in all patients. The beneficial effect of *in vivo* T-cell depletion is the low incidence of acute and chronic GvHD; the detrimental effect is the elimination of the graft *vs* myeloma (GvM) effect.[19] The importance of immune-competent donor T cells for graft *vs* myeloma effect is illustrated by responses to DLI and the occurrence of chronic GvHD.[20] European study groups, including the Dutch Haemato-Oncology Association (HOVON), Spain's Programa para el estudio y tratamiento de las hemopatias malignas (PETHEMA), and the European Group for Blood and Marrow Transplantation (EBMT), are performing comparable prospective donor *vs* no-donor studies. The results of these studies have to be awaited for more definite conclusions about the value of NMA in multiple myeloma. In anticipation of the outcome of these studies it is necessary to explore new strategies which are aimed at stimulating the cytotoxic efficacy of the donor T cells towards the residual myeloma cells without enhancing GvHD. The suggestion that the novel antimyeloma agents such as bortezomib, thalidomide, and lenalidomide may preferentially stimulate the graft-*vs*-tumour effect and not GvHD is fascinating in this respect.[21,14]

In conclusion, NMA ASCT as part of first-line treatment of multiple myeloma is feasible, is associated with acceptable transplant-related mortality and may induce a high percentage of complete remissions of good quality and prolonged duration. The outcome of prospective donor *vs* no donor studies, however, has to be awaited to better define the role of this treatment for multiple myeloma. In extensively pretreated patients response rate and progression-free survival are disappointing and in this category of patients new strategies need to be explored. These strategies should be aimed at enhancing the graft-*vs*-tumour effect probably by incorporating novel agents.

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Exhibition of the covers of the Netherlands Journal of Medicine 16 May-24 June 2007

Five years ago, Professor J.W.M. van der Meer, then chief editor of the Netherlands Journal of Medicine, came up with the idea of embellishing the cover of 'his' journal with graphic art. A very keen amateur etcher himself and infected with the 'graphic virus', this was a logical choice. Together with Caroline Koenders, graphic artist, lecturer and owner of Galerie Unita in Beek-Ubbergen, a simple formula was created. Every month a graphic artist selected by Galerie Unita submits a print for the cover. Inside the journal, a photo of the artist with a short CV and a comment on the work in question is included. In this way, art and science literally come together.

In the course of time, a nice way of showing our appreciation for this cooperation was devised: each year, three promising young internists are awarded a prize for the best article published in the Netherlands Journal of Medicine in three categories.
The lucky winners can choose one of the prints that has decorated the cover in the year in which their article was published; a stimulating prize, greatly appreciated by the authors.
Over the years, graphic artists from The Hague, Rotterdam, Amsterdam, Nijmegen and sometimes the border regions have supplied prints using all manner of graphic techniques. This provides a superb kaleidoscope of what is being produced in this field of art.
Now, after five years, the collaboration has come to an end and the Radboud University Medical Centre is offering the artists who have submitted prints in the last two years space to exhibit their work. We are proud that the fruits of this exceptional initiative can be seen here.

The exhibition will be held from 16 May-24 June 2007 in the South corridor of the Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, Nijmegen, and will officially be opened on 24 May at 16.30 by Professor J.W.M. van der Meer.

A.F.H. Stalenhoef
Editor in chief, the Netherlands Journal of Medicine

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CASE REPORT

Papillary thyroid carcinoma in a patient with sarcoidosis treated with minocycline

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ABSTRACT

Long-term treatment with minocycline is occasionally associated with the development of black thyroid syndrome in which thyroid cancer is frequently found. Here, we report a patient with cutaneous, pulmonary and thyroid sarcoidosis who developed papillary thyroid carcinoma in the presence of a black thyroid syndrome after being treated with minocycline for 2.5 years.

KEYWORDS

Black thyroid, minocycline, papillary thyroid carcinoma, sarcoid reaction, sarcoidosis

INTRODUCTION

Long-term treatment with minocycline is occasionally associated with the development of black thyroid syndrome, first described in humans in 1976.[1] Fourteen years later an association between this syndrome and thyroid cancer was made. To date eight cases of thyroid carcinoma have been found in 29 cases with black thyroid syndrome.[2-9]
Minocycline is commonly used in the treatment of severe acne. Recently patients with cutaneous sarcoidosis have been effectively treated with minocycline.[10]
We describe a patient with cutaneous, pulmonary and thyroid sarcoidosis, who developed a papillary carcinoma during minocycline therapy.

CASE REPORT

A 35-year-old female with a medical history of cutaneous and pulmonary sarcoidosis visited the outpatient clinic with a swelling in her neck. Initially the sarcoid skin lesions were treated with isotretinoin and long-wave (UVA1) therapy. When this treatment proved to be inadequate, minocycline (200 mg/day) was started. She had been treated for a period of 2.5 years when a papillary thyroid carcinoma was diagnosed. The first time our patient detected the swelling in her neck was after seven months of minocycline therapy. Ultrasound repeatedly showed a nodule in the left lobe of the thyroid. Cytological examination of fine needle aspirates did not show any signs of malignancy until two years later, when multiple papillary cell groups suspect for papillary thyroid carcinoma were detected. Thyroid function was within normal limits throughout (FT_4 13.2 to 17.6 pmol/l and TSH 0.84 to 1.64 mU/l). Minocycline therapy was stopped and a total thyroidectomy performed.
The total thyroidectomy specimen weighing 29 g had a greyish-white appearance. In the left lobe an encapsulated tumour was found measuring 2.7 x 1.8 x 2.6 cm. Light microscopy revealed a tumour encapsulated by fibrous tissue. The tumour cells showed nuclear clearing and nuclear grooves (*figure 1*). No pigmentation was seen in the tumour.
The surrounding nonneoplastic thyroid parenchyma contained intracytoplasmic dark-brown pigmented granules (*figure 2*). In the thyroid, especially surrounding the tumour, sarcoid granulomas were seen (*figure 3*).

DISCUSSION

Minocycline is a broad-spectrum antibiotic, commonly used in the treatment of severe acne. Recently it has been shown to also be effective in the treatment of cutaneous sarcoidosis.[10]
The most relevant side effects of minocycline are dizziness, nausea, diarrhoea, hyperpigmentation of the

Figure 1. *Papillary carcinoma cells of the thyroid, demonstrating nuclear clearing and nuclear grooves (haematoxylin and eosin stain; original magnification, 200x)*

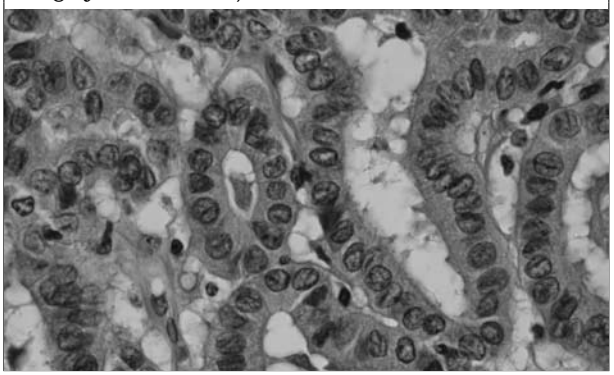
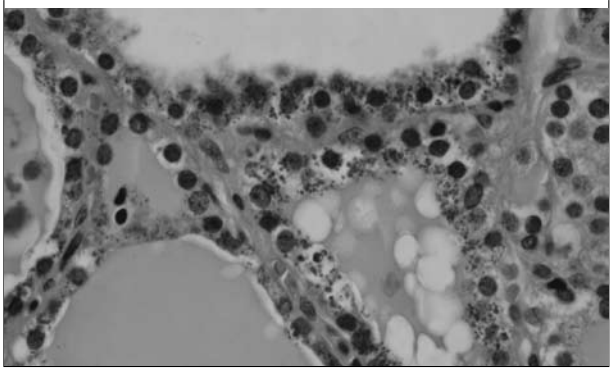
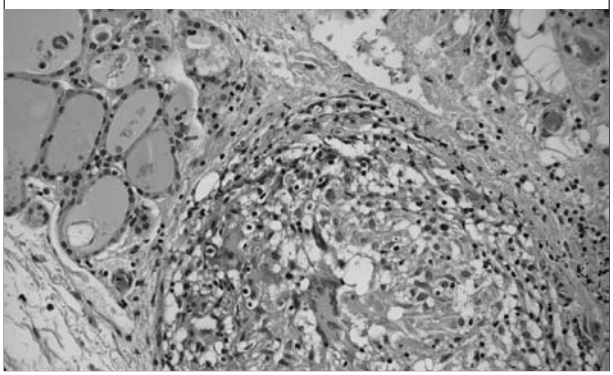


Figure 2. *Intracytoplasmic pigment granules in nonneoplastic thyroid (haematoxylin and eosin stain; original magnification, 100x)*



skin and a macroscopic black discoloration of the thyroid gland, designated 'black thyroid syndrome'. This black discoloration of the thyroid is almost pathognomonic for the use of minocycline. Other causes such as haemochromatosis, ochronosis and cystic fibrosis have to be excluded. The mechanism of the pigment deposition that causes the black colouring of the thyroid gland is still subject of debate. The most favoured opinion is that pigment is formed by oxidation of minocycline by thyroid peroxidase. Thyroid peroxidase is the key enzyme in the synthesis of T4 and T3 and therefore essential for normal thyroid function.[11]

Figure 3. *Sarcoid granuloma with epithelioid cells and Langhans giant cells (haematoxylin and eosin stain; original magnification, 50x)*



A total of 30 cases of black thyroid associated with the use of minocycline have been identified thus far, including the one we report here. Of these 30 cases, eight exhibit thyroid papillary carcinoma,[2-9] and one case follicular carcinoma (*table 1*).[8] The duration of minocycline therapy was usually one or more years before the malignancy was discovered.

A causal relationship between minocycline-induced black thyroid and malignancy has never been proven. Many case reports describe an association, however Hecht *et al.* describe seven cases with black thyroid with no malignancies.[2-9] Our patient first noticed a swelling in her neck after seven months of minocycline therapy. A malignancy could not be found until 2.5 years later.

The incidence of thyroid carcinoma in the general population is approximately 3/100,000. In the 30 described cases of black thyroid syndrome nine malignancies exist, which gives a frequency of 3/10. This high frequency is

Table 1. *Thyroid carcinoma during/after minocycline therapy*

Reference	Age	Sex	Thyroid function	Minocycline therapy in years	Presentation
Onya *et al.*[2]	29	M	N	1	Incidental
Landas *et al.*[3]	27	M	N	2.5	Metastatic neck mass
Pastolero *et al.*[4]	27	F	N	1	Metastatic neck mass
Pastolero *et al.*[4]	43	F	N	Not known	Neck swelling
Rhagavan *et al.*[5]	18	M	N	>2	Neck swelling
Birkedal *et al.*[6]	27	F	N	>2	Nodule
Thompson *et al.*[7]	44	F	N	Not known	Cold nodule
Jennings *et al.*[8]	36	F	N	Not known	Neck swelling*
Bruins *et al.*	35	F	N	2.5	Neck swelling

*Follicular carcinoma; N = normal.

indicative of a possible association; however, this result may also be due to selection.

Sarcoidosis is a chronic systemic granulomatous disease. The lungs, skin, eyes and liver are mostly affected. Rarely the thyroid gland is involved.[12] Other thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease are known to be associated with systemic sarcoidosis.[13] One case report describes a possible association between systemic sarcoidosis and papillary cancer[14] and in another case report a patient is described with systemic sarcoidosis, Graves' disease, thyroid sarcoid granuloma and papillary carcinoma.[15] It remains unclear if there is a causative relationship between sarcoidosis of the thyroid and the development of papillary carcinoma.

The same is true for the association between sarcoid reaction and malignancy. In approximately 4% of cancer patients sarcoid reaction occurs. The malignancy is usually localised in lung, breast or uterus. We found only seven cases that describe the combination of sarcoid reaction of the thyroid gland and papillary carcinoma.[16,17] Six of these cases were Japanese. To our knowledge this is the first report of a patient who used minocycline for sarcoid skin lesions and subsequently developed a black thyroid and papillary thyroid cancer in a thyroid that was also affected by sarcoidosis. Treatment of sarcoid skin lesions with minocycline is relatively new. Possibly patients with sarcoidosis are at more risk of developing thyroid carcinoma when using minocycline. Maybe when more patients are treated an association will become clear.

In summary, we describe a patient with sarcoidosis and minocycline therapy who developed a black thyroid and papillary carcinoma. It is still unclear if there is an association between sarcoidosis and thyroid cancer. The minocycline therapy is possibly the trigger for developing malignancy. When minocycline is used in patients, close monitoring for the development of a thyroid swelling is mandatory.

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CASE REPORT

An itchy holiday

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ABSTRACT

A 33-year-old Dutch woman developed itchy skin lesions during a beach holiday in Thailand. She was treated for various diagnoses, without success. Finally she was successfully treated for a clinically suspected hookworm-related folliculitis. A brief overview of hookworm-related folliculitis is given.

KEYWORDS

Cutaneous larva migrans, folliculitis, hookworm, parasitic

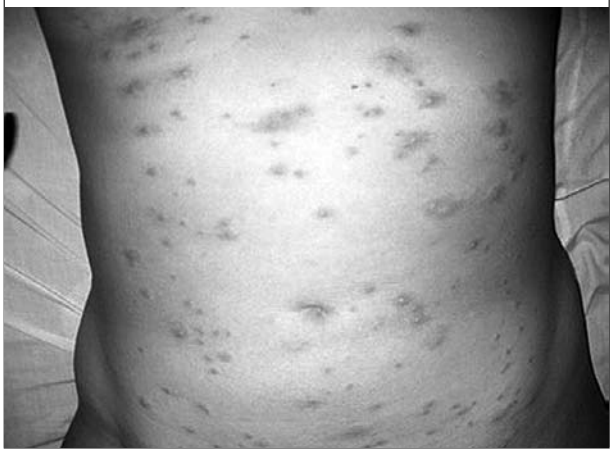
INTRODUCTION

The ever-increasing frequency of travel to tropical and subtropical destinations results in an equal rise in imported diseases. Therefore, physicians with little knowledge of 'tropical diseases' will also occasionally encounter these imported diseases. This case illustrates an unusual presentation of an infection frequently acquired on tropical beaches.

CASE REPORT

A 33-year-old woman from the Netherlands developed an itchy rash on her trunk and upper legs during her stay in Thailand, where she enjoyed a beach holiday in October. On the first day of her holiday she had been lying on a sandy beach without a towel. She did not recall any insect bites or stings. During the following days she developed an increasing number of small papules of ± 3mm in diameter, which changed colour from bluish to red and became increasingly itchy. She had no medical or dermatological history and was not taking any medications. Her partner was unaffected. She visited a local medical institution for her symptoms and was treated with antibiotics (amoxicillin/clavulanic acid) and an H1-receptor blocker without effect. Four weeks later, after returning to the Netherlands, she was seen by her general practitioner (GP) because of persisting itchy abdominal and submammary erythematous papules, with purpuric lesions (*figure 1*). As the GP suspected scabies, he treated her with lindane, but without success. The patient was therefore referred to a dermatologist. Laboratory investigations at that time revealed a leucocyte count of 15.2 x 10^9/l (reference value 4.3-10.0), eosinophils 44% (0-5%), Hb 8.3 mmol/l (7.5-10.0), aspartate transaminase 43 IU/l (<31 IU/l), alanine aminotransferase (<31 IU/l) and IgE titre 169 kU/l (<100 kU/l). Her faeces were tested for parasites, which revealed a hookworm infection.

Figure 1. *This figure shows the abdomen of our patient approximately two weeks after the infection at the beach*



A skin biopsy showed eosinophilic infiltrates with no microorganisms. The follicular canal did not seem to be affected. The results were interpreted at that time as eosinophilic invasion of the skin as the consequence of a hookworm infection and she was treated with mebendazole.

As the skin lesions had not improved after three to four weeks and she continued to complain of severe itching and progressive fatigue, she was referred to the department of infectious diseases. She was seen three months after onset. Physical examination at that time revealed pink to red papular and pustular lesions, mainly localised in the pubic region, trunk and breasts. No creeping dermatitis was seen within these cutaneous lesions. A repeated stool test did not show hookworm.

Clinically she was suspected of hookworm folliculitis and she was treated with albendazole at a daily dose of 1000 mg for five consecutive days. The pruritic lesions disappeared slowly within two weeks.

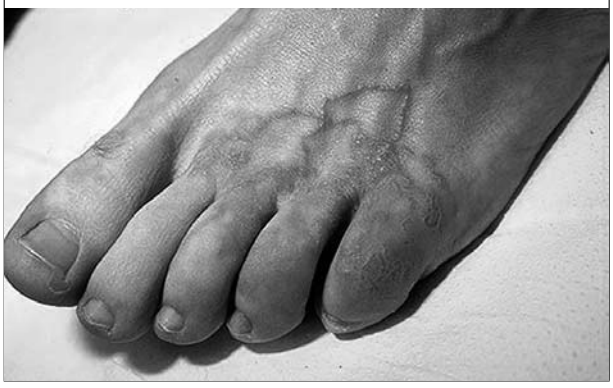
DISCUSSION

Hookworm folliculitis is an uncommon clinical form of hookworm-related cutaneous larva migrans (HCLM).[1] It is one of the most common acquired tropical dermatoses. It is usually associated with a creeping eruption but it may also give rise to folliculitis, mostly located on the buttocks.[1-3] Even though the causative parasite may be similar, the response to classical treatment is less prompt. The majority of cases of HCLM are caused by cutaneous hookworm infestation. The human species is an accidental host. Typically larvae of the animal (cat or dog) hookworm *Ancylostoma braziliense* are the cause. Other animal hookworms of the *Ancylostomidae* family (*A. caninum, A. duodenale*) may cause similar pictures. Other parasitic causes, such as *Uncinaria stenocephala, Bunostomum phlebotomum, Strongyloides stercoralis* (larva currens), *S. procyonis, Gnathostoma spinigerum, Spirurina* spp., *Fasciola gigantica* and *Dirofilaria repens* may also cause creeping eruptions whereas *Pelodera strongyloides* has been associated with hookworm folliculitis.[1]

Eggs are excreted in feline or canine faeces and hatch in the soil. Contaminated soil is typically found in (sub)tropical climates. In these areas the larvae are found on sandy beaches, in sandpits and under dwellings. Infestation occurs when the filariform larvae penetrate the human skin and migrate between the stratum germinativum and stratum corneum.[4,5] Several days after penetration severely itchy cutaneous lesions appear. Typically HCLM clinically presents as a creeping eruption with an erythematous linear or serpiginous tract with extreme pruritis.[1] In other cases, many larvae may penetrate the skin simultaneously and cause multiple itchy follicular papules and pustules, as in our patient. An eosinophilic inflammatory reaction occurs, which causes the erythematous aspect of the lesion. The histological picture only rarely reveals the causative larvae in HCLM. In hookworm folliculitis, the histological aspect is characteristic by showing an eosinophilic folliculitis due to an inflammatory reaction to the presence of larvae trapped within the follicular canal.[1,6] Histological confirmation, however, often fails.[2] Only a few cases of hookworm folliculitis have been reported in the literature and the largest series includes seven cases.[1,3,7] Hookworm folliculitis should be recognised as one of the less typical presentations of HCLM. Although the disease is self-limiting, many infested patients require treatment to reduce the often debilitating symptoms, and to prevent or treat superinfection. Treatment for cutaneous larva migrans consisted of local application of thiabendazole when this drug was marketed. However, systemic therapy with albendazole or ivermectin is also effective.[7] Nonetheless hookworm folliculitis responds less to ivermectin than creeping dermatitis.[8] Mebendazole is registered for treatment of (intestinal) hookworm as well. Failure to respond to the initial treatment in our patient may be explained by the differences in rate of absorption and efficiency between mebendazole and albendazole in the treatment of (H)CLM.

In summary HCLM is easily recognised if it occurs in its typical clinical form of creeping dermatitis. Hookworm folliculitis, however, is a less common clinical presentation of the same parasitic infection. Persistent itching folliculitis in a patient who has recently returned from an area where hookworm infestation is endemic should raise the suspicion of atypical hookworm folliculitis. Histological confirmation is required to make a definite diagnosis of a hookworm folliculitis in the absence of the characteristic creeping eruption. Treatment should be started based on typical clinical findings. A single oral dose of ivermectin or a three-day course of albendazole suffices as treatment in most cases.[9]

Figure 2. *Illustration of typical cutaneous larva migrans (with courtesy of the ITG, Belgium)*



ACKNOWLEDGEMENT

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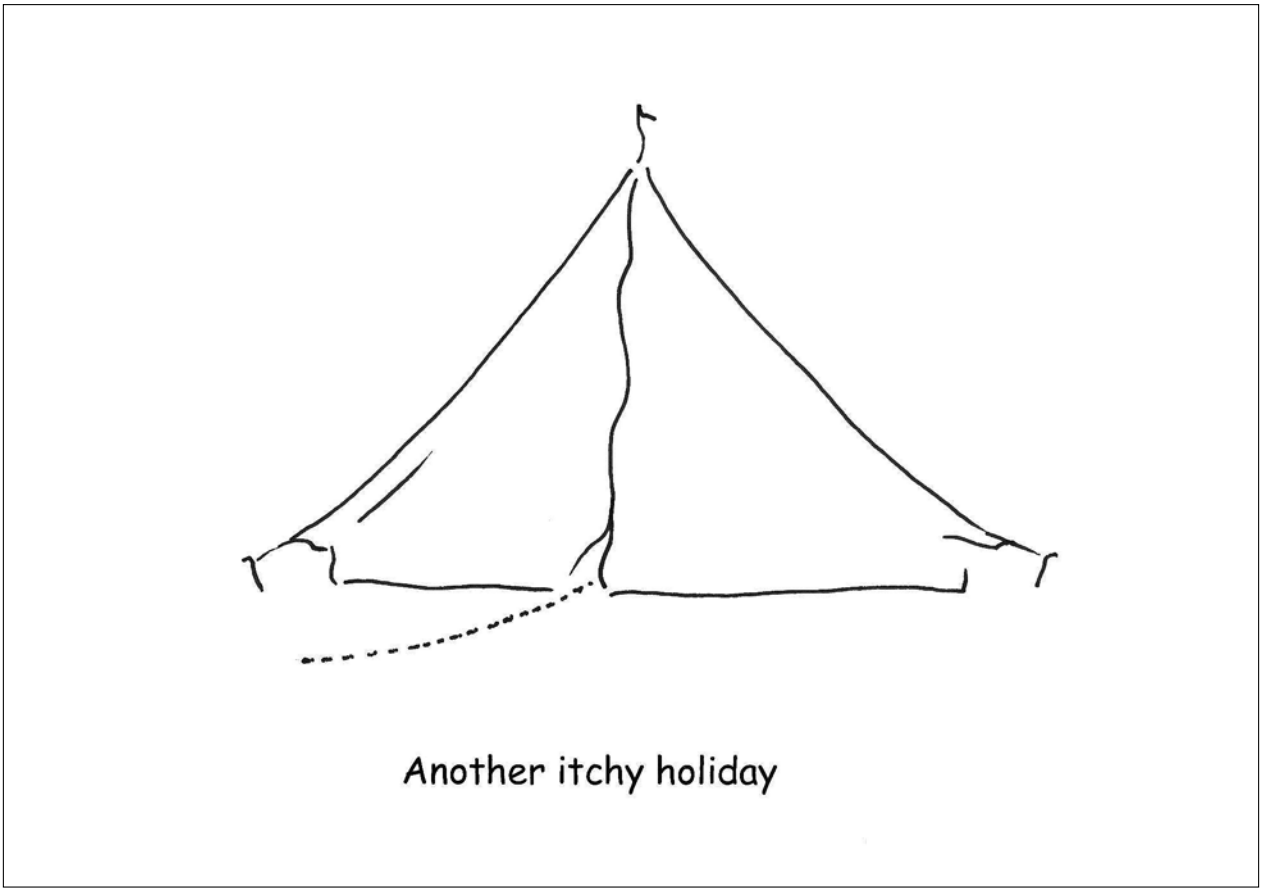

Van Nispen tot Pannerden, et al. An itchy holiday.

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PHOTO QUIZ

Rare localisation of air

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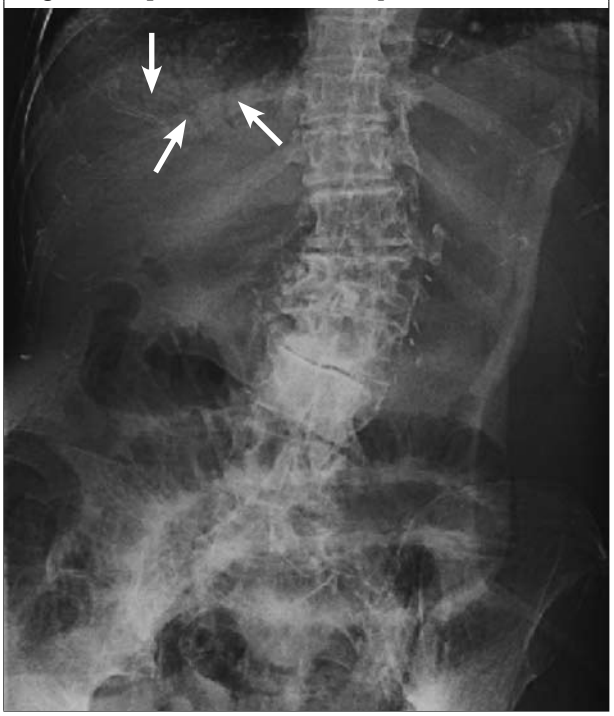
CASE REPORT

A 75-year-old woman came to the emergency room with diffusely localised, non-colicky abdominal pain which was constant in nature. In the emergency room she was restless and anxious. Medical history denotes haemodialysis since December 2003 due to terminal reno-vascular insufficiency. Physical examination showed an ill, anxious patient with a blood pressure of 130/70 mmHg, pulse 88 beats/min and body temperature 34.8°C. Abdominal examination revealed sparse, high-pitched bowel sounds, hypertympanic percussion with intact liver dullness and pain located diffusely in the abdomen. During rectal examination, dark-red blood was seen. Laboratory investigation showed a low blood count (Hb 6.1 mmol/l, MCV 93 fl), stable renal insufficiency (urea 18.3 mmol/l, creatine 464 µmol/l), leucocytes 3.7 x 10^9/l, with a differentiation of 12% polymorph nuclear cells, lactate dehydrogenase 434 U/l, creatine kinase 404 U/l and C-reactive protein 190 mg/l. Lactate was not measured. On a supine chest X-ray no evidence of free air under the diaphragm was seen. A plain abdominal X-ray is shown here (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 195 for the answer to this photo quiz.

Figure 1. *A plain abdominal X-ray*



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SPECIAL REPORT

Recurrent pericardial effusion with a common clinical disorder

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ABSTRACT

We present a case of recurrent pericardial effusion in a patient with Down's syndrome in whom the underlying cause was not considered because of unfamiliarity with the care of people with Down's syndrome. The diagnosis hypothyroidism only became apparent by means of a routine panel of biochemical tests.

KEYWORDS

Down's syndrome, hypothyroidism, pericardial effusion

CASE REPORT

A 34-year-old man with Down's syndrome was referred by his general practitioner to a cardiologist because of cardiomegaly on an X-ray of the chest (*figure 1*). After having had a cold, he complained of fatigue and shortness of breath present for several months. On physical examination the patient had a normal body temperature, his resting heart rate was 60 beats/min. There were no murmurs, no signs of heart failure, blood pressure was 110/80 mmHg and no pulsus paradoxus. Electrocardiography showed low QRS voltages compatible with pericardial effusion (*figure 2A*). Echocardiography revealed a large amount of pericardial fluid, with normal function of the left ventricle and valves. The right atrium was not collapsed (*figure 3*). He was then treated with acetylsalicylic acid 1200 mg three times a day, without

Figure 1. *Anteroposterior view of the chest showing cardiomegaly*

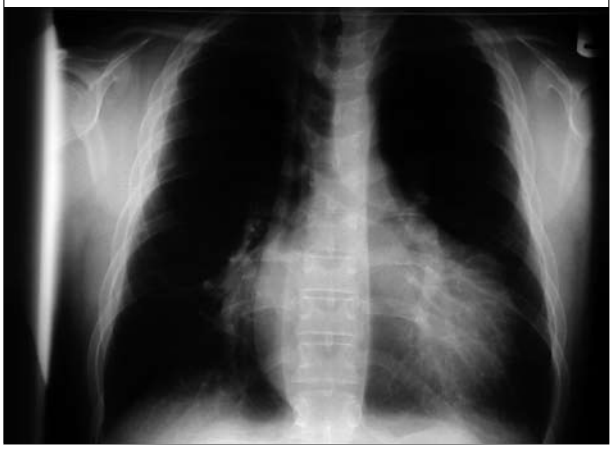


Figure 2A. *ECG on presentation with low QRS voltages compatible with pericardial effusion*

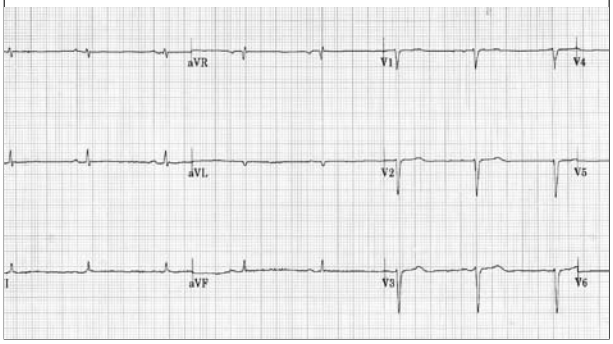
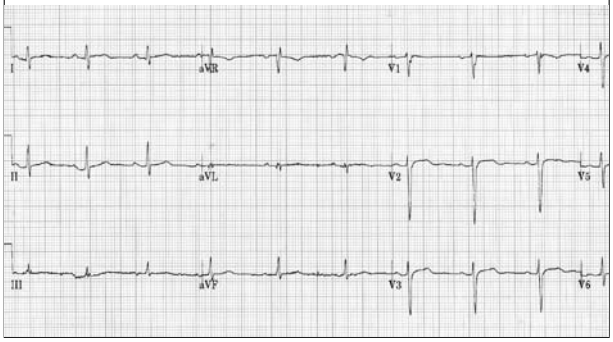


Figure 2B. *After two months of treatment with levothyroxin, disappearance of pericardial effusion and normalisation of ECG*

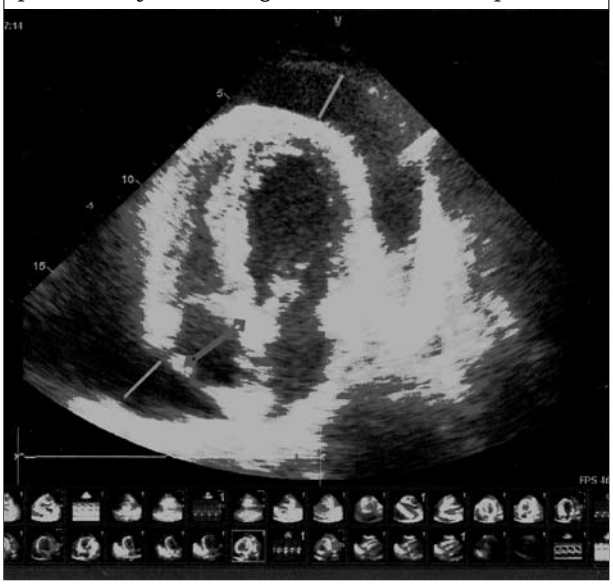


response. The next step was pericardial drainage; 1000 ml transsudate was obtained. Cytological and microbiological examination showed no malignant cells, neither bacterial growth, nor information supporting possible tuberculosis. Autoimmune markers were examined. Data of routine blood and biochemical examination are summarised in *table 1*. Within two weeks the pericardial effusion reoccurred and the patient started prednisolone, 60 mg/day.

This strategy did not improve the course since the patient developed progressive pericardial effusion for which a new drainage procedure was performed, seven weeks after the first procedure. Four weeks hereafter pericardial effusion recurred for which pericardial fenestration was considered. For this procedure the patient was referred to a thorax centre. Surprisingly, on admission the diagnosis of a pronounced primary hypothyroidism (TSH > 150mU/l, FT4 <1.3 pmol/l) was made by means of routine standardised biochemical tests. This routine screening included metabolic causes of pericardial diseases such as uraemia and hypothyroidism.[1] This latter differential diagnostic possibility had not been considered previously.

The patient was then treated by levothyroxine with a starting dose of 50 µg/day. An improvement in symptoms, normalisation of the ECG (*figure 2B*), as well as the cardiac silhouette on chest X-ray developed after two months and the pericardial fluid disappeared.

Figure 3. *Echocardiograph showing large amount of pericardial fluid; the right atrium is not collapsed*



DISCUSSION

This patient with Down's syndrome had an unusual presentation of hypothyroidism: an impressive amount of pericardial effusion. Other signs such as myxoedema, mild macrocytic anaemia, elevated creatine kinase[2] and symptoms of hypothyroidism such as fatigue may have been overlooked in this situation. Other clinical findings, which previously did not draw much attention, can in retrospect be judged in favour of a metabolic cause, in particular hypothyroidism. The first working diagnosis was postviral pericardial effusion because the history started with a cold, two months before admission. During his stay in the department of cardiology the patient had normal body temperature. CRP was only marginally elevated and there was a normal leucocyte count, making an infectious cause of pericardial effusion unlikely. In our

Table 1. *Results of blood and biochemical examination*

	Normal values	On admission to hospital	In thorax centre 16 weeks after initial presentation	Ten weeks after start of levothyroxine treatment
TSH	0.3-5.2 mU/l	-	>150	1.2
FT4	12.0-28.0 pmol/l	-	<1.3	17
CRP		16		
Haemoglobin	8.8-11.2 mmol/l	7.3		7.5
MCV	82-92 fl	99		99
Leucocytes	4-11 /nl	7.3		5.9
CRP	0-5 mg/l	16		13
Sodium	135-145 mmol/l	128		143
Potassium	3.5-5.0 mmol/l	4.4		3.6
Creatinine	70-115 µmol/l	114		89
ASAT	0-40 U/l	86		17
ALAT	0-45 U/l	35		20
CK	0-200 U/l	1003		22
Troponin	0-0.1 µg/l	0.08		
A-TPO	0-35 kU/l			50
RF	0-20 U/ml	6		
ANA	Negative	Negative		

patient pericardial fluid was accompanied with bradycardia, an odd combination of signs since one would expect tachycardia instead. The combination of pericardial effusion and bradycardia might suggest hypothyroidism. The low voltage in the ECG (*figure 2A*) was interpreted as a sign of pericardial effusion. However, it can also be seen in hypothyroidism. It remains speculative if the low-voltage ECG in hypothyroidism is caused by hypothyroidism per se or by its very frequently accompanying, but undetected, pericardial effusion.[3,4] Unfortunately, we have no ECG shortly after pericardial drainage in order to disentangle these two possibilities. Low QRS voltage is a common finding in patients with severe pericardial effusion. Mechanisms to explain the origin of this low voltage are mechanoelectrical alteration of the myocardium, distance of the heart to the body surface electrodes, reduction of cardiac size and volume. Other investigators have found arguments in favour of inflammation and electrical alterations of the myocardium but not pericardial effusion per se. Their arguments are supported by the findings that QRS voltage does not increase one day after pericardiocentesis.[5]

When our patient became euthyroid and when the pericardial effusion had resolved, the ECG voltages normalised (*figure 2B*) and his resting heart rhythm became 68 beats/min.

Although there were no significant signs of inflammation and while results of autoimmune markers were examined, it was decided to start prednisolone therapy because of the recurrence of pericardial fluid. In retrospect, this decision can be deemed as an aggressive one since we had no clear working hypothesis in which a systemic autoimmune process was likely. The relapsing character of large amounts of pericardial effusion, although without signs indicating development of cardiac tamponade, in a young man with Down's syndrome made us decide that an immune suppressive therapy by means of corticosteroids was justifiable. In retrospect, the decision to start with high-dose prednisone may be seen as a relatively aggressive therapy.

Patients with trisomy of chromosome 21 have a prevalence of 15 to 20% of autoimmune hypothyroidism.[6,7] Although it is recommended to screen patients with Down's syndrome on an annual basis for thyroid function, this patient had never been screened.

Pericardial effusions occur in a variable frequency in patients with hypothyroidism.[8,9] The effusions are usually small and escape detection, but occasionally patients with severe long-standing hypothyroidism have large effusions.[3] Myxoedema may be accompanied with pericardial effusion. Occasionally, the pericardial effusions are quite large, causing the appearance of cardiomegaly on routine chest radiographs. Echocardiography demonstrates small to moderate effusions in as many as 30% of overtly hypothyroid patients. The presence of pericardial fluid in hypothyroid patients does not compromise cardiac output, cardiac tamponade is exceedingly rare, and the effusion resolves over a period of weeks to months after initiation of thyroid hormone replacement.[1,4]

That the common clinical disorder of hypothyroidism was not considered in this 'unexplained' pericardial effusion may be influenced by the uncommon magnitude of it and by the fact that the patient has Down's syndrome, which made the estimation of his clinical condition difficult.

In this case hypothyroidism became apparent by means of a routine panel of examinations when pericardiocentesis was scheduled. Furthermore, blood and biochemical tests also showed less common signs of hypothyroidism: a mild macrocytic anaemia, elevated levels of CK.[2] These markers normalised with suppletion with levothyroxine.

In conclusion, patients with trisomy of chromosome 21 should be regularly monitored for hypothyroidism and thyroid function should be tested in patients with unexplained pericardial effusions. In the Netherlands guidelines for medical follow-up of children with Down's syndrome are available for paediatricians. Internists have to be familiar with these guidelines because we can expect an increasing number of patients with Down's syndrome who will be transferred from their paediatrician to an internist.[10,11]

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ANSWER TO PHOTO QUIZ (ON PAGE 191)

RARE LOCALISATION OF AIR

Plain abdominal X-ray (*figure 1*) showed air in the portal circulation (arrows). Additionally, fluid levels and dilated bowel consistent with ileus can be seen. Surgery clips from an aorta-renal bypass are visible to the left of the spinal canal as well as a left total hip prosthesis.

The precise mechanism of gas formation in the portomesenteric system is not elucidated. Predisposing factors are: 1. Mucosal injury caused by necrosis due to ischaemia of the mesenteric artery, inflammatory bowel disease or peptic ulcer. 2. Dilatation of the stomach or bowel. 3. Intra-abdominal sepsis. Finally there is a group of idiopathic causes (transplantation, corticosteroid therapy, chronic obstructive pulmonary disease (COPD).
Radiological criterion for portal gas on a conventional X-ray is a branching radiolucency, stretching within 2 cm of the hepatic margin.[1] Conventional radiology has low sensitivity in detecting portal gas. Although air in the portal vein can be detected, a substantial amount of air must be present to be visible. A substantial amount of portal gas is almost always caused by bowel ischaemia and direct surgical intervention is mandatory. Portal gas predicts neither severity of bowel ischaemia nor mortality.[2] Mortality depends on the underlying disease process causing the portomesenteric air.
Computer tomography (CT) scan and ultrasound have higher sensitivities because smaller quantities of air can be detected.[3] Smaller quantities of air are relatively often caused by factors other than bowel ischaemia. Multiple intra-abdominal diseases can lead to this (cholecystitis, diverticulitis, peptic ulcer), but iatrogenic causes such as endoscopic retrograde cholangio-pancreatico-duodenography (ERCP) can translocate some air transmucosal leading to a small amount of air visible on CT or ultrasound.[4]

DIAGNOSIS

Portomesenteric gas probably caused by mesenteric artery ischaemia.

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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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