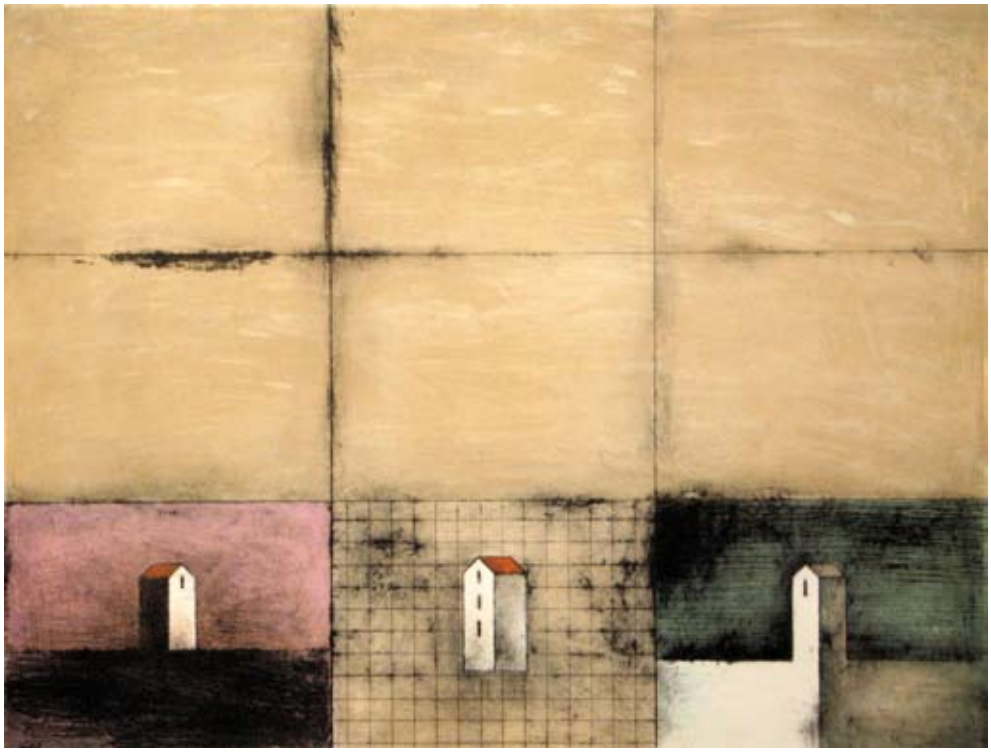
Netherlands
The Journal of Medicine
PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE



November 2006, Vol. 64, No. 10, ISSN 0300-2977

VAN ZUIDEN COMMUNICATIONS

Netherlands
The Journal of Medicine

PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

MISSION STATEMENT

The mission of the journal is to serve the need of the internist to practice up-to-date medicine and to keep track with important issues in health care. With this purpose we publish editorials, original articles, reviews, controversies, consensus reports, papers on speciality training and medical education, book reviews and correspondence.

EDITORIAL INFORMATION

Editor in chief
Anton F.H. Stalenhoef, Radboud University Nijmegen Medical Centre, Department of General Internal Medicine, Nijmegen, the Netherlands

Associate editors
Joost P.H. Drenth, Nijmegen, the Netherlands
Paul Smits, Nijmegen, the Netherlands
Theo Thien, Nijmegen, the Netherlands

Editorial board
J.V. Bonventre, Massachusetts, USA
H. Brunner, Nijmegen, the Netherlands
J.J. Cornelissen, Rotterdam, the Netherlands
S.A. Danner, Amsterdam, the Netherlands
J.T. van Dissel, Leiden, the Netherlands
J.P. Droz, Lyon, France
R.O.B. Gans, Groningen, the Netherlands
A.R.J. Girbes, Amsterdam, the Netherlands
D.E. Grobbee, Utrecht, the Netherlands
D.L. Kastner, Bethesda, USA
R.B.M. Landewé, Maastricht, the Netherlands
M.M. Levi, Amsterdam, the Netherlands
B. Lipsky, Seattle, USA
Ph. Mackowiak, Baltimore, USA
J.W.M. van der Meer, Nijmegen, the Netherlands
G. Parati, Milan, Italy
H.A.P. Pols, Rotterdam, the Netherlands
A.J. Rabelink, Leiden, the Netherlands
D.J. Rader, Philadelphia, USA
J.A. Romijn, Leiden, the Netherlands
P. Speelman, Amsterdam, the Netherlands
C.D.A. Stehouwer, Maastricht, the Netherlands
E. van der Wall, Utrecht, the Netherlands
R.G.J. Westendorp, Leiden, the Netherlands

Editorial office 'The Netherlands Journal of Medicine'
Geeralien Derksen-Willemsen
Radboud University Nijmegen Medical Centre
Department of General Internal Medicine 463
PO Box 9101, 6500 HB Nijmegen
The Netherlands
Tel.: +31 (0)24-361 04 59
Fax: +31 (0)24-354 17 34
E-mail: g.derksen@aig.umcn.nl
http://mc.manuscriptcentral.com/nethjmed

CITED IN

Biosis database; embase/excerpta medica; index medicus (medline) science citation index, science citation index expanded, isi alerting services, medical documentation services, current contents/clinical medicine, PubMed.

VAN ZUIDEN communications

Contents

Cover
Lithography by Jurjen Ravenhorst. For details about the artist, his work and how to order see elsewhere in this journal.

Copyright
© 2006 Van Zuiden Communications B.V. All rights reserved. Except as outlined below, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the publisher. Permissions may be sought directly from Van Zuiden Communications B.V.

Photocopying
Single photocopies of single articles may be made for personal use as allowed by national copyright laws. Permission of the publisher and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale, and all forms of document delivery. Special rates are available for educational institutions that wish to make photocopies for non-profit educational classroom use.

Derivative works
Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the publisher is required for resale or distribution outside the institution. Permission of the publisher is also required for all other derivative works, including compilations and translations.

Electronic storage
Permission of the publisher is required to store or use electronically any material contained in this journal, including any article or part of an article.

Responsibility
No responsibility is assumed by the publisher for any injury and/or damage to persons or property as a matter of product liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of the rapid advances in the medical sciences, independent verification of diagnoses and drug dosages is advised.
Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made of it by its manufacturer.

Subscriptions
General information
An annual subscription to The Netherlands Journal of Medicine (ISSN 0300-2977) consists of 11 issues. Issues within Europe are sent by standard mail and outside Europe by air delivery. Cancellations should be made, in writing, at least two months before the end of the year.

Subscription fee
The annual subscription fee within Europe is € 650, for the USA € 665 and for the rest of the world € 765. Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis.

Payment method
Please make your check payable to Van Zuiden Communications B.V., PO Box 2122, 2400 CC Alphen aan den Rijn, the Netherlands or you can transfer the fee to ING Bank, account number 67.89.1 0.872, Castellumstraat 1, Alphen aan den Rijn, the Netherlands, swift-code: ING BNL 2A. Do not forget to mention the complete delivery address of the Journal.

Claims
Claims for missing issues should be made within two months of the date of dispatch. Missing issues will be mailed without charge. Issues claimed beyond the two-month limit must be prepaid at back copy rates.

Orders, preprints, advertising, changes in address, author or general enquiries
Please contact the publisher.

Van Zuiden Communications B.V.
PO Box 2122
2400 CC Alphen aan den Rijn
The Netherlands
Tel.: +31 (0)172-47 61 91
Fax: +31 (0)172-47 18 82
E-mail: njm@zuidencomm.nl
Internet: www.njm-online.nl

Netherlands
The Journal of Medicine

EDITORIAL

Implementation of colorectal cancer screening

L.G.M. van Rossum*, J.B.M.J. Jansen

Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, *corresponding author: tel.: +31 (0)24-361 72 72, fax: +31 (0)24-654 01 03, e-mail: L.vanRossum@mdl.umcn.nl

According to the United European Gastroenterology Federation, colorectal cancer (CRC) has become the most frequent cancer in Western Europe. The pathogenesis of CRC has been subject of intense research efforts over the past decades. It has been established that CRC slowly evolves from normal mucosa to precancerous polyps and ultimately to invasive carcinoma.

It has become clear that CRC fulfils all major requirements to allow population-based screening.[1] Studies from different countries have confirmed that screening for CRC reduces mortality[2-4] at favourable costs compared with the screening programmes already implemented for breast cancer and cervical cancer. In 2001 the Dutch Health Council recommended the design of studies to investigate the feasibility of CRC screening in the Netherlands.[5] In 2003 the European Commission wrote a council recommendation for CRC screening.[6] In the same year, a number of research questions for the Dutch situation were formulated in the COCAST report.[7] In addition, the Minister of Health promulgated a policy letter to inform the government of his planning for the actual implementation of a nationwide CRC screening programme.[8] Two trials sponsored by the Dutch Organisation for Health Research and Development are currently running to investigate whether a nationwide screening programme for CRC can be implemented in the Netherlands. These studies mainly focus on response and adequacy of screening tools, but many questions remain.[9] In this issue of the Netherlands Journal of Medicine, two papers deal with other aspects of the implementation of a nationwide screening programme for CRC. One paper focuses on the question who should be screened, whereas the other calculates possible problems with endoscopic capacity following the implementation of screening.

The issue of identifying and narrowing down the population considered to be at risk is important, because screening should only be offered to people at risk. The European Commission currently advises an age range limit of 50 to 75 years, but the optimal age still needs to be determined.[6] Another possibility to narrow down the population at risk is to follow the course of De Jong *et al.* and aim to identify families with an increased risk for CRC.[10] Several high-risk groups, such as hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP), have already been identified. At present, these groups are only screened opportunistically as there is no system in place that identifies families with a genetic predisposition. De Jong *et al.* used a questionnaire to actively identify families at risk in the population. Although it has been suggested and it even seems obvious that identification of high-risk groups might increase the cost-effectiveness for preventive measures, it has not been proven that this is indeed the case. The only evidence there is to date builds on the intensive screening for CRC within families with HNPCC and FAP leads, and suggests that this would result in a better survival. Whether this is also true for families at lower risk, such as those identified by De Jong *et al.*'s questionnaire, remains to be proven and is highly doubtful. Introduction of an arguably rather wide age range for screening, as proposed by the European Commission, might help to answer this question, since patients with and without a family history of CRC can be distinguished and followed up. Based on these data, it may be possible to narrow down the population to screen in the future. Prerequisite is that screening for CRC should not be implemented as routine care but on a continued research basis. Due to low awareness of CRC risk in the Netherlands, we think that it is currently more important to provide the general public with simple and accurate information to ensure high participation in a screening programme than to confuse them with details such as high or low risk and intensive or less intensive screening.

It is to be expected that screening the general asymptomatic population will result in an increase in the number of colonoscopies. This leads to the next question addressed in this issue of the Journal: Is the current endoscopic capacity adequate once nationwide screening for CRC screening is implemented?[11,12] The authors report that the total number of endoscopies increased by 25% from 1999 to

© 2006 Van Zuiden Communications B.V. All rights reserved.

2004. Unfortunately, we lack information on which types of endoscopic procedures are responsible for this increase. It might be that the number of colonoscopies is increasing faster than the number of gastroscopies or vice versa. In addition, we are not informed about the indications that led to the procedure. For instance, if the increase is the result of an increase in the number of colonoscopies due to random screening for CRC, the implementation of focused CRC screening could even lead to a decrease in the number of colonoscopies. On the other hand, we think that the reported returns of a faecal occult blood test (FOBT)-based screening programme by the authors are rather conservative. Positivity rates for FOBT vary with the method used. Immunochemical FOBT has much higher positivity rates of up to 9% and results in better compliance, with equal or better positive predictive value than the guaiac-based FOBT.[13] The Nijmegen-Amsterdam implementation study is currently focused on this question for the Dutch population. Another issue which only applies at the start of a screening programme is the prevalent cases of CRC and adenoma in the general population, resulting in an initially higher expected FOBT positivity rate. This rate will drop to the level of incidental cases if population screening is continued at regular intervals and eventually prevalent cases will have all but been identified. The reported positivity rate of 2% is an estimation of the rate after several years of screening. Therefore, sensitivity analysis of the assumptions that have to be made for the increase in necessary capacity for endoscopy range from a slight decrease to an increase of about 75,000. The fact that the Minister of Health could decide on another form of CRC screening than guaiac-based FOBT and the consideration of the implications of recent technical developments such as virtual colonoscopy have not been taken into account. We argue for a gradual and structured implementation of a nationwide FOBT-based CRC screening programme in subjects between 50 and 75 years, tightly linked to research in order to optimise the programme in future and control quality of care and costs.

REFERENCES

1. De Visser M, van Ballegooijen M, Bloemers SM, et al. Report on the Dutch consensus development meeting for implementation and further development of population screening for colorectal cancer based on FOBT. Cell Oncol 2005;27:17-29.
2. Kronborg O, Fenger C, Olsen J, Jorgensen D, Sondergaard O. Randomised study of screening for colorectal cancer with fecal-occult-blood test. Lancet 1996;348:1467-71.
3. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71.
4. Hardcastle J, Chamberlain J, Robinson M, et al. Randomised controlled trial of fecal-occult-blood test. Lancet 1996;348:1472-7.
5. Health Council of the Netherlands. Population screening for colorecal cancer. The Hague: Health Council of the Netherlands, 2001; publication no. 2001/01.
6. Proposal for a Council Recommendation on cancer screening presented by the European Commission, Brussels 5.5.2003. COM(2003) 230 final.
7. Van Ballegooijen M, Habbema JD, Loeve F, et al. Screening for colorectal cancer in the Netherlands: time to start. COCAST report; 2003.
8. Nadere standpuntbepaling bevolkingsonderzoek darmkanker. De Minister van Volksgezondheid, Welzijn en Sport, H. Hoogervorst Kamerstuk 2006, Kenmerk PG/ZP 2.645.183 (no English reference available).
9. Coebergh JW. Challenges and pitfalls of mass-screening in the European union. Eur J Cancer 2000 Aug;36(12):1469-72.
10. De Jong AE, Vasen HF. Frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 2006;64:367-70.
11. Terhaar sive Droste JS, Craanen ME, Kolkman JJ. Dutch endoscopic capacity in the era of colorectal cancer screening. Neth J Med 2006;64:371-3.
12. Hughes K, Leggett B, Del Mar C, et al. Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community. Aust N Z J Public Health 2005;29:358-64.

Netherlands
The Journal of Medicine

REVIEW

Chronic idiopathic thrombocytopenic purpura: present strategy, guidelines and new insights

W. Stevens[1*], H. Koene[2], J.J. Zwaginga[3], G. Vreugdenhil[1]

[1]Department of Internal Medicine, Maxima Medical Centre Veldhoven, PO Box 777, 5500 MB Veldhoven, the Netherlands, [2]Department of Haematology, Academic Medical Centre, Amsterdam, the Netherlands, [3]Department of Immunohaematology and Blood Transfusion, Leiden University Medical Centre, Leiden, the Netherlands, *corresponding author: e-mail: wbc_stevens@hotmail.com

ABSTRACT

Idiopathic thrombocytopenic purpura (ITP) is an immune-mediated thrombocytopenia. The diagnosis is made after exclusion of other secondary causes of thrombocytopenic disorders. The primary treatment goal is to prevent severe bleeding rather than achieve normal platelet counts. In adults ITP usually has an insidious onset and chronic course. Although ITP is a relatively common haematological disorder, there are important unresolved issues in its management, especially for chronic refractory ITP patients. New therapeutic agents have changed strategies for ITP treatment. This article reviews the treatment indications and options of chronic ITP in adults in the literature and compares them with the treatment indications and treatment options used by the Dutch internist.

KEYWORDS

Chronic, idiopathic thrombocytopenic purpura, present strategy, treatment overview

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) was first described by P.G. Werlhof in 1735 as 'Morbus Maculosus Hemorrhagicus.[1] The disease is characterised by premature destruction of autoantibody-coated platelets, causing thrombocytopenia and subsequent mucocutaneous bleeding.

In children the onset is typically abrupt, and the course is usually self-limiting, requiring only supportive management. ITP in adults often has a more persistent course; it may last for many years and is characterised by recurrent relapses, frequently requiring medical intervention.

Since Harrington's studies more than 50 years ago, the pathophysiology of the disease is known to be immune-mediated.[1] Harrington developed severe transient thrombocytopenia after injecting himself with plasma from chronic ITP patients.

ITP is the result of accelerated platelet destruction by the reticuloendothelial system, primarily the spleen.[2,3] Although the main problem in ITP is increased platelet destruction, studies in the 1980s showed that megakaryocyte maturation and platelet production in some chronic ITP patients are also impaired, possibly due to megakaryocyte-reactive autoantibodies.[4] Low platelet counts in ITP patients may therefore be the result of both increased platelet destruction and a decreased platelet production.

ITP remains a diagnosis made after exclusion of other causes of thrombocytopenia (e.g. multisystem autoimmune diseases, lymphoproliferative disease, drug-induced thrombocytopenia, infections, and myelodysplastic syndromes). Although there are techniques available to measure antibodies with glycoprotein IIb/IIIa and Ib/IX, IV and V specificity, both platelet-associated and free in the plasma, the lack of sufficient sensitivity makes them of little diagnostic value.[2,3,5,6] The diagnosis of ITP is based principally on the patient's history, findings during physical examination, complete blood count and peripheral smear, which should exclude other causes of thrombocytopenia (*table 1*).[6-8] Bone marrow examination is recommended in adults with atypical features at diagnosis or in those >60 years and in patients scheduled for splenectomy.

© 2006 Van Zuiden Communications B.V. All rights reserved.

Table 1. *Diagnostic criteria for ITP*

History
Bleeding symptoms (type, severity, and duration of bleeding)
Systemic symptoms (weight loss, fever, headache, and symptoms of autoimmune disorders)
Risk factors for HIV infection
Pregnancy status
Medication (heparin, alcohol, quinine, sulphonamides, aspirin)
Family history
Physical examination
Bleeding signs
Liver, spleen, lymph nodes, and jaundice
Evidence of infection, autoimmune disease, and thrombosis
Isolated thrombocytopenia (low platelet count with an otherwise normal complete blood count and blood smear)
Exclusion of pseudothrombocytopenia (EDTA artefact)
Absence of
Other autoimmune diseases
Disseminated intravascular coagulation
Drug-induced thrombocytopenia
HIV infection
Lymphoproliferative disorders
Myelodysplasia
Agammaglobulinaemia
Allo immune, congenital or hereditary thrombocytopenia

No firm data on incidence and prevalence are available, although ITP seems to be a relatively common haematological disorder. Estimations on incidence for adults in the US and UK are about 60 per million per year.[6] In adults ITP occurs 1.7 times more among women than in men.[9] The median age at presentation is 38 to 49 years and the incidence increases with age.[9,10]

In this review we summarise the treatment strategies for chronic ITP in adults and report the present therapy strategy among Dutch internists.

METHODS

For the literature review, we searched Medline via PubMed using the following criteria: 'autoimmune thrombocytopenic purpura', 'ITP', 'idiopathic thrombocytopenic purpura', 'immune thrombocytopenic purpura', 'ITP + treatment', 'autoimmune thrombocytopenic purpura + treatment', 'ITP + steroid', 'intravenous immunoglobulin + ITP', 'ITP + anti-D'. 'ITP + splenectomy', 'ITP + danazol, 'ITP + vinca alkaloids, 'ITP + cyclophosphamide', 'ITP + cyclosporine', 'ITP + dapsone', 'ITP + Helicobacter pylori', 'ITP + stem cell transplantation', 'ITP + chemotherapy', 'ITP + mycophenolate mofetil' and 'ITP + anti-CD20 antibody'.

RESULTS OF LITERATURE REVIEW

Indications for treatment

Since 21% of ITP patients are asymptomatic at diagnosis, it is important to establish criteria for timing the initial treatment, because of the increased frequency of discovering asymptomatic patients (21% of the ITP patients.[10] In view of the possible adverse effects of treatment, and the unpredictable and frequently transient outcomes, caution is recommended.[11]

Several studies have shown that ITP patients with platelet counts persistently <30 x 10^9/l are at risk of a life-threatening bleed.[10,12]

In general, most doctors decide to start treatment when platelet counts fall below this threshold.[8,13] Starting treatment when platelet counts are between 30 and 50 x 10^9/l may be appropriate in patients at higher risk of haemorrhage due to lifestyle, concomitant medications, hypertension, any scheduled surgery, or head trauma.[14,15]

Emergency treatment

Hospitalisation should be considered for patients with extremely low platelet counts (<5 x 10^9/l) and/or significant bleeding. The main goal is to increase the platelets to safe levels and immediately stop the bleeding. The treatment generally consists of intravenous immunoglobulin (1.0 g/kg/day for two days),[16] prednisone (1.0 g/kg/day iv for three days) or a combination of both.[13] Combination therapy is preferred if a swift increase in platelet count is warranted.[17] In cases of severe haemorrhage, platelet transfusions may be necessary,[6,7] although the survival time of transfused platelets is short.

Initial treatment

Steroids

Oral prednisone is the generally accepted strategy of choice for ITP patients who require treatment. The therapeutic mechanisms of prednisone in ITP are not completely clear. The suggestion is that prednisone impairs the clearance of antibody-coated platelets, increases platelet production by interfering with the platelet destruction of the macrophages within the bone marrow, and stimulates megakaryocyte progenitors.[2,18]

There is a large variability in treatment regimens regarding the dose, the duration of full-dose treatment (two to six weeks) and the mode of tapering. About two-thirds of patients achieve a complete or partial response with prednisone 1 to 2 mg/kg, usually within seven to ten days.[19,20] Treatment is regarded to have failed when patients have not responded within three weeks.[19,20] Most patients relapse when the dose is reduced.[20,21] Around 20 to 40% have a durable remission.[7,13,14] Lower doses of corticosteroids (0.25 to 0.50 mg/kg/day) have been shown to have similar

efficacies to conventional doses (1 mg/kg/day) in adults.[22,23] Shorter courses of corticosteroid therapy have been investigated. Three studies examined the response rate of high-dose dexamethasone (30 to 40 mg/day in courses, four days a month) as first-line treatment.[24-26] The initial response was 80 to 89% with 42 to 59% of patients still in complete remission after a median follow-up of 31 months.[24,26] Initial treatment with high-dose dexamethasone might be safer and seems at least as effective as the conventional prednisone treatment as initial treatment. Despite these studies the optimal dose of therapy is unknown and some patients may be overtreated by aiming at complete remission.

Potential adverse effects of corticosteroids include signs and symptoms of hypercortisolism, diabetes, opportunistic infections and osteoporosis,[7] especially in patients who are ≥60 years, rendering long-term prednisone treatment less attractive.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has been studied primarily in patients who were unresponsive to corticosteroids or who had contraindications to corticosteroids, such as uncontrolled diabetes mellitus. The mechanisms of action of IVIg are complex and not fully understood. Until recently, the effect was thought to be due to interference Fcγ-receptors (FcγR) mediated clearance of opsonised platelets,[27] but recent work has shown that IVIg slows the antibody-coated platelet destruction by increasing the expression of inhibitory FcRγRIIb on splenic macrophages.[28] Other mechanisms include the saturation of FcRn with IVIg, thereby increasing the clearance of autoantibodies.[27]

IVIg (0.4 g/kg/day for five days or 1.0 g/kg/day for two days) is effective in elevating the platelet count in approximately 75 to 92% of the patients.[7,29,30] Complete remission rates vary from 50 to 65%.[29] The responses are generally transient, lasting no more than three to four weeks, after which the platelet counts decrease to pretreatment levels.[7,14,29] The adverse effects of IVIg are generally mild. Approximately half of the patients have headaches, usually during the first infusion, sometimes combined with nausea and vomiting. In rare cases patients experience rigidity, drowsiness or lethargy, fever, photophobia, and painful eye movements.[29,30] Although IVIg is a plasma-derived product that can contain infectious agents, the nanofiltered formulation has proven to be efficacious, well tolerated, and safe.[31] The exact role of IVIg in adults with severe ITP is still controversial, mainly because of the transient effect and high costs. There is general agreement that IVIg should be administered in emergency situations and that it is a safe therapy in preparing patients for surgery.[11,29]

Anti D

Anti-D immunoglobulin is only effective in Rhesus D-positive non-splenectomised patients.[27] There are no extensive studies regarding the mechanism of action of anti-D. A direct interaction with macrophage FcγRs, thereby hampering destruction of platelets, is probably involved and is in agreement with the fact that anti-D is not effective after splenectomy.[27] Another effect might be the increased levels of inflammatory and other cytokines which can be observed immediately after anti-D infusion.[27]

In one study 70% of the adult patients responded to anti-D, and 33% had a complete or partial response.[32] The duration of response is highly variable from days up to several months.[32,33] There are questions regarding the dose: 50 μg/kg is usually sufficient, but 70 to 80 μg/kg could induce a faster response.[34,35] Repeated infusions can be used to maintain adequate platelet counts and such a strategy may enable patients to postpone or even avoid splenectomy.[32,34]

The adverse effects consist of flu-like symptoms such as headache, nausea, chills, fever, and dizziness. The expected extravascular haemolysis is usually mild, with clinically significant drops in haemoglobin levels being rare.[32,36]

Anti-D is an option for children with an acute ITP and elderly patients who are unfit to undergo splenectomy or have severe corticosteroid toxicity.[32] The delayed response of 48 to 72 hours after injection implies that this treatment can not be used in situations when an immediate rise in platelet count is necessary.[6,37]

Second-line treatment

Splenectomy

The first splenectomy for ITP was performed in 1916. Until the introduction of corticosteroids in the 1950s, splenectomy was considered the first-line therapy.[1]

After splenectomy 60 to 86% of patients have a partial or complete response and need no additional treatment.[10,12,38-41] More than 80% of platelet responses occur within several days after splenectomy, responses after ten days being unusual.[7,42] The relapse rate decreases as the interval from the time of splenectomy increases, and relapses after two years are rare.[38,41] Patients refractory after splenectomy should be evaluated for an accessory spleen, which is the case in 11%.[38]

Although the laparoscopic procedure has reduced surgical complications, splenectomy is not without risks. Apart from significant morbidity, perioperative mortality is 0.3 to 0.9%, and the long-term risk of sepsis and thrombosis has been described to be up to 6.3%.[12,38-40,43] Patients who are scheduled to undergo splenectomy should be immunised against streptococcal infections at least two weeks prior to splenectomy. Patients must be informed about the risk of infections with encapsulated micro-organisms and should have emergency antibiotics directly available.

Splenectomy is still regarded as the second-line therapy in refractory disease or corticosteroid dependency (>10 mg/day).[5,7,10,12,35]

Third-line and/or experimental treatment

Patients who do not respond to initial treatment or splenectomy are considered refractory (25 to 30% of the ITP patients).[19,29] These patients constitute a difficult management dilemma.[19] The chances of inducing a durable and sustained remission are low and options for treatment carry relatively high risks of adverse effects.[29]

Before starting the treatment the balance between bleeding risk and the risk of complications due to therapy should be carefully considered. Portielje *et al*. showed that death due to lethal infections, to which immune suppressive therapy probably contributed, exceeded death by bleeding.[10]

Evidence-based guidelines for treating refractory patients are not available, partly because very few patients have severe thrombocytopenia after splenectomy, the follow-up durations are short, the outcomes other than platelet counts are rarely described, and the case series are small and uncontrolled.[13]

Platelet clearance inhibitors

Danazol (200 mg 2-4 times daily), an attenuated androgen, is effective in 50 to 80% of patients,[39,44,45] sometimes inducing durable remissions. Responses occur slowly and therefore treatment should be continued for at least three to six months.[2,46] Older patients appear to respond best.[14,39,44,45] The adverse effects are mostly reversible and include hepatotoxicity (30%), virilisation and amenorrhoea in women, rash and weight gain.[2,39,44]

Vinca alkaloids (vincristine and vinblastine) stimulate thrombocytopoiesis and suppress humoral and cellular immunity. Vinca alkaloids infused intravenously over six to eight hours have a higher sustained response rate.[47] Vincristine is often complicated by substantial neuropathy,[2,14,29] vinblastine with leukopenia. Slowly infused vinca alkaloids have less and mild adverse effects.[47] Vinca alkaloids are used infrequently because response rates are low (<10%), and responding patients return to pretreatment platelet levels within days to weeks after cessation of therapy.[7,12,14]

Immunosuppressive therapy

Cyclophosphamide reduces the number of T and B lymphocytes and suppresses their function. Pulsed therapy with 1.0 to 1.5 g/m^2 at four-week intervals results in a response rate of 85%, with durable responses in up to 50% of patients.[48] Adverse effects, neutropenia, infections and thrombosis, were seen in 22% of the treatment courses.[48] Long-term adverse effects such as secondary malignancies[14,49] and sterility were not seen, although follow-up was short. Due to the possible long-term adverse effects, cyclophosphamide should only be used in severe cases of ITP not responding to other treatment.[50]

Cyclosporine suppresses the T-cell function, inhibits antigen-induced activation of $CD4^+$ T lymphocytes and the production of interleukin 2 and other cytokines.[51,52] Responses are seen in 50 to 55% of the patients, of which 30 to 40% have a complete response.[51,53] The induced response can persist for several months and even years after treatment has been discontinued.[49,51]

The majority of the patients experienced adverse effects, most frequently hypertension, severe muscle pain, increased creatinine, and headache. Up to one third of patients on high doses (5-6 mg/kg/day) discontinued treatment due to the adverse effects.[51] Lower doses (5 mg/kg/day for six days than reduced to 2.5 to 3 mg/kg/day) are generally well tolerated.[53]

Although large studies have not been performed and the toxicity profile is suboptimal, low-dose cyclosporine seems an effective alternative in refractory ITP patients.

Autologous peripheral blood stem cell transplantation (PBSCT) leads to a sustained response in a significant minority of chronic refractory ITP patients. Stem cells can be harvested after high-dose cyclophosphamide[54,55] with G-CSF or with G-CSF alone.[56] Passweg reported a remission in 50% of the patients and a sustained remission in 33%, lasting from seven to more than 48 months.[55,56] The treatment-related mortality is high 17%.[55] Because PBSCT is associated with a high toxicity rate, it might only be an option for patients who have a severe bleeding risk and who have not responded to any other treatment.

Experimental treatment

Experimental treatments are enthusiastically approached by clinicians because of the limitations of conventional therapy options. Most of the experimental agents have been described in case reports and case series.

Dapsone (75-100 mg/day orally) increases platelet counts by an as yet unknown mechanism. Competitive inhibition of the reticuloendothelial system could be one mechanism: dapsone induces haemolysis, phagocytosis of red blood cells might replace the destruction of antibody-coated platelets.[57] Dapsone has been shown to produce a partial or complete response in 40 to 50% of patients.[57-60] It seems less effective in patients with severe ITP. Adverse effects include cyanosis and methaemoglobinaemia, haemolysis, rash, nausea, vomiting, and headache.[57-60] The decrease in the haemoglobin level due to haemolysis is not correlated with the platelet count increase.[59] Treatment with dapsone can reduce the need for steroids in some patients.[60] Dapsone is well-tolerated and inexpensive, but most of the patients relapse when treatment is withdrawn. Removal of the spleen is superior to dapsone, but for patients unfit to undergo splenectomy it could be of value.

Helicobacter pylori (H. pylori) eradication therapy as treatment of ITP has primarily been described in Japanese and Italian studies.[61-65] Their clinical observations suggest that *H. pylori* could be involved in the pathogenesis of chronic ITP. The mechanisms responsible for the trigger of antiplatelet autoantibody production are unknown. *H. pylori* infection is seen in 43 to 75% of the ITP patients, the prevalence depending on the prevalence of *H. pylori* in the healthy population of the country in question.[61,63,64] The eradication treatment is effective in 84 to 100% of the infected chronic ITP patients.[61,63] Of the *H. pylori*-eradicated ITP patients 25 to 46% had a complete remission and 8 to 44% had a partial remission.[61,64,65] Predictive factors for response are high initial platelet count, short duration of illness and treatment in Italy or Japan. Although the evidence and follow-up are limited, treatment is simple, inexpensive, has limited toxicity and the advantage of avoiding long-term immunosuppressive treatment for those who respond. For severe ITP, with platelet levels <30, eradication therapy seems to be less effective. Investigation and eradication of *H. pylori* infection in chronic ITP patients with platelets count >30 might therefore be worthwhile.

Combination chemotherapy (cyclophosphamide, vincristine, prednisone, and procarbazine (CHOPP), cyclophosphamide, vincristine, etoposide (CEP), cyclophosphamide, vincristine, and prednisone (CVP)) was reported in 1993 by Figueroa *et al*. Six out of ten chronic refractory ITP patients, previously treated with at least steroids and splenectomy, had a complete response, four of which were durable after combination chemotherapy.[66] Another two patients had a partial response with one durable response and two of the ten patients died of intracerebral haemorrhage. The number of treated patients is small. The risk of inducing secondary malignancies and other toxicity should be carefully considered. Combination chemotherapy can prove to be a two-edged sword in treating patients who suffer from ITP in the context of a lymphoreticular malignancy.

Mycophenolate mofetil (MMF) is an immunsuppressive drug which is licensed for the prevention of acute rejection of allergenic organ transplants and haemopoietic stem cell transplantation. Additionally, it is used as second-line treatment in several autoimmune diseases.[67] Studies showed that MMF (1.5 to 2 g/d orally) results in response rates of 55 to 80% with 24 to 33% complete responses, lasting from two to more than 13 months.[67,68] The adverse effects were mild and reversible (nausea, diarrhoea, headache, and backache).[68] MMF merits further investigation to fully assess its efficacy and safety as a second-line treatment in refractory ITP patients.

Anti-CD20 monoclonal antibody (Rituximab) was originally used in patients with relapsed, low-grade B-cell non-Hodgkin's lymphoma and has obtained a central role in the treatment of B-cell malignancies. It binds specifically to CD20 antigen present on B-cells. *In vitro* studies have demonstrated induction of complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and apoptosis of the B cell. In ITP, B-cell depletion results in decreased autoantibody production.[69] After one infusion of rituximab, B-cells remain undetectable for four to nine months.[70] When used in ITP patients, rituximab has a response rate of 25 to 75%, with 25 to 50% being partial or complete remissions.[70-73] Remissions seem to be longer in patients who achieve a complete response and have been reported to last for up to three years.[72,73] Most patients respond quickly, within one to three weeks, but a minority of patients have a delayed response, nine to eleven weeks after treatment is started.[71,73,74] The mechanisms of action of the two types of response are unclear. The fast response may partly be due to a mechanism of Fc-receptor saturation by opsonised CD20-positive cells.[71,73] The delayed and maintained response is probably due to the B-cell depletion and its potential interference with the autoantibody production.[71,73] The great advantage is the lack of toxicity. Most studies describe minor toxicity such as grade 1 to 2 infusion reactions but delayed onset of neutropenia has also been described.[70,71,73-77] Recently, reactivation of hepatitis B virus (HBV) during rituximab therapy for chronic lymphocytic leukaemia was reported.[78] Rituximab seems to be a very promising treatment option for refractory ITP patients and is nowadays considered and investigated as a possible second-line therapy before splenectomy. The HOVON is investigating the possible place of rituximab in the treatment of chronic ITP in the Netherlands.

THERAPEUTIC STRATEGIES IN THE NETHERLANDS

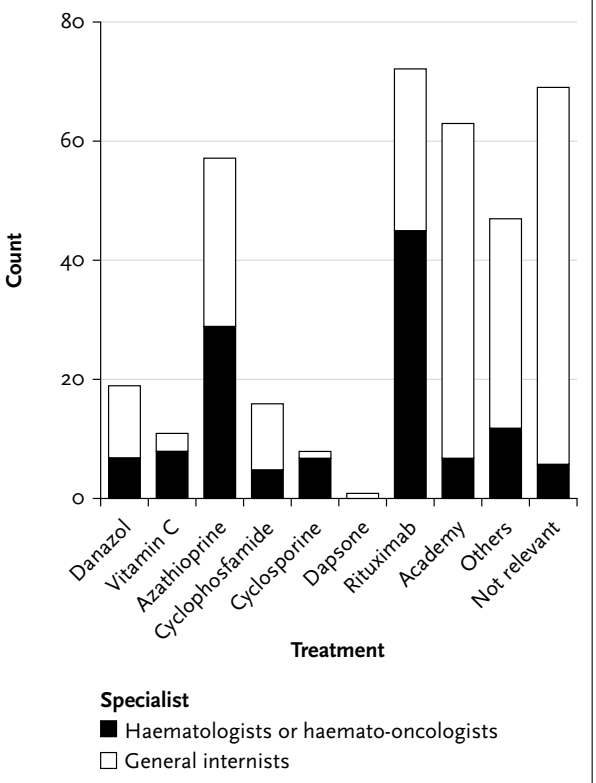
To examine which strategies are currently being used for the treatment of ITP, we contacted all registered internists in the Netherlands. In January 2005 we sent a simple and short questionnaire to all Dutch internists. Questions involved treatment indications, first- and second-line therapy preferences, as well as therapy preferences for refractory ITP. The collected data were analysed using SPSS-12.01.

The questionnaire was sent to 1542 Dutch internal medicine physicians, 388 (25%) of whom responded. Of the 388 respondents, 25 (6%) were no longer in practice, 105 (27%) were haematologists or haemato-oncologists, and 258 (66%) were general internists. Of the returned inquiries 363/388 (94%) were analysed.

Platelet counts <30 x 10^9/l are regarded as a treatment indication by 70% of the haematologists or haemato-oncologists and 52% of general internists. The other 30% of the haematologists or haemato-oncologists start treatment when platelet count is <50 x 10^9/l, or if there is

diathesis, or a combination of diathesis with low platelet count (*table 2*). Almost one third of the general internists refer ITP patients to a haematologist for treatment.
A majority of internists prescribe prednisolone 1 mg/kg/day for three weeks as the first-line therapy (232/363, 64%). The remaining internists use other steroid regimes such as dexamethasone 40 mg/day for four days or methylprednisone 500 mg for three days (*table 3*).
Splenectomy is regarded to be second-line therapy by 44%, while 105/363 (29%) use steroids for refractory or relapse ITP, and 27% use an other treatment (*table 4*).
Rituximab (72/363 (20%)) is the mostly commonly used treatment for refractory ITP patients after they have had a splenectomy and 57/363 (16%) use azathioprine. All the other treatments are used less frequently (*figure 1*). General internists referred 58/258 (22%) of the refractory ITP patients to a university hospital.

Figure 1. *Treatment options for chronic refractory ITP patients used by a number of haemotologists and haemato-oncologists versus general internists*



CONCLUSIONS

Although specific autoantibody tests are available, ITP remains a diagnosis of exclusion. The risk of severe bleeding is low, treatment is generally not indicated until platelet levels drop below 30 x 10^9/l. First-line treatment options remain corticosteroids and splenectomy.
Although a randomised comparison with other first-line treatments has not been performed, short courses of high-dose dexamethasone seem to be at least as effective and might avoid long-term maintenance therapy with low-dose corticosteroids.

Table 2. *Treatment indication according to speciality*

Specialist	Indication for treatment					
	Platelet count					
	<10	<20	<30	<50	Diathesis	Others
Haematologist or haemato-oncologist	4	29	40	10	5	17
General internists	25	67	43	29	20	74
Total	*29*	*96*	*83*	*39*	*25*	*91*

Table 3. *First-line treatment*

Specialist	Prednisone 20 mg	Prednisone 1 mg/kg per day for 3 weeks	Dexamethasone 40 mg per day for 4 days	Methylprednisone 500 mg for 3 days	Others
Haematologist or haemato-oncologist	2	77	8	13	5
General internists	12	155	10	17	64
Total	*14*	*232*	*18*	*30*	*69*

Table 4. *Treatment of refractory or relapses of idiopathic thrombocytopenic purpura*

Specialist	Steroids again	Splenectomy	Others
Haematologist or haemato-oncologist	25	73	7
General internists	80	87	91
Total	*105*	*160*	*98*

Splenectomy is still the most effective option for patients who are refractory or have a relapse after corticosteroids, but other treatments are emerging. Most third-line options are more or less experimental, with many adverse effects and limited or poorly studied therapeutic value. Low-dose cyclosporine seems an effective alternative in refractory patients. *H. pylori* eradication has the advantage of possibly avoiding long-term immune suppression for those who achieve a remission. Rituximab has also proven to be effective with few adverse effects, although large trials are lacking. Azathioprine and rituximab are used most frequently in the Netherlands as third-line treatment. Given the low rate of adverse events, rituximab seems an attractive, albeit expensive, alternative for splenectomy. The HOVON has opened a prospective, randomised phase II trial, the HOVON 64, exploring the role of different doses of rituximab in the treatment of refractory ITP.

REFERENCES

1. Imbach P, Kühne T, Signer E. Historical aspects and present knowledge of idiopathic thrombocytopenic purpura. Br J Haematol 2002;119:894-900.
2. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med 2002;346:995-1008.
3. McMillan R. The pathogenesis of chronic immune (idiopathic) thrombocytopenic purpura. Semin Hematol 2000; 37(suppl 1):5-9.
4. McMillan R, Wang L, Tomer A, Nichol J, Pistollo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. Blood 2004;103:1364-9.
5. Bussel JB, Graziano JN, Kimberly RP, Pahwa S, Aledort LM. Intravenous anti-D treatment of immune thrombocytopenic purpura: analysis of efficacy, toxicity, and mechanism of effect. Blood 1991;77:1884-93.
6. British Committee for Standards in Haematology General Haematology Task Force. Guidelines in the investigation and management of idiopathic thrombocytopenic purpura in adults, children an in pregnancy. Br J Haematol 2003;120:574-96.
7. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3-40.
8. Diagnosis and treatment of idiopathic thrombocytopenic purpura: recommendations of the American Society of Hematology. Ann Intern Med 1997;126:319-26.
9. Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. Blood 1999;94:909-13.
10. Portielje JEA, Westendorp RGJ, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood 2001;97:2549-54.
11. Provan D, Newland A. Fifty years of idiopathic thrombocytopenic purpura (ITP): management of refractory ITP in adults. Br J Haematol 2002;118:933-44.
12. Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med 2000;160:1630-8.
13. Blanchette V, Freedman J, Garvey B. Management of chronic immune thrombocytopenic purpura in children and adults. Semin Hematol 1998;35(suppl 1):36-51.
14. Rodeghiero F. Idiopathic thrombocytopenic purpura: an old disease revisited in the era of evidence-based medicine. Haematologica 2003;88:1081-7.
15. Mead AJ. Newland AC, Provan D. Adult idiopathic thrombocytopenic purpura. Hematol 2003;8:345-57.
16. Godeau B, Lesage S, Divine M, Wirquin V, Farcet JP, Bierling P. Treatment of adult chronic autoimmune thrombocytopenic purpura with repeated high-dose intravenous immunoglobulin. Blood 1993;82:1415-21.
17. Vesely SK, Perdue JJ, Rizvi MA, Terrell DR, George JN. Management of adult patients with persistent idiopathic thrombocytopenic purpura following splenectomy. Ann Int Med 2004;140:112-24.
18. Gernsheimer T, Stratton J, Ballem PJ, Slichter SJ. Mechanisms of response to treatment in autoimmune thrombocytopenic purpura. N Engl J Med 1989;320:974-80.
19. McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. Ann Intern Med 1997;136:307-14.
20. George JN, El-Harake MA, Raskob GE. Chronic idiopathic thrombocytopenic purpura. N Engl J Med 1994;331:1207-11.
21. George JN. Idiopathic thrombocytopenic purpura in adults: current issues for pathogenesis, diagnosis and management. Hematol J 2004;5(suppl 3):S12-14.
22. Bellucci S, Charpark Y, Chastang C, Tobelem G. Low doses v conventional doses of corticoids in immune thrombocytopenic purpura (ITP): results of a randomized clinical trial in 160 children, 223 adults. Blood 1988;71:1165-9.
23. Ohmine K, Izumi T, Muroi K, et al. Low-dose prednisolone therapy for idiopathic thrombocytopenic purpura, Rinsho Ketsueki 2000 jan;41:8-11.
24. Cheng Y, Wong RS, Soo YO, Chui CH, Lau FY, Chou NP. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. N Engl J Med 2003;349:831-6.
25. Alpdogan O, Budak-AldoGan T, Ratip S, et al. Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with idiopathic thrombocytopenic purpura. Br J Haemat 1998;103:1961-3.
26. Borst F, Keuning JJ, van Hylsteijn H, Sinnige H, Vreugendil G. High-dose dexamethasone as a first- and second-line treatment of idiopathic thrombocytopenic purpura in adults. Ann Hematol 2004;83:764-8.
27. Cooper N, Heddle NM, Haas de M, et al. Intravenous (IV) anti-D and IV immunoglobulin achieve acute platelet increases by different mechanisms: modulation of cytokine and platelet responses to IV anti-D by FcγRIIa and FcγRIIIa polymorphisms. Br J Haematol 2004;124:511-8.
28. Ravetch JV. A full complement of receptors in immune complex diseases. J Clin Invest 2002 Dec;110:1759-61.
29. Stasi R, Provan D. Management of immune thrombocytopenic purpura in adults. Mayo Clin Proc 2004;79:504-22.
30. Colovic M, Dimitrijevic M, Sonnenberg C, Suvajdzic N, Donfrid M, Bogdanovic A. Clinical efficacy and safety of a novel intravenous immunoglobulin preparation in adult chronic ITP. Hematol J 2003;4:358-62.
31. Wolf HH, Davies SV, Borte M, Caulier MT, Williams PE, Burnuth HV. Efficacy, tolerability, safety and pharmacokinetics of a nanofiltered intravenous immunglobine: studies in patients with immune thrombocytopenic purpura and primary immunodeficiencies. Vox Sanguinis 2003;84:45-53.
32. Scaradavou A, Woo B, Woloski BMR, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. Blood 1997;89:2689-700.
33. Bussel JB, Graziano JN, Kimberly RP, Pahwa S, Aledort LM. Anti-D Ig for treatment of immune thrombocytopenic purpura. Blood 1991;78:3157-8.
34. Bussel JB. Recent advance in the treatment of idiopathic thrombocytopenic purpura: the anti-D clinical experience. Semin Hematol 1998;35:1-4.
35. Newman GC, Novoa MV, Fodero EM, Lesser ML, Woloski BM, Bussel JB. A dose of 75 μg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 μg/kg/d in adults with immune thrombocytopenic purpura. Br J Haematol 2001;112:1076-8.

36. Tarantino MD, Buchanan G. The pros and cons of drug therapy for immune thrombocytopenic purpura in children. Hematol Oncol Clin N A 2004;18:1301-14.

37. Scaradavou A, Bussel JB. Clinical experience with anti-D in the treatment of idiopathic thrombocytopenic purpura. Semin Hematol 1998;35:52-7.

38. Schwartz J, Leber MD, Gillis S, Giunta A, Eldor A, Bussel JB. Long term follow-up after splenectomy for immune thrombocytopenic purpura (ITP). Am J Hematol 2003;72:94-8.

39. Andrès E, Zimmer J, Noel E, Kaltenbach G, Koumarianou A, Malaisel F. Idiopathic thrombocytopenic purpura: a retrospective analysis in 139 patients of the influence of age on the response to corticosteroids, splenectomy and danazol. Drugs Aging 2003;20:841-6.

40. Vianelli N, Galli M, Vivo de A, et al. Efficacy and safety of splenectomy in immune thrombocytopenic purpura : long-term results of 402 cases. Haematologica 2005;90:72-7.

41. Bourgeois E, Caulier MT, Delarozee C, Brouillard M, Bauters F, Fenaux P. Long-term follow-up of chronic autoimmune thrombocytopenic purpura refractory to splenectomy: a prospective analysis. Br J Haematol 2003;120:1079-88.

42. Karpatkin S. Autoimmune (idiopathic) thrombocytopenic purpura. Lancet 1997;349:1531-6.

43. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood 2004;104:2623-34.

44. Maloisel F, Andrès E, Zimmer J, et al. Danazol therapy in patients with chronic idiopathic thrombocytopenic purpura: long-term results. Am J Med 2004;116:590-5.

45. Ahn YS, Rocha R, Mylvaganam R, Garcia R, Duncan R, Harrington WJ. Long-term danazol therapy in autoimmune thrombocytopenia: unmaintained remission and age-dependent response in women. Ann Int Med 1989;111:723-9.

46. Cines DB, Bussel JB, McMillan RB, Zehnder JL. Congenital and acquired thrombocytopenia. Hematology (Am Soc Hematol Educ Program) 2004;390-406.

47. Ahn YS, Harrington WJ, Mylvaganam R, Allen LM, Pall LM. Slow infusion of vinca alkaloids in the treatment of idiopathic thrombocytopenic purpura. Ann Int Med 1984;100(2):192-6.

48. Reiner A, Gernsheimer T, Slichter SJ. Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. Blood 1995;85:351-8.

49. George JN, Kojouri K, Perdue JJ, Vesely SK. Management of patients with chronic, refractory idiopathic thrombocytopenic purpura. Semin Hematol 2000;37:290-8.

50. Reid DM, Shulman NR. Pulse cyclophosphamide to treat idiopathic thrombocytopenic purpura. Blood 1995;86:414-5.

51. Kappers-Klunne MC, van het Veer B. Cyclosporin A for the treatment of patients with chronic idiopathic thrombocytopenic purpura refractory to corticosteroids or splenectomy. Br J Haematol 2001;114:212-5.

52. Perrota S, Amendola G, Locatelli F, et al. Treatment with short-term, high-dose cyclosporine A in children with refractory chronic idiopathic thrombocytopenic purpura. Br J Haematol 2003;121:143-7.

53. Emilia G, Morselli M, Luppi M, et al. Long-term salvage therapy with cyclosporine-A in refractory idiopathic thrombocytopenic purpura. Blood 2002;99:1482-5.

54. Skoda RC, Tichelli A, Tyndall A, Hoffmann T, Gillessen S, Gratwohl A. Autologous peripheral blood stem cell transplantation in a patient with chronic autoimmune thrombopenia. Br J Haematol 1997;99(1):56-7.

55. Lim SH, Kell J, al-Sabah A, Bashi W, Bailey-Wood R. Peripheral blood stem-cell transplantation for refractory autoimmune thrombocytopenic purpura. Lancet 1997;349:475.

56. Passweg JR, Rabusin M, Musso M, et al. Haematopoietic stem cell transplantation for refractory autoimmune cytopenia. Br J Haematol 2004;125:749-55.

57. Godeau B, Durand JM, Roudot-Thoraval F, et al. Dapsone for chronic autoimmune thrombocytopenic purpura: a report of 66 cases. Br J Haematol 1997;97:336-9.

58. Godeau B, Oksenhendler E, Bierling P. Dapsone for autoimmune thrombocytopenic purpura. Am J Hematol 1993;44(1):70-2.

59. Hernández F, Linares M, Colomina P, et al. Dapsone for refractory chronic idiopathic thrombocytopenic purpura. Br J Haematol 1995;90(2):473-5.

60. Radaelli F, Calori R, Goldaniga M, Guggiari E, Luciano A. Adult refractory chronic idiopathic thrombocytopenic purpura: can dapsone be proposed as second-line therapy? Br J Haematol 1999;104(3):614-22.

61. Kohda K, Kuga T, Kogawa K, et al. Effect of Helicobacter pylori eradication on platelet recovery in Japanese patients with chronic idiopathic thrombocytopenic purpura and secondary autoimmune thrombocytopenic purpura. Br J Haematol 2002;118:584-8.

62. Franchini M, Veneri D. Helicobacter pylori infection and immune thrombocytopenic purpura. J Hematol 2003;88:1087-91.

63. Takahashi T, Yujiri T, Shinohara K, et al. Molecular mimicry of Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori-associated chronic idiopathic thrombocytopenic purpura. Br J Haematol 2004;124:91-6.

64. Emilia G, Longo G, Luppi M, et al. Helicobacter pylori eradication can induce platelet recovery in idiopathic thrombocytopenic purpura. Blood 2001;97:812-4.

65. Sato R, Murakami K, Watanabe K, et al. Effect of Helicobacter pylori eradication on platelet recovery in patients with chronic idiopathic thrombocytopenic purpura. Arch Intern Med 2004;164:1904-7.

66. Figueroa M, Gehlsen J, Hammond D, et al. Combination chemotherapy in refractory immune thrombocytopenic purpura. N Engl J Med 1993;328:1226-9.

67. Howard J, Hoffbrand AV, Prentice HG, Mehta A. Mycophenolate mofetil for the treatment of refractory auto-immune haemolytic anaemia and auto-immune thrombocytopenia purpura. Br J Haematol 2002;117:712-5.

68. Hou M, Peng J, Shi Y, et al. Mycophenolate mofetil (MMF) for the treatment of steroid-resistant idiopathic thrombocytopenic purpura. Eur J Haematol 2003;70:353-7.

69. Koulova L, Alexandrescu D, Dutcher JP, O'Boyle KP, Eapen S, Wiernik PH. Rituximab for the treatment of refractory idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP): report of three cases. Am J Hematol 2005;78:49-54.

70. Giagounidis AA, Anhuf J, Schneider P, et al. Treatment of relapsed idiopathic thrombocytopenic purpura with the anti-CD20 monoclonal antibody rituximab: a pilot study. Eur J Haematol 2002;69:95-100.

71. Zaja F, Vianelli N, Sperotto A, et al. The B-cell compartment as the selective target for the treatment of immune thrombopenias. Haematology 2003;88:538-46.

72. Shanafelt TD, Madueme HL, Wolf RC, Tefferi A. Rituximab for immune cytopenia in adults: idiopathic thrombocytopenic purpura, autoimmune haemolytic anemia, and Evans syndrome. Mayo Clin Proc 2003;78:1340-6.

73. Cooper N, Stasi R, Cunningham-Rundles S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. Br J Haematol 2004;125:232-9.

74. Stasi R, Stipa E, Forte V, Meo P, Amadori S. Variable patterns of response to rituximab treatment in adults with chronic idiopathic thrombocytopenic purpura. Blood 2002;99:3872-3.

75. Stasi R, Pafano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. Blood 2001;98:952-7.

76. Zaja F, Iacona I, Masoline P, et al. B-cell depletion with rituximab as treatment for immune haemolytic anemia and chronic thrombocytopenia. Haematol 2002;87:189-95.

77. Chaiwatanatorn K, Lee N, Grigg A, Filshie R, Firkin F. Delayed-onset neutropenia associated with rituximab therapy. Br J Haematol 2003;121:913-8.

78. Sarrecchia C, Cappelli A, Aiello P. HBV reactivation with fatal fulminating hepatitis during rituximab treatment in a subject negative for HBsAg and positive for HBsAb and HBcAb. J Infect Chemother 2005;11:189-91.

Netherlands
The Journal of Medicine

REVIEW

The consequences of lost gallstones during laparoscopic cholecystectomy

R.J.L.F. Loffeld

Department of Internal Medicine, Zaans Medical Centre, Zaandam, the Netherlands,
tel.: +31 (0)75-650 27 79, fax: +31 (0)75-650 23 79, e-mail: r.loffeld@chello.nl

ABSTRACT

Laparoscopic cholecystectomy has become the preferred surgical technique for symptomatic gallstone disease. The technique generally is safe. Probably one of the most common intra-operative complications is gallbladder perforation with stones spreading into the peritoneal cavity. In this paper the sequelae of lost gallstones after laparoscopic cholecystectomy and the diagnostic problems facing the clinician are reviewed. Abscesses and fistula formation in the abdominal wall occur. A long delay can be present between the initial operation and the complications of the lost stones. Although rupture of the gallbladder is usually noticed during preparation and retrieval, the surgeon may not be aware of losing stones. Due to the long delay, the occurrence of intra-abdominal abscesses and fistula is often not linked to the prior procedure.

KEYWORDS

Abscess, cholecystectomy, complication, fistula, laparoscopic lost gallstones

INTRODUCTION

Laparoscopic cholecystectomy has become the preferred surgical technique for symptomatic gallstone disease. In experienced hands it is a safe procedure with low morbidity and mortality. However, complications do occur. Well-known are leakage from the cystic duct, injury to the major bile duct with the occurrence of bilomas, retained stones in the common bile duct and perforation of the gallbladder.[1] Probably one of the most common intra-operative complications is gallbladder perforation with stones spreading into the peritoneal cavity.[2] The sequelae of lost gallstones after laparoscopic cholecystectomy and the occurring complications may go unnoticed for a long time and can be a diagnostic challenge.

PATHOLOGY OF LOST GALLSTONES

In the beginning of the era of laparoscopic cholecystectomy, retained stones in the peritoneal cavity were considered harmless. Animal models even suggested that loss of stones did not pose a clinically important problem.[3] No deleterious effects could be demonstrated and, hence, there was no indication for retrieval of lost stones.[4] On the other hand gallstones, whether or not contaminated by bacteria, led to formation of abscesses and adhesions in a mouse model.[5] Placing a gallstone in the peritoneal cavity together with bile and a culture of *E. coli* led to the formation of abscesses in 8 out of 40 mice. In control experiments abscess formation did not occur, even though inoculation with *E. coli* was also used in the control animals. In another experiment, gallstones were placed in the peritoneal cavity of rats, together with either saline and sterile or infected bile. In the control experiment, animals received an injection with saline, or sterile or infected bile, but without insertion of a gallstone. Only the group in which a gallstone with bile (sterile or infected) was inserted developed adhesions and intra-abdominal abscesses.[6] Contrary to this finding is the experiment in which only gallstones were placed in the abdomen. No adhesions nor formation of abscesses were noted during a follow-up of one year.[7] From these experiments it is clear that the combination of bile and stones can lead to deleterious effects. Sterile pigment concrements lead to mesenchymal reactions such as granulomas, whereas contaminated stones, especially with gram-negative bacteria, lead to abscess formation.[8] The gallstones behave like foreign bodies.

THE CONSEQUENCES OF LOST GALLSTONES

Lost stones can be the source of potentially serious complications.[9] There are not many data on the occurrence of spilled gallstones in the literature. It is thought to occur in approximately 40% of laparoscopic cholecystectomies.[10]

© 2006 Van Zuiden Communications B.V. All rights reserved.

However, lower numbers have been reported. Perforation of the gallbladder is reported in 10 to 32% of cases.[11]

In a published large analysis of laparoscopic cholecystectomies performed in many clinics, gallbladder perforation (20%) and stone spillage (9%) were the two most common complications. Stone spillage mainly occurred during the dissection (75%) and removal (25%) of the gallbladder. Predisposing factors for developing complications after stone spillage were older age, male sex, acute cholecystitis, spillage of pigment stones, number of stones (>15) or size of the stone (diameter >1.5 cm), and perihepatic localisation of lost stones.[12] In a study of more than 3500 laparoscopic cholecystectomies carried out in one centre, perforation of the gallbladder occurred in 17%. In 254 cases (7%) spillage of stones occurred. In the majority of cases, the stones could be retrieved.[13] In 40 cases it was not possible to retrieve the stones. Twelve of these patients developed complications: abdominal abscesses (n=4), intestinal obstruction (n=1), paraumbilical tumour (n=1), and stones in the port site (n=6).[14]

A specific risk factor for spilling stones and bile is rupture of the gallbladder during retrieval via the umbilical port. Due to the very small incision in the abdominal wall, retrieving the gallbladder can be problematic. This is especially true if the gallbladder contains large stones.

The problems occurring after lost gallstones can occur a long time after surgery.[15] The interval is reported to range from 4 days to 29 months.[9] But problems may occur many years after the operation.[16] More than 80 cases of gallstone-related complications after laparoscopic cholecystectomy have been reported.[9] Some of them are noted in *table 1*. Among the complications are transabdominal fistula and intra-abdominal abscesses.[9] Retained stones have been described to form fistula towards the colon[17] or urinary bladder.[11,18] Even pleural empyema has been reported.[19] The most prevalent form is a transabdominal fistula through the umbilical canal. Also cholelithiasis of the ovary after loss of gallstones has been reported.[20]

Recently three patients were seen in our clinic with abscesses and fistula occurring seven weeks to almost ten years after laparoscopic cholecystectomy. All three patients underwent an endoscopic retrograde cholangiogram with papillotomy, because of stones in the common bile duct, prior to the operation. Only in one case was the surgeon aware of rupture of the gallbladder, in one case the pathologist noted a small hole in the fundus of the gallbladder, in the third patient the removed gallbladder was entirely intact. The surgeon is usually aware of rupture of the gallbladder during retrieval or preparation. All three patients developed abscesses or fistula in the vicinity of the umbilical port. The gallbladder usually ruptures in the umbilical canal during retrieval. In 30%, stones can be found in the port sites.[13] One of our patients also developed a fistula in a trocart port on the right side of the abdomen.

The long delay is clearly demonstrated in the literature. Either the surgeon is not aware of losing stones or he thinks he retrieved all lost stones. Because of the long delay between the initial operation and the presentation with the abscesses or fistula, gallstones are not considered in the differential diagnosis of abdominal complaints. This is the reason for considerable diagnostic delay. Abscesses can be easily detected with ultrasound examination of the abdomen or computer tomography scanning. Gallstones are not always detected in the fistula or abscess. In one of our own cases both diagnostic modalities failed to detect gallstones as being responsible for abscesses and fistula formation.

Table 1. *Reported cases of lost gall stones in the literature*

Author	Number	Time after laparoscopic cholecystectomy	Complication
Botterill[16]	1	2-5 years	Abscesses
Van Hoecke[15]	1	5 years	Fistula
Weiler[22]	1	Immediately	Fistula
Daoud[17]	1	7 months	Fistula
Castro[11]	1	2-11 months	Fistula
Lutken[18]	1	9 months	Fistula
Patterson[21]	1	14 months	Abscess and fistula
Memon[10]	1	8 months	Fistula
Willekes[19]	1	17 months	Empyema
Catarci[2]	1	3 months	Fistula
Whiting[23]	1	12 months	Abscess
Vadlamidi[24]	1	20 months	Abscess
Lauffer[25]	1	3 months	Abscess
McDonald[26]	6	Immediately-18 months	Abscess and fistula
Groebli[27]	2	15 months/24 months	Abscess/abscess
Van der Lugt[28]	2	15 months/38 months	Abscess/abscess
Zaans Medical Centre	3	7 weeks-7 months/24 months/10 years	Fistula/abscess/fistula

If gallstone loss occurs, all efforts should be made to retrieve the lost stones.[21] Whether loss of stones is a reason for conversion to a open procedure is not clear. Lost stones can be collected laparoscopically. When numerous or large pigment stones are lost, which cannot be retrieved by laparoscopy, intraoperative conversion to open surgery can be justified.[12] As soon as the gallbladder is dissected off the liver it should be placed in a specimen bag in order to prevent spilling of stones while removing the gallbladder via the umbilical port opening. The risk for rupture depends on whether the gallbladder is inflamed or not. Gallbladder perforation is more frequent in acute cholecystitis.[14] Peroperative perforation of the gallbladder seems to carry no morbidity, provided a total and complete recovery of the lost stones and local treatment of bile contamination with local irrigation is carried out.[14] Our own patients started with complicated gallstone disease. Whether this poses an extra risk factor for losing stones is not obvious. However, two patients developed subhepatic abscesses immediately after the operation.

The surgeon should always be aware of the consequences of lost stones. The occurrence of an abscess or fistula in the abdominal wall in a patient who has undergone a laparoscopic cholecystectomy in the past, even if the operation was performed many years ago, should lead to the differential diagnosis of lost stones even if rupture of the gallbladder was not obvious during the operation.

REFERENCES

1. Soper NJ, Flye MW, Brunt LM, et al. G. Diagnosis and management of biliary complications of laparoscopic cholecystectomy. Am J Surg 1993;165:663-9.
2. Catarci M, Zaraca F, Scaccia M, Carboni M. Lost intraperitoneal stones after laparoscopic cholecystectomy: harmless sequela or reason for reoperation. Surg Laparosc Endosc 1993;3:318-22.
3. Clinc RW, Poulos E, Clifford EJ. An assessment of potential complications cause by intraperitoneal gallstones. Am Surg 1994;60:303-5.
4. Welch N, Hinder RA, Fitzgibons RJ Jr, Rouse JW. Gallstones in the peritoneal cavity. A clinical and experimental study. Surg Laparosc Endosc1991;1:246-7.
5. Agalar F, Sayek L, Agalar C, Cakmakci M, Hayran M, Kavuklu B. Factors that may increase morbidity in a model of intra-abdominal contamination by gallstones lost in the peritoneal cavity. Eur J Surg 1997;163:909-14.
6. Johnston S, O'Malley K, McEntee G, Grace P, Smyth E, Bouchier-Hayes D. The need to retrieve the dropped stone during laparoscopic cholecystectomy. Am J Surg 1994;167:608-10.
7. Zisman A, Loshkov G, Negri M, Herbert M, Halpern Z, Lin G, Halevy A. The fate of long-standing intraperitoneal gallstone in the rat. Surg Endosc 1995;9:509-11.
8. Hornof R, Pernegger C, Wenzl S, et al. Intraperitoneal cholelithiasis after laparoscopic cholecystectomy – behavior of "lost" concrements and their role in abscess formation. Eur Surg Res 1996;28:179-89.
9. Gretschel S, Engelmann C, Estevez-Schwarz L, Schlag PM. Wolf in sheep's clothing: spilled gallstones can cause severe complications after endoscopic surgery. Surg Endosc 2001;15:98
10. Memon MA, Jenkins HJ Jr, Fitzgibbons RJ Jr. Spontaneous erosion of a lost intra-abdominal gallstone through the back eight months following laparoscopic cholecystectomy. JSLS 1997;1:153-7.
11. Castro MG, Alves AS, Oliveira CA, Vieira Junior A, Vianna JL, Costa RF. Elimination of biliary stones through the urinary tract: a complication of the laparoscopic cholecystectomy. Rev Hosp Clin Fac Sao Paulo 1999;54:209-12.
12. Brockmann JG, Kocher T, Senninger NJ, Schurman GM. Complications due to gallstones lost during laparoscopic cholecystectomy. Surg Endosc 2002;16:1226-32.
13. Diez J, Arozamena C, Gutierrez L, Bracco J, Mon A, Sanchez Almeyra R, Secchi M. Lost stones during laparoscopic cholecystectomy. HPB Surg 1998;11:105-8.
14. Barrat C, Champault A, Matthyssens L, Champault G. Iatrogenic perforation of the gallbladder during laparoscopic cholecystectomy does not influence the prognosis. Prospective study. Ann Chir 2004;129:25-9.
15. Van Hoecke M, Lissens P, Vuylsteke M, Verdonk R. Lost gallstones: a relaparoscopic solution to laparoscopic pollution. Acta Chir Belg 2004;104:104-6.
16. Botterill ID, Davides D, Vezakis A, McMahon MJ. Recurrent septic episodes, following gallstone spillage at laparoscopic cholecystectomy. Surg Endosc 2001;15:897.
17. Daoud F, Awwad ZM, Masad J. Colovesical fistula due to a lost gallstone following laparoscopic cholecystectomy: report of a case. Surg Today 2001;31:255-7.
18. Lutken W, Berggren P, Maltback J. Passing of gallstones via the urethra: a complication of laparoscopic cholecystectomy. Surg Laparosc Endosc 1997;7:495-7.
19. Willekes CL, Widmann WD. Empyema from lost gallstones: a thoracic complication of laparoscopic cholecystectomy. J Laparoendosc Surg 1996;6:123-6.
20. Tursi JP, Reddy UM, Huggins G. Cholelithiasis of the ovary. Obstet Gynecol 1993;82:653-4.
21. Patterson EJ, Nagy AG. Don't cry over spilled stones? Complications of gallstones spilled during laparoscopic cholecystectomy: case report and literature review. Can J Surg 1997;40:300-4.
22. Weiler H, Grandel A. Postoperative fistula of the abdominal wall after laparoscopic cholecystectomy due to lost gallstones. Eur J Ultrasound 2002;15:61-3.
23. Whiting J, Welch NT, Hallissey MT. Subphrenic abscess caused by gallstones "lost" at laparoscopic cholecystectomy one year previously: management by minimally invasive techniques. Surg Laparosc Endosc 1997;7:77-8.
24. Vadlamudi G, Graebe R, Khoo M, Schinella R. Gallstones implanting in the ovary. A complication of laparoscopic cholecystectomy. Arch Pathol Lab Med 1997;121:155-8.
25. Lauffer JM, Krahenbuhl L, Baur HU, Mettler M, Buchler MW. Clinical manifestations of lost gallstones after laparoscopic cholecystectomy: a case report with review of the literature. Surg Laparosc Endosc 1997;7:103-12.
26. McDonald MP, Munson JL, Sanders L, Tsao J, Buyske J. Consequences of lost gallstone. Surg Endosc 1997;11:774-7.
27. Groebli Y, Hebert D, Tschanz P. The migrating spilled stone. Int Surg 1998;83:31-2.
28. Van der Lugt JCT, de Graaf PW, Dallinga RJ, Stassen LPS. Abcesvorming door verloren stenen bij een laparoscopische cholecystectomie. Ned Tijdschr Geneeskd 2005;149:2683-6.

Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands

A.E. de Jong, H.F.A. Vasen*

The Netherlands Foundation for the Detection of Hereditary Tumours, Leiden, the Netherlands, Department of Gastroenterology, Leiden University Medical Centre, Leiden, the Netherlands, *corresponding author: tel.: +31 (0)71-526 26 87, fax: +31 (0)71-521 21 37, e-mail: stoet@xs4all.nl

ABSTRACT

Background: Subjects with a positive family history of colorectal cancer (CRC) have an increased risk of developing CRC themselves. This risk depends on the number of affected relatives and the age at diagnosis.
Aim: The aim of this study was to assess the prevalence of a positive family history of CRC, within a random cohort among the Dutch population.
Methods: A total of 5072 subjects aged between 45 and 70 years were invited to fill in an anonymous questionnaire about the occurrence of CRC in their first-degree relatives (FDR).
Results: The questionnaire was returned by 3973 subjects (78.3%). Thirty responders (0.8%) had CRC themselves. Of all unaffected responders, 441 (11.2%) subjects reported a positive family history of CRC. Ninety (2.3%) responders reported having an FDR with CRC diagnosed before the age of 50, or reported two or more FDRs with CRC.
Conclusion: The prevalence of a positive family history of CRC is substantial. Identification of this high-risk group by obtaining a thorough family history is the first step in targeting preventive measures.

KEYWORDS

Familial colorectal cancer, general population, prevalence

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality in well-developed countries. Most cases of CRC (around 80%) are probably caused by environmental factors. In up to 5% of all colorectal cancers, genetic factors play a dominant role.[1,2] The most common hereditary syndromes are Lynch syndrome (hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP).[3-6] Predisposed individuals from Lynch syndrome families have a life-time risk of developing CRC of 60 to 85%,[7,8] individuals from MAP families have a life-time risk of 50 to 60%[9] and polyposis patients almost inevitably develop CRC if they are left untreated.

In around 10 to 15% of all CRC cases, a positive family history of colorectal cancer is observed. It is probable that dietary and other environmental risk factors,[10] acting solely or in concert with genetic factors, influence aggregation of the disease.[11]
The risk associated with a family history of CRC depends on the number of affected relatives and the age at diagnosis.[12-14] Subjects with one FDR with CRC diagnosed at age >50 years have a relative risk (RR) of developing CRC of 2 to 3.[15] Subjects with two (or more) FDR with CRC diagnosed at any age, or with one FDR with CRC diagnosed before the age of 50 years have a relative risk of 4 to 6 for developing CRC.[13,16-18]
Surveillance is strongly recommended for subjects from families with hereditary syndromes. Most experts also advise colonoscopic surveillance for subjects with a moderately increased risk of developing CRC (RR ≥4). In most countries subjects with one FDR with CRC >50 years of age are not offered regular colonoscopy. In the USA, surveillance colonoscopy is recommended from the age of 40, or ten years younger than the earliest diagnosis in their family, if one (or more) family member has been diagnosed with CRC or adenomatous polyps before the age of 60.[19,20]
The proportion of the Dutch population with an increased risk of developing CRC on the basis of a positive family history is unknown. We need to know the size of this high-

© 2006 Van Zuiden Communications B.V. All rights reserved.

risk group when planning public health programmes aimed at reducing incidence and mortality from this disease, as those at higher risk can be subject to more intense strategies. The aim of this study was to assess the prevalence of the frequency of a positive family history of CRC, within a random cohort among the Dutch population.

PATIENTS AND METHODS

The study was performed in a rural town, Coevorden, which is located in the east of the Netherlands. Approximately 16,500 subjects are registered with one of the nine general practitioners of this town. All subjects aged between 45 and 70 years (n = 5072) (30.8%) were eligible for the study. In the first week of January 2005, these subjects were invited on behalf of their general practitioner to complete a short questionnaire and to return it within two weeks. The questionnaire included questions on current age, gender of the participant, the number of brothers and sisters; and on the occurrence of CRC (and age of diagnosis) in any of their FDR (father, mother, sibling, children). The questionnaire was anonymous, which means that we were not able to confirm the diagnosis of colorectal cancer.

In order to evaluate whether this sample was representative for the Dutch population, we compared the age distribution of our cohort with the general Dutch population (http://statline.cbs.nl).

For statistical analyses the Fisher's exact test was used. The study was approved by the ethics committee of the Leiden University Medical Centre.

RESULTS

Completed questionnaires were received from 3973 (78.3%) of the 5072 subjects. *Table 1* shows the proportion of subjects aged 45 to 70 years for the study cohort and the general population. No difference was observed in the age distribution. Females and elderly people responded more often than males and younger subjects (*table 1*). Thirty responders (0.8%; 63% male) had a history of colorectal cancer themselves. Seven of them (23.3%) were diagnosed before the age of 50 years. Six of these 30 responders (20.0%) had one (n=3) or two (n=3) FDR with CRC.

Of all unaffected responders (n=3943), 441 subjects (11.2%) reported having one (n=399) or more (n=42) FDR with CRC. Of the responders, 306 (7.8%) had a parent with CRC and three subjects (0.08%) a child. A total of 158 (4.2%) of 3757 unaffected responders with at least one sibling reported having a sibling with CRC. Of all unaffected responders, 90 subjects (2.3%) reported having two or more FDRs with CRC or one FDR with CRC diagnosed at age <50 years. Ten subjects (0.3%) had three or more FDRs with CRC. In *table 2*, the results are summarised.

Table 1. *Age distribution in Dutch population and in Coevorden and number of receivers and responders of the questionnaire*

	General population 2004	Receivers			Responders		
Age	**Total**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**
45-49 years	1,183,325	1185	612	573	822 (69.4)	399 (65.2)	423 (73.8)
50-54 years	1,113,623	1134	622	512	893 (78.7)	465 (74.8)	428 (83.6)
55-59 years	1,084,753	1013	492	521	811 (80.1)	378 (76.8)	433 (83.1)
60-64 years	795,586	866	421	445	719 (83.0)	346 (82.2)	373 (83.8)
65-70 years	663,208	874	440	434	728 (83.3)	358 (81.4)	370 (85.3)
Total (% of population)	*4,840,495 (29.8%)*	*5072 (30.8%)*	*2587*	*2485*	*3973 (78.3)*	*1946 (75.2)*	*2027 (81.6)*

Table 2. *Number of unaffected responders and their family history*

Family history	**Number of responders*(%)**
Total	3943
No colorectal cancer in direct family	3502 (88.8)
≥1 first-degree relative with colorectal cancer	441 (11.2)
1 first-degree relative, diagnosed at age <50	48 (1.2)
2 first-degree relative, any age	32 (0.8)
• 2 first-degree relative, 1 diagnosed at age <50	6 (0.2)
≥3 first-degree relative, any age	10 (0.3)
• ≥3 first-degree relative, 1 diagnosed at age <50	3 (0.08)

*Responders without a history of colorectal cancer.

The proportion of responders with at least one affected FDR increased with the age of the (unaffected) responder; the proportion was 9.1% in the responders aged between 45 and 49 years, 10% in the age group 50 to 54 years, 11.6% in the age group 55 to 59 years, 12.5% in the age group 60 to 64 years and 13.1% in the age group 65 to 70 years. The difference between the youngest and oldest age group was statistically significant (p=0.02, two-sided Fisher's exact test).

For 3850 out of the 3973 responders, we received information about the number of siblings. The responders had a total of 15,721 siblings. The average number of siblings in our cohort (including the responder) was 5.1 per family, (range 1 to 18; median 4). The proportion of families with at least one affected sib significantly increased with the size of the family (p<0.0001, χ^2 test): in families with 1 to 3 siblings, this proportion was 3.1% (43/1385), in families with 4 to 6 siblings it was 4.6% (66/1432), in families with 7 to 9 siblings it was 6.4% (44/691), in families with 10 to 12 siblings it was 9.5% (24/253), and in families with 13 to 15 siblings it was 11.8% (9/76). Only 14 families had 16 to 18 siblings, and in one family a sib was affected with CRC (7.7%).

DISCUSSION

This study is the first manuscript on the prevalence of a positive family history of CRC among a large, population-based, Dutch cohort of subjects aged between age 45 and 70 years. Of all subjects in this age group, 11.2% had at least one FDR with CRC, 2.3% of the responders had two or more FDRs with CRC or had one FDR with CRC diagnosed at age <50 years, and 0.3% of the subjects had three or more FDRs with CRC. A positive family history was associated with the size of the family and age of the index person.
Most studies on family history of CRC were performed in cohorts of patients with CRC.[12-14,18,21,22] These studies reported a proportion of 10 to 15% of the index cases having an FDR with CRC. In the present series, this proportion was higher (20%) but the number of CRC cases (n=30) in our series was relatively small.

Information on the prevalence of a positive family history of subjects not affected with CRC may be derived from case-control studies.[13,16,18,22] The reported family history for colorectal cancer in the control groups varied in these studies from 4 to 10%. However, these figures are probably not representative for the population prevalence, because cohorts of controls will be elderly people when matched by age with CRC patients in case-control studies. The potential bias of the elderly is minimised in the study by Fuchs *et al.*[16] They studied two groups of health care professionals, aged 30 to 75 (n=119,116). The reported family history of CRC among their FDRs was similar (10%) to our study.

Several factors could influence the present findings and might result in an over- or underestimation of the true prevalence of a positive family history. First, our study is based on the reported family histories and not on pathology reports. Indeed some studies reported that the accuracy of self-reporting for CRC is not very good.[23-25] Other studies on the reliability of a family history showed that patient-reported family cancer histories of FDR are accurate and valuable for colon cancer risk assessments.[26,27] Second, despite the high response rate (78.3%) in this study, it can not be excluded that subjects with a positive family history for CRC responded more often than subjects with unaffected FDRs. Moreover, the responders were more often female and of an older age than all subjects who received a questionnaire. This may also influence the results. Third, the prevalence of a positive family history depends on the size of the family, and the age of the responder. With respect to age, the proportion of subjects in age group 45 to 70 years in Coevorden is similar to that of the general population (*table 1*). However, within this age group there are some differences between the general population and the studied population (*table 1*). Unfortunately, information on differences in family size between Dutch regions is not available. At the national level, the mean number of siblings in each family is not available either. Although such information is not available, the impression from this study is that we are dealing with relatively large families with many siblings per family. If this is indeed the case, this might have led to overestimation of the calculated prevalence of a positive family history. Environmental factors can also effect the frequency of (familial) colorectal cancer. However, according to data from the National Cancer Registry, there are no significant differences in CRC incidence between regions within the Netherlands. Although it seems rather difficult to be sure how representative the risk of colon cancer in the city of Coevorden is for the Netherlands as a whole, we think that our results are representative for the general Dutch population.[28]

Our study demonstrated that the proportion of subjects in the general population with an increased risk of developing CRC based on their reported family history is substantial. Based on the findings, we estimate that more than 500,000 subjects in the Netherlands in the age group 45 to 70 years have an at least two to three times increased risk of developing CRC. Approximately 100,000 of these subjects have an increased relative risk of four or more. If all subjects with a positive family history are identified and encouraged to participate in surveillance protocols, more than 10 to 15% of all colorectal cancers (900 to 1400 cases every year in the Netherlands) might be prevented. Colonoscopy is currently the appropriate surveillance method for this high-risk group. Studies are needed to elucidate the best surveillance interval for this high-risk group.

ACKNOWLEDGMENTS

We thank A.H. de Boer, J. Stoffels, G.F. v/d Woude, P.H.T. Hermans, M.L.F. Wortelboer, H.W Koelemeijer, B.G.J. Geertjes , P.W.W.M. Valks and P. Wattel; general practitioners in Coevorden for their cooperation.

REFERENCES

1. Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998;338:1481-7.
2. Bussey HJ. Familial polyposis coli: family studies, histopathology, differential diagnosis, and results of treatment. The John Hopkins University Press: Baltimore, 1975.
3. Campbell WJ, Spence RA, Parks TG. Familial adenomatous polyposis. Br J Surg 1994;81:1722-33.
4. Lynch HT, Smyrk T, Lynch J. An update of HNPCC (Lynch syndrome). Cancer Genet Cytogenet 1997;93:84-99.
5. Croitoru ME, Cleary SP, Di Nicola N, et al. Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. J Natl Cancer Inst 2004;96:1631-4.
6. Al Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. Nat Genet 2002;30:227-32.
7. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 1999;81:214-8.
8. Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology 1996;110:1020-7.
9. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med 2003;348:791-9.
10. Slattery ML. Diet, lifestyle, and colon cancer. Semin Gastrointest Dis 2000;11:142-6.
11. Walach N, Novikov I, Milievskaya I, Goldzand G, Modan B. Cancer among spouses: Review of 195 couples. Cancer 1998;82:180-5.
12. Kune GA, Kune S, Watson LF. The Melbourne Colorectal Cancer Study. Characterization of patients with a family history of colorectal cancer. Dis Colon Rectum 1987;30:600-6.
13. St John DJ, McDermott FT, Hopper JL, Debney EA, Johnson WR, Hughes ES. Cancer risk in relatives of patients with common colorectal cancer. Ann Intern Med 1993;118:785-90.
14. Stephenson BM, Finan PJ, Gascoyne J, Garbett F, Murday VA, Bishop DT. Frequency of familial colorectal cancer. Br J Surg 1991;78:1162-6.
15. Hemminki K, Chen B. Familial risks for colorectal cancer show evidence on recessive inheritance. Int J Cancer 2005;115:835-8.
16. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med 1994;331:1669-74.
17. Ponz dL, Antonioli A, Ascari A, Zanghieri G, Sacchetti C. Incidence and familial occurrence of colorectal cancer and polyps in a health-care district of northern Italy. Cancer 1987;60:2848-59.
18. Slattery ML, Kerber RA. Family history of cancer and colon cancer risk: the Utah Population Database. J Natl Cancer Inst 1994;86:1618-26.
19. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2003. CA Cancer J Clin 2003;53:27-43.
20. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology 2003;124:544-60.
21. Olsson L, Lindblom A. Family history of colorectal cancer in a Sweden county. Fam Cancer 2003;2:87-93.
22. Bonelli L, Martines H, Conio M, Bruzzi P, Aste H. Family history of colorectal cancer as a risk factor for benign and malignant tumours of the large bowel. A case-control study. Int J Cancer 1988;41:513-7.
23. Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol 1997;146:244-8.
24. Bergmann MM, Calle EE, Mervis CA, Miracle-McMahill HL, Thun MJ, Heath CW. Validity of self-reported cancers in a prospective cohort study in comparison with data from state cancer registries. Am J Epidemiol 1998;147:556-62.
25. Glanz K, Grove J, Le Marchand L, Gotay C. Underreporting of family history of colon cancer: correlates and implications. Cancer Epidemiol Biomarkers Prev 1999;8:635-9.
26. Murff HJ, Spigel DR, Syngal S. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. JAMA 2004;292:1480-9.
27. Sijmons RH, Boonstra AE, Reefhuis J, et al. Accuracy of family history of cancer: clinical genetic implications. Eur J Hum Genet 2000;8:181-6.
28. Association of Comprehensive Cancer Centres. Netherlands Cancer Registry. 2002, 2005.

Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Dutch endoscopic capacity in the era of colorectal cancer screening

J.S. Terhaar sive Droste[1*], M.E. Craanen[1], J.J. Kolkman[2], C.J.J. Mulder[1]

[1]Department of Gastroenterology, VU University Medical Centre, Amsterdam, the Netherlands,
[2]Department of Gastroenterology, Medisch Spectrum Twente, Enschede, the Netherlands,
[*]corresponding author: tel.: +31 (0)20-444 06 13, fax: +31 (0)20-444 05 54, e-mail: js.terhaar@vumc.nl

ABSTRACT

Background: Future colorectal cancer (CRC) screening programmes should not (greatly) interfere with regular health care. Hence, we analysed the Dutch endoscopic practice to provide a clear insight into endoscopic workload and manpower with a special emphasis on the current ability to facilitate a successful implementation of a faecal occult blood test (FOBT)-based nationwide CRC screening programme.

Methods: A questionnaire was sent to all Dutch endoscopy units (n=100) in the spring of 2005. The questionnaire included topics ranging from the numbers and specifications of endoscopies performed in 2004 and the numbers of endoscopists per unit to expected vacancies for gastroenterologists and waiting times.

Results: The response rate was 98%, representing a total of 49,253 hospital beds. Overall, a 26% increase in the number of endoscopies from 325,000 in 1999 to almost 410,000 in 2004 was found, accompanied by a 25% increase in manpower. The total number of endoscopists was 598. Regional differences were observed in the number of endoscopists, the total number of endoscopies and colonoscopies, and the number of endoscopies per endoscopist. A biannual FOBT-based screening programme would yield an additional workload of 25,385 colonoscopies a year amounting to a 22% increase in the total number of colonoscopies performed. However, the workload per unit would only have to increase by five extra colonoscopies a week.

Conclusion: Whereas an FOBT-based CRC screening programme is currently feasible without strongly interfering with regular health care, future plans regarding the scale and preferred mode of screening should incorporate solid data on the (regional) endoscopic capacity and manpower needed for a successful implementation.

KEYWORDS

Colonoscopy, colorectal cancer, Dutch, endoscopy, screening

INTRODUCTION

In view of the demographic changes and altered morbidity patterns in the Dutch general population, it is questionable whether the anticipated qualitative and quantitative changes in routine daily endoscopic practice can be met in the (near) future. In addition to an expected increase in the total number of endoscopies performed, the widespread clinical implementation of advanced imaging techniques, such as magnifying endoscopy, video capsule endoscopy and double-balloon enteroscopy, will undoubtedly lead to a qualitative change in endoscopic practice as well. If not adequately managed, these quantitative and qualitative changes will not only hamper future endoscopic practice but may also frustrate the successful implementation of a nationwide colorectal cancer (CRC) screening programme. Although the scale and optimal mode of screening is still controversial,[1-4] it is likely that a future Dutch CRC screening programme will use a biannual faecal occult blood test (FOBT)-based screening strategy for the general population between 50 to 75 years.[1] However, despite many arguments in favour of a screening programme,[5-7] a future CRC screening programme should not (greatly) interfere with regular health care in terms of endoscopic capacity and manpower. Hence, we analysed the current Dutch endoscopic practice to provide a clear insight into endoscopic workload and manpower with special emphasis for the additional requirements, if any, to accommodate a biannual FOBT-based CRC screening programme.

METHODS

A questionnaire was sent, by mail and by e-mail, to all Dutch endoscopy units, either single- or multi-institutional (n=100) in the spring of 2005. Nonresponders were sent several reminders and, if necessary, where contacted by phone at regular intervals of three to six weeks. The questionnaire included general topics ranging from the

© 2006 Van Zuiden Communications B.V. All rights reserved.

numbers and specifications of endoscopies performed in 2004 and the numbers of endoscopists and nurses per unit to waiting times and expected vacancies for gastroenterologists. The mean numbers of endoscopies, gastroscopies, colonoscopies, sigmoidoscopies and endoscopic retrograde cholangiopancreatographies (ECRPs) per 100,000 inhabitants were calculated. Finally, the geographical distribution of endoscopic procedures, manpower and workload per endoscopist were assessed. SPSS for Windows version 11.0 was used for descriptive statistical analysis of the data.

RESULTS

The response rate was 98%, representing a total of 49,253 hospital beds. Two centres with a combined total of 509 hospital beds did not respond despite several reminders. The total number of endoscopists was 598 (221 gastroenterologists, 213 internists, 123 surgeons and 41 paediatricians). Specification of the numbers of endoscopies per 100,000 inhabitants and the geographical distribution of endoscopic procedures are listed in *tables 1* and *2*, respectively. The number of endoscopists per province and number of endoscopies per endoscopist are shown in *table 3*. The ratio between the number of colonoscopies and sigmoidoscopies was 1.7:1 (*table 1*). The mean waiting time for routine gastroscopy and colonoscopy was 3.0 weeks (range: 1 to 12 weeks) and 5.1 weeks (range 1 to 15 weeks), respectively. The expected number of vacant positions for gastroenterologists amounted to 60.4 FTE and 61.4 FTE in the period 2005-2006 and 2007-2010, respectively.

DISCUSSION

Overall, a 26% increase in the number of endoscopies from 325,000 in 1999 to almost 410,000 in 2004 was found. This was accompanied by a 25% increase in manpower, i.e. from 480 endoscopists in 1999 to 598 endoscopists in 2004.[8] The endoscopic workload was nearly equally divided between gastroscopies and colonoscopies/sigmoidoscopies. The number of ERCPs represented less than 4% in total, despite a 22% increase compared with 1999.[8] The total number of endoscopies showed remarkable geographical differences ranging from 5687 in Flevoland to 92,172

Table 1. *Number of endoscopies in the Netherlands in 2004, based on a 98% response rate*

	Total number in the Netherlands	Endoscopies per 100,000 inhabitants/year*
Gastroscopies	184,915	1137
Colonoscopies	116,815	719
Sigmoidoscopies	70,049	431
Endoscopic retrograde cholangiopancreatography	14,596	90
Other**	22,607	139
Total	*408,982*	*2514*

*Dutch population 2004: 16,258,032 (www.cbs.nl). **Other endoscopic procedures, i.e. duodenal feeding tubes, gastrostomies, paediatric endoscopies, endoscopic ultrasound imaging and emergency procedures for haematemesis or haematochezia.

Table 2. *Number of endoscopies per province, based on a 98% response rate*

Province	Number of endoscopies	Number of colonoscopies	Endoscopies per 100,000 inhabitants/year*	Colonoscopies per 100,000 inhabitants/year*
Noord-Holland	62,359	16,798	2410 (±71)	649 (±17)
Zuid-Holland	92,172	26,992	2670 (±66)	782 (±19)
Noord-Brabant	51,128	11,932	2124 (±66)	496 (±17)
Utrecht	34,905	10,498	3003 (±171)	903 (±65)
Gelderland	47,181	13,716	2399 (±132)	697 (±45)
Overijssel	31,921	9799	2887 (±353)	886 (±127)
Groningen	19,767	5739	3441 (±671)	999 (±205)
Flevoland	5687	1822	1580 (±62)	506 (±35)
Zeeland	9026	2691	2381 (±5)	710 (±52)
Limburg	29,767	9487	2613 (±195)	833 (±72)
Friesland	14,880	4680	2318 (±271)	729 (±115)
Drenthe	10,189	2661	2112 (±94)	552 (±48)
The Netherlands	408,982	116,815	2514 (±14)	719 (±4)

*Mean number (± standard deviation) per 100,000 inhabitants.

Table 3. *Number of endoscopists per province and number of endoscopies per endoscopist/year*

Province	Number of endoscopists	Number of endoscopies per endoscopist/year
Noord-Holland	101	617
Zuid-Holland	139	663
Noord-Brabant	69	741
Utrecht	47	743
Gelderland	68	694
Overijssel	34	939
Groningen	33	599
Flevoland	9	632
Zeeland	15	602
Limburg	42	709
Friesland	24	620
Drente	17	599
The Netherlands	598	684

in Zuid-Holland. This difference of up to 17-fold in all probability results from differences in the number of endoscopists per province and demographic characteristics, such as number of inhabitants, age distribution and, although speculative, morbidity patterns. Hence, it is not surprising that, in contrast to the 17-fold difference in total number of endoscopies, only a modest twofold difference was observed between the highest and lowest ranking province after correction for the number of inhabitants. Within this context, an interesting finding was the observation that the province Groningen, ranking 8th in total number of endoscopies, ranked first after correction for the number of inhabitants. Whether this finding is solely caused by demographic characteristics, morbidity patterns and/or differences in clinical practice, and endoscopic practice in particular, remains elusive. However, the number of endoscopies per endoscopist, being lowest in Groningen and Drenthe, suggests that differences in attitude towards endoscopic indications do not play a major role, if any. Similar geographical differences were observed with regard to the total number of colonoscopies, yielding a tenfold difference between the highest and lowest ranking province. Correction for number of inhabitants reduced the difference to less than twofold with the province Groningen ranking first in the number of colonoscopies per 100,000 inhabitants. Interestingly, the colonoscopy/sigmoidoscopy ratio of 1.7:1 was rather low compared with other countries, ranging from 4.1:1 in the United States to 9:1 in France.[9-11] This difference presumably reflects national differences in routine clinical practice with regard to for instance endoscopic indications, practice guidelines, CRC screening guidelines and reimbursement. Finally, the waiting times for routine endoscopy were fairly uniform. Yet, unacceptable waiting times of up to 12 to 15 weeks were encountered as well.

In view of the above, it is important to consider the impact of a nationwide CRC screening programme on (regional) endoscopic capacity, manpower and waiting times. Our data indicate that a biannual FOBT-based screening strategy[1] is currently feasible without greatly interfering with regular health care. Assuming a maximal compliance rate of 60% and an FOBT positivity rate of 2% analogous to other studies,[12-14] the programme would yield an additional workload of 25,385 colonoscopies per year (www.cbs.nl) amounting to a 22% increase in the total number of colonoscopies performed in 2004. However, the workload per unit would have to increase by only a modest five extra colonoscopies per week.

CONCLUSION

Whereas an FOBT-based CRC screening programme is currently feasible, future plans regarding the scale and preferred mode of screening should incorporate solid data on the (regional) endoscopic capacity and manpower needed for a successful implementation.

REFERENCES

1. De Visser M, van Ballegooijen M, Bloemers SM, et al. Report on the Dutch consensus development meeting for implementation and further development of population screening for colorectal cancer based on FOBT. Cell Oncol 2005;27:17-29.
2. Van Ballegooijen M, Habbema JD, Loeve F, et al. Screening for colorectal cancer in the Netherlands: time to start. COCAST report; 2003.
3. KWF Cancer signalling committee. Early detection of colorectal cancer. Reducing mortality by means of a national screening program. KWF report; 2001.
4. Coebergh JW. Colorectal cancer screening in Europe: first things first. Eur J Cancer 2004;40:638-42.
5. Loeve F, van Ballegooijen M, Snel P, Habbema JD. Colorectal cancer risk after colonoscopic polypectomy: a population-based study and literature search. Eur J Cancer 2005;41:416-22.
6. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med 2005;352:476-87.
7. Schrag D. The price tag on progress – chemotherapy for colorectal cancer. N Engl J Med 2004;351:317-9
8. Kolkman J.J, Mulder C.J. The nature of the Dutch endoscopic practice in 1999. MAGMA 2000; 6:28-31
9. Agency for Health Care Policy and Research. Report 2005. www.apcpr.gov/consumer/surgery.html.
10. Deux jours d'endoscopie digestive en France. Enquete nationale prospective de la Societe Francaise d'Endoscopie Digestive [report]; 1999.
11. SNFGE. Le Livre Blanc de l'Hepato-Gastroenterologie [report]; 2001.
12. Kronborg O, Jorgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol 2004;39:846-51.
13. Segnan N, Senore C, Andreoni B, et al. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. J Natl Cancer Inst 2005;97:347-57.
14. UK Colorectal Cancer Screening Pilot Group. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. BMJ 2004;329:133.

Netherlands
The Journal of Medicine

CASE REPORT

Vascular type of Ehlers-Danlos syndrome in a patient with a ruptured aneurysm of the splenic artery

P.W.B. Nanayakkara[1*], C.C. van Bunderen[1], S. Simsek[2], Y.M. Smulders[1], G. Pals[3]

Departments of [1]Internal Medicine, [2]Endocrinology and [3]Clinical Genetics, VU University Medical Centre, Amsterdam, the Netherlands, [*]corresponding author: tel.: +31 (0)20-444 44 44 (ext. 986791), fax: +31 (0)20-444 05 05, e-mail: p.nanayakkara@vumc.nl

ABSTRACT

A 39-year-old woman presented with a ruptured aneurysm of the splenic artery. The postoperative course was complicated by poor wound healing. This, in combination with a history of easy bruising and joint hypermobility, made us consider a connective tissue disease as underlying cause. The vascular type of Ehlers-Danlos syndrome was diagnosed by identifying collagen III deficiency and the corresponding gene mutation in cultured fibroblasts from a skin biopsy.

KEYWORDS

Aneurysm, Ehlers-Danlos syndrome, hypertension, splenic artery

INTRODUCTION

Ehlers-Danlos syndromes (EDS) are a group of heritable connective tissue disorders characterised by fragility of the skin and hypermobility of the joints. The Villefranche classification, introduced in 1997, differentiates six types of EDS.[1] The most severe form, the vascular type (type IV according to the old classification),[2] results from mutations in the gene for type III procollagen (*COL3A1*) and is life-threatening, often resulting in premature death because of arterial, bowel or uterine rupture.[3] We describe the case history of a young woman who presented with a ruptured aneurysm of the splenic artery that turned out to be the first complication of vascular type EDS.

CASE REPORT

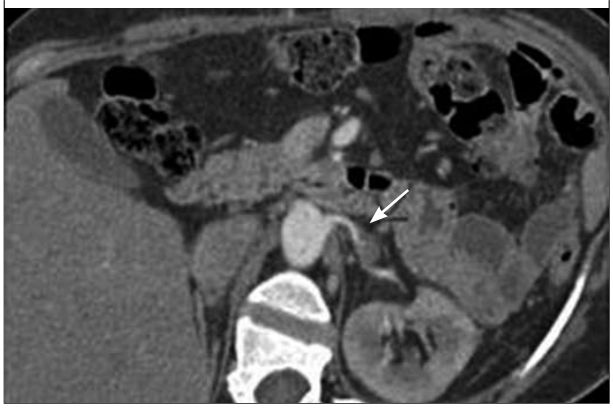
In July 2002, a 39-year-old woman presented to the emergency department of our hospital. She complained of mild upper abdominal discomfort during the previous 24 hours. One hour before presentation she had collapsed after sudden worsening of her abdominal pain. At presentation she was unconscious (Glasgow coma score: 5), blood pressure was 80/40 mmHg and the abdominal examination showed rigidity and guarding. Haemoglobin level was 3.1 mmol/l and ultrasound examination showed free fluid in the abdominal cavity. Immediate laparotomy revealed a ruptured aneurysm of the splenic artery. Splenectomy was performed and more than 2.5 litres of blood were drained from the abdominal cavity. The postoperative course was complicated by multiple pancreatic pseudocysts and intra-abdominal fluid collections. Abdominal wound recovery was slow. After four weeks, the patient was discharged. On discharge, the diagnosis of pregnancy-related aneurysm of the splenic artery was made.[4] Her medical history was uneventful, and included a normal pregnancy with vaginal delivery 18 months prior to the event.

An abdominal computed tomography angiography (CTA), performed in September 2002 to examine for aneurysms in other visceral arteries, was considered to show no abnormalities. A couple of days after the CTA, the patient developed progressive, severe headache and nausea. Physical examination showed a blood pressure of 180/120 mmHg with no neck stiffness, papilloedema or other neurological signs. Laboratory results and revision of the abdominal CTA made a couple of days before showed no abnormalities and CTA cerebrum revealed no cerebral aneurysms or signs of haemorrhage or reversible posterior leucoencephalopathy syndrome. Labetalol 200 mg three

© 2006 Van Zuiden Communications B.V. All rights reserved.

times a day was administered and successfully lowered her blood pressure. Ten days later, she was admitted again with headache and a blood pressure of 210/130 mmHg. Long-acting nifedipine 60 mg/day was added to her medication with a good result. During the subsequent year her blood pressure medication was tapered and finally stopped altogether, and her blood pressure stabilised at 120/80 mmHg. Because we did not have a clear diagnosis, we decided to perform a full review of her medical history. In retrospect, her medical history also included repeated luxation of her patellae and easy bruising. In addition, re-examination of the abdominal CTA carried out in September 2002 showed two left renal arteries, one of which had a dissecting aneurysm with complete occlusion (*figure 1*), which was overlooked at first. This combined with her prolonged wound healing after surgery and aneurysm of the splenic artery made us consider a connective tissue disease as underlying cause. She had no dysmorphic features consistent with Marfan syndrome.[5] However, there were clear signs of joint hypermobility (according to Beighton's scoring system).[1] By means of skin biopsy and fibroblast culture, a collagen type III deficiency was found as a result of a mutation in the corresponding gene *COL3A1* (*figure 2*).[3] The vascular type of Ehlers-Danlos syndrome was diagnosed.

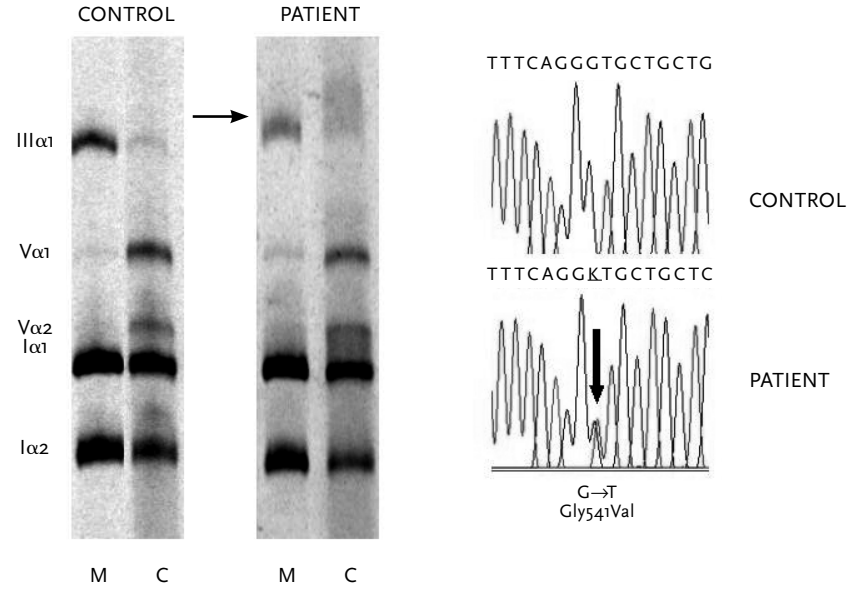
Figure 1. *CT scan showing a dissecting aneurysm of one of the left renal arteries*



DISCUSSION

The vascular type of Ehlers-Danlos syndrome is a rare connective tissue disorder caused by type III procollagen deficiency due to *COL3A1* gene mutation. The inheritance is autosomally dominant and in about half of the patients a *de-novo* mutation is found. The clinical diagnosis is established from two of four major clinical criteria: thin, translucent skin; extensive bruising; characteristic facial appearance

Figure 2. *Autoradiograph of SDS-PAGE electrophoresis of collagen from cultured fibroblasts (left), after metabolic labelling with ^{14}C-proline*



The types of collagen chains are indicated. M = media from tissue culture; C = cell contents. The excreted amount of collagen type III is reduced in the patient's fibroblasts and there is accumulation of overmodified material in the cells. This is caused by a glycine to valine substitution in the triple helix of collagen III due to a G to T base substitution at position 541 (right).

(large eyes, thin nose, lobeless ears, thin scalp hair and decrease in the subcutaneous adipose tissue) and arterial, bowel or uterine fragility or rupture. Hypermobility of large joints and hyperextensibility of the skin are unusual in the vascular type. However, our patient had clear features of hyperlaxity of the joints. The diagnosis can be confirmed by identification of the previously mentioned gene mutation. Vascular type EDS can be life-threatening due to weak arteries, bowel or uterus, which can lead to spontaneous ruptures. Most patients have the first complication by the age of 20 years. The mean life expectancy is 48 years.[3] The cause of death is usually due to vascular complications.[6] In our patient, a ruptured aneurysm of the splenic artery was the first complication. Dissection of one of the left renal arteries with total occlusion, which probably occurred after injection of contrast for CTA, could explain the hypertensive period. A CTA performed after normalisation of blood pressure showed a patent lumen in the previously occluded renal artery. Temporary renal hypoperfusion due to the dissecting aneurysm with transient occlusion of the left renal artery probably activated the renin-angiotensin-aldosterone system, resulting in the hypertensive period.[7] Despite of luxation of her patella, which was treated conservatively, no other complications had occurred following these events. The patient was advised to avoid pregnancy, avoid activities that put pressure on locked joints, minimise skin trauma risks and avoid forms of invasive diagnostic tests where possible. Genetic counselling was provided and the patient's mother and brother were tested, the results of which were negative. As for our patient's four-year-old daughter, the parents have postponed testing because of the minimal risk of complications at such a young age.

CONCLUSION

In young patients with unexplained ruptures of arteries, bowel or uterus, with or without a positive family history, the diagnosis of vascular type Ehlers-Danlos syndrome should be considered. Although no specific treatment is available, knowledge of the diagnosis may influence the management of surgery, pregnancy and major complications, and may have implications for genetic counselling.

REFERENCES

1. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos Syndromes. Am J Med Genet 1998;77:31-7.
2. Beighton P, Paepe A De, Danks D, et al. International nosology of heritable disorders of connective tissue. Am J Med Genet 1988;29:581-94.
3. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med 2000;342:673-80.
4. Selo-Ojeme DO, Welch CC. Review: Spontaneous rupture of splenic artery aneurysm in pregnancy. Eur J Obstet Gynecol Reprod Biol 2003;109:124-7.
5. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996;62:417-26.
6. Oderich GS, Panneton JM, Bower TC, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: A 30-year experience. J Vasc Surg 2005;42:98-106.
7. Goldblatt H, Lynch J, Hanzal RF, et al. Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med 1937;59:347-78.

ERRATUM

In the photo quiz entitled 'The ECG in hypothermia: Osborn waves' by T.J. Olgers and F.L. Ubels (Neth J Med 2006;64(9):350,353) the top ECG (p. 350) should have been shown only. Furthermore on the page were the answer to this photo quiz is given (p. 353), only the top ECG of figure 1 and the bottom ECG of figure 2 should have been shown. We apologize for any inconvenience caused.

Netherlands
The Journal of Medicine

CASE REPORT

Risk factors of acute hepatic failure during antituberculosis treatment: two cases and literature review

F. Smink[1], B. van Hoek[2], J. Ringers[3], R. van Altena[4], S.M. Arend[1*]

Departments of [1]Infectious Diseases, [2]Gastroenterology and Hepatology, and [3]Surgery, Leiden University Medical Centre, Leiden, the Netherlands, [4]Tuberculosis Centre Beatrixoord, University Medical Centre Groningen, University of Groningen, Haaren, the Netherlands, [*]corresponding author: tel.: +31 (0)71-526 26 20, fax: +31 (0)71-526 67 58, e-mail: s.m.arend@lumc.nl

ABSTRACT

Hepatotoxicity is a well-known side effect of antituberculosis treatment (ATT). If not recognised in time, drug-induced hepatitis can develop, which may rapidly progress to acute liver failure. We describe two patients with acute hepatic failure caused by ATT, whose pretreatment liver function had been normal. Both patients successfully underwent liver transplantation. Possible risk factors predisposing towards ATT-induced hepatic failure were evaluated, and at least four risk factors were present in these patients. Although available guidelines do not advocate routine monitoring of liver function during ATT unless baseline values are elevated or in the case of pre-existent liver disease, this is nevertheless common practice. Liver function should always be measured in patients who develop symptoms during ATT, and rising liver function parameters should prompt immediate action to prevent the occurrence of liver failure. This report underscores that regular monitoring of liver function parameters and adherence to guidelines is especially important in patients with risk factors for ATT-induced liver disease. An evaluation of chronic viral hepatitis in risk groups before starting ATT could be worthwhile.

KEYWORDS

Acute liver failure, case report, drug-induced liver disease, hepatitis, liver transplantation, *Mycobacterium tuberculosis*, risk factors

INTRODUCTION

Tuberculosis is still a major problem worldwide. The incidence of tuberculosis in the Netherlands is 10 per 100,000 inhabitants per year, with more than half of all cases occurring in risk groups for tuberculosis, such as asylum seekers and immigrants. In countries where tuberculosis is not endemic, as the Netherlands, knowledge and experience in treating tuberculosis has diminished. Drug-induced liver disease is a well-known side effect of several drugs that are used for the treatment of active tuberculosis or latent tuberculosis infection. Mild hepatic dysfunction, defined as an increase in serum transaminases to less than five-fold the upper limit of normal levels in the absence of clinical symptoms occurs in about 10 to 20% of patients receiving antituberculosis treatment (ATT).[1,2] This is usually reversible even if treatment is continued.[1,3-5] More serious liver disease induced by ATT occurs in 1 to 3% of patients.[4,6] Higher incidences have been reported in India ranging from 8 to 39%.[6] If not recognised in time, ATT-induced liver disease can progress to acute hepatic failure and may result in death unless liver transplantation can be performed.

Several risk factors for ATT-induced hepatic dysfunction have been described, including age, sex, race, pre-existing liver disease, extent of tuberculosis, alcohol consumption, low body mass index, acetylator status, use of hepatotoxic drugs, and a high dosage of ATT in relation to body weight.[7-16] Available guidelines advocate baseline testing of liver function in all patients before starting ATT, while routine measurement of hepatic function during treatment is indicated in patients with baseline abnormalities or those with documented hepatitis B or C virus infection or alcohol abuse.[1,17,18] We describe two patients who developed liver disease and acute liver failure during ATT. Both

© 2006 Van Zuiden Communications B.V. All rights reserved.

successfully underwent liver transplantation, one with a temporary auxiliary graft, the other orthotopically. In both patients, baseline liver function tests had been normal, there was no alcohol abuse and no information on viral hepatitis before starting ATT. However, several other risk factors for development of ATT-induced liver failure were present. The clinical course in these patients suggests that an evaluation of all potential risk factors before starting ATT could guide the monitoring of liver function tests during ATT. Moreover, these cases illustrate that strict adherence to the guidelines during treatment remains important to recognise ATT-induced liver dysfunction in time and prevent progression to acute liver failure.

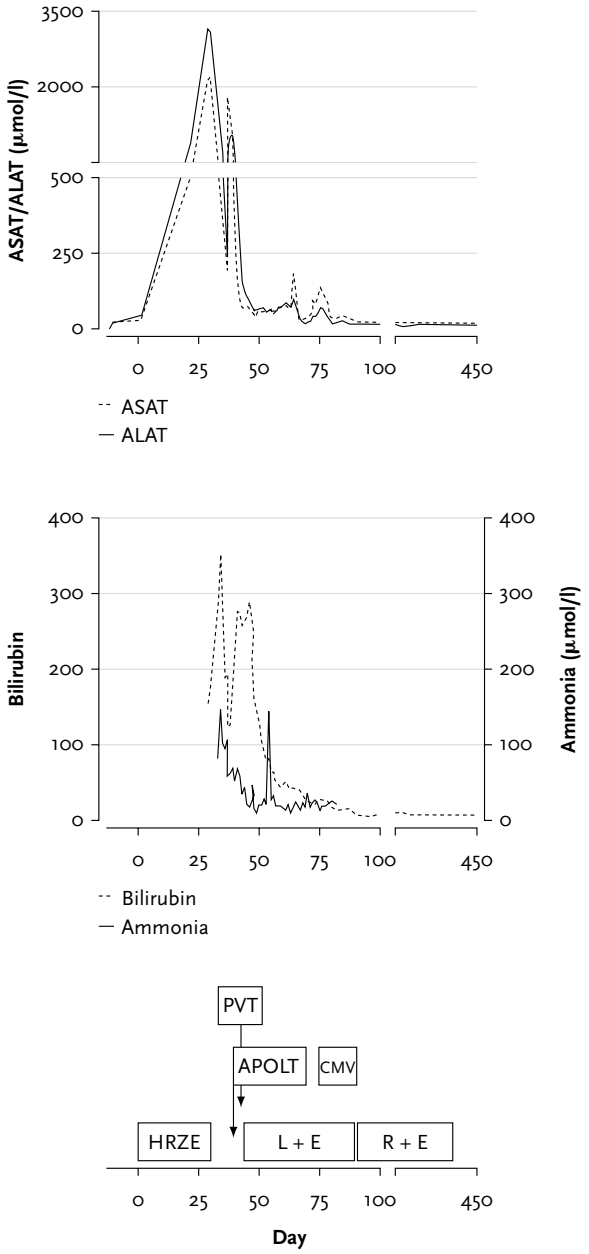
CASE REPORT

Case 1

In July 2003, tuberculous lymphadenitis of the right axilla was diagnosed in a 25-year-old woman of Philippine origin (patient A) in another hospital after a recent visit to the Philippines. A chest X-ray showed no signs of pulmonary tuberculosis. Baseline values of liver function tests (normal values between parentheses) were normal: aspartate aminotransferase (ASAT) 23 U/l (<45 U/l), alanine aminotransferase (ALAT) 19 U/l (<45 U/l), bilirubin 3 μmol/l (14 μmol/l), gamma-glutamyl-transferase (γ-GT) 18 U/l (5-35 U/l), alkaline phosphatase (AP) 59 U/l (40-120 U/l), and lactate dehydrogenase (LDH) 235 U/l (150-400 U/l). She was treated with a combination of rifampin 600 mg/day, isoniazid 300 mg/day, ethambutol 1200 mg/day and pyrazinamide 1500 mg/day (day 0). Her body weight was about 50 kg (110 lbs). On day 14, she developed fever up to 40°C lasting for three days. On day 22 she presented with an extremely itchy rash, which was ameliorated by menthol cream. The patient also complained of upper right abdominal pain, anorexia and nausea without vomiting. Liver function tests in the referring hospital showed the following abnormalities: ASAT 499 U/l (<45 U/l), ALAT 837 U/l (<45 U/l), γ-GT 28 U/l (5-35 U/l), AP 61 U/l (40-120 U/l), and LDH 788 U/l (150-400 U/l). Serum level of bilirubin and clotting parameters were not determined.

Due to a communication problem, the ATT was continued despite these findings. The symptoms worsened in the course of the following week. In addition, she became jaundiced, started vomiting and the vomit and urine were orange coloured. On day 29, isoniazid and rifampin were discontinued when progressive liver function disturbances were found: ASAT 2046 U/l, ALAT 3010 U/l, total bilirubin 156 μmol/l, AP 104 U/l, and γ-GT 71 U/l. The time course of the laboratory results is depicted in *figure 1*. One day later she presented to the other hospital with malaise. She was admitted with a diagnosis of drug-induced liver disease caused by ATT and all medication was stopped. During the next few days, her condition deteriorated with development of hepatic encephalopathy grade I/II as defined by the West Haven criteria.[19] Acute liver failure was suspected since the encephalopathy had developed within two weeks of the onset of jaundice.[20] On day 34, she was transferred to the intensive care unit of Leiden University Medical Centre (LUMC), a centre for liver transplantation.

Figure 1. *Liver function parameters in patient A, the X-axis denotes days after starting antituberculosis treatment*



APOLT = auxiliary partial orthotopic liver transplantation; HRZE = isoniazid (H), rifampin (R), pyrazinamide (Z), ethambutol (E); L + E = levofloxacin plus ethambutol; R + E = rifampin plus ethambutol; CMV = treatment for primary cytomegalovirus infection; PVT = portal vein thrombosis.

Other possible causes of liver failure were evaluated but not found. Apart from the ATT, the patient had not been on any other prescribed or self-administered drugs, besides acetaminophen 500 mg once on day 33. She and her family denied alcohol and substance abuse. IgM antibodies to hepatitis A virus, antibodies to hepatitis C virus, hepatitis B surface antigen, antibodies to hepatitis B core antigen, IgM and IgG antibodies to cytomegalovirus and antibodies to human immunodeficiency virus were all negative. There was no indication of autoimmune disease. Tests for antinuclear, antimitochondrial and antismooth muscle antibodies were negative. The ceruloplasmin level was 0.24 g/l (0.20 to 0.60 g/l), α-1 antitrypsin was 1.19 g/l (0.85 to 2.13 g/l), serum iron was 32 μmol/l (10 to 25 μmol/l) and transferrin saturation was 80%. Abdominal ultrasonography showed a normal liver and spleen. There was no ascites. Thus, the diagnosis of ATT-induced acute liver failure with grade II encephalopathy, progressive hyperbilirubinaemia and deteriorating clotting parameters was made. Based on the King's College criteria for liver transplantation as shown in *table 1*, the patient was placed on the high urgency waiting list for liver transplantation following national guidelines.[21-23] Supportive treatment was initiated, including mild cooling (35°C), administration of antibiotics and lactulose, and albumin dialysis with the Molecular Adsorbent Recirculating System, an experimental method for temporary support of liver function.

On day 38, four days after admission to the ICU, a donor liver became available. On laparotomy the recipient's liver was found to be collapsed. Histologically, the liver showed mainly centrilobular necrosis with preservation of the pre-existing architecture, without fibrosis and with a vital aspect of the remaining parenchyma. The biomarker expression of proliferation index Ki-67 showed proliferation of hepatocytes. Together, this indicated the possibility of regeneration. It was thus decided to reduce the graft to an extended left graft (segments 2, 3 and 4) for auxiliary partial orthotopic liver transplantation (APOLT). Only segment 1 of the native liver was resected. Immunosuppressive treatment consisted of basiliximab (monoclonal antibodies inhibiting the effect of interleukin-2 on lymphocytes), (methyl)prednisolone and tacrolimus. The postoperative course was complicated by partial graft portal vein thrombosis on day 39, which was treated with anticoagulation, and by primary cytomegalovirus infection diagnosed on day 72 and treated with ganciclovir. There were no episodes of rejection.

After transplantation, renewed treatment of tuberculosis was indicated because the initial treatment had been inadequate, while the immunosuppressive regimen for prevention of graft rejection is associated with a high risk of progressive tuberculosis.[24] In order to avoid toxicity and difficulties in interpreting liver function parameters, isoniazid, rifampin and pyrazinamide were avoided and nonhepatotoxic antituberculosis drugs were chosen, knowing that their effectiveness may not be optimal. On day 44, five days after APOLT and the start of immunosuppression, ethambutol at 1200 mg/day and levofloxacin at 500 mg/day were started. After recovery of the native liver, the graft could be removed on day 66. The removed graft was reused in another patient, as described in another report (submitted for publication).

After discharge from hospital on day 88, ATT with levofloxacin and ethambutol was changed to rifampin 450 mg/day and ethambutol 800 mg/day. Liver function parameters remained stable, but the patient experienced itching and gastrointestinal problems. The measured peak serum level of rifampin was 13.0 mg/l. Peak serum levels of 3 mg/l are considered adequate. After reduction of the rifampin dose to 300 mg/day all symptoms subsided. Serum levels at 0, 3 and 6 hours after intake were undetectable, 5.7 mg/l and 3.3 mg/l, respectively. She completed nine months of treatment without further complications and has fully resumed her former activities.

Case 2

In April 1996, a 54-year-old male of Chinese descent (patient B) started coughing without sputum production. In October 1996, smear-positive pulmonary tuberculosis was

Table 1. *Assessment of patients A and B according to King's College criteria for liver transplantation*

	Patient A, day 34	Patient B, day 249
PT >100 s *or*	No	No
INR >6.5 *or*	No	No
≥3 of following criteria:	Yes	Yes
• Jaundice >7 days before encephalopathy	Yes	Yes
• Age <10 *or* > 40 year	No	Yes
• PT >50 s *or* INR >3.5	Yes (PT 67.9 s; INR 5.9)	No (PT 26.1 s; INR 2.7)
• Bilirubin > 300 μmol/l	Yes (337 μmol/l)	Yes (613 μmol/l)
• Aetiology: non-A, non-B, halothane or (non-acetaminophen) drug-induced	Yes	Yes
Number of criteria present	4	4

The complete criteria include separate criteria for patients with liver failure associated with acetaminophen intoxication.[21] PT = prothrombin time; INT = international normalised ratio.

diagnosed at another hospital and therapy with isoniazid 300 mg/day, rifampin 600 mg/day, and pyrazinamide 2000 mg/day was started (day 0). His body weight was 78 kg, length 1.67 m. Pretreatment liver function parameters were normal (ASAT 12 U/l, ALAT 19 U/l, bilirubin 12 μmol/l). Three months later, there was a transient rise in the liver enzymes ASAT and ALAT. ATT was continued without modifications. Diagnostic tests for viral hepatitis were not performed at that time.

On day 208, patient B was admitted to hospital with complaints of pain in the epigastric region, anorexia, exhaustion, dizziness and a slight jaundice. ASAT was 320 U/l, ALAT 577 U/l, AP 86 U/l, γ-GT 29 U/l, LDH 363 U/l and bilirubin 27 μmol/l. The ATT was discontinued and tests were performed to determine the cause of the hepatitis. IgG antibodies to hepatitis A were positive, IgM negative. Hepatitis B surface antigen was positive, anti-HBs was negative, anti-HBc was positive with anti-HBc IgM negative, HBe Ag was negative, anti-HBe was positive, all consistent with chronic hepatitis B virus (HBV) infection. IgG antibodies to Epstein-Barr virus and to cytomegalovirus were positive. The patient was negative for human immunodeficiency virus, hepatitis C and hepatitis D antibodies.

During the ensuing weeks, ASAT and ALAT rose to 2000 U/l. Bilirubin rose to 550 μmol/l. Liver synthetic function was affected, as reflected by decreased albumin, increased prothrombin time; arterial ammonia was 46 μmol/l. He developed oedema for which diuretics were given. No other specific therapy was prescribed.

On day 242, patient B was released from the referring hospital in good clinical condition. At that time, liver function was stable, albeit grossly abnormal. On day 249 he returned to hospital complaining of increasing drowsiness. The ASAT was 124 U/l, ALAT 136 U/l, bilirubin 613 μmol/l and ammonia 68 μmol/l. The international normalised ratio was elevated at 2.7. Serum creatinine was 114 μmol/l (68-115 μmol/l), while it had been 65 μmol/l one week earlier, suggestive of developing hepatorenal syndrome. The differential diagnosis consisted of acute liver failure caused by ATT with inactive chronic HBV infection or acute liver failure due to a flare of chronic HBV infection. Patient B was transferred to the LUMC. Ultrasonography of the abdomen showed a small but homogenous liver with a normal flow in the portal vein and a normal-sized spleen. Results of repeated serology for HBV infection were identical to those reported above. HBV DNA in the serum was undetectable, so ATT-induced acute liver disease in a patient with a currently inactive chronic HBV was considered likely. Besides ATT, patient B had not taken any other drugs in the recent past. He smoked 10 to 15 cigarettes a day and the patient and his family denied alcohol abuse. The King's College criteria for liver transplantation were met (*table 1*).

His condition further deteriorated with development of hepatic encephalopathy grade IV on day 254. He was transferred to the intensive care unit. ASAT was 294 U/l, ALAT 160 U/l, bilirubin 595 μmol/l and ammonia 168 μmol/l. Prothrombin time was 30.5 seconds and international normalised ratio was 2.5. Biopsy of the liver revealed a disrupted architecture without normal liver parenchyma, massive hepatic necrosis, bridging fibrosis, interface hepatitis and cholestasis. On day 256, patient B underwent orthotopic liver transplantation. Intravenous hepatitis B hyperimmune globulin (HBIG) was administered during and after transplantation, at a later stage converted to monthly intramuscular HBIG with oral lamivudine 100 mg daily. HBsAg has remained negative after transplantation. As the patient had been treated for tuberculosis for at least seven months, no further treatment for tuberculosis was given. There has been no recurrence of tuberculosis.

ASSESSMENT OF RISK FACTORS FOR ATT-INDUCED LIVER DISEASE

Patient A had five risk factors for ATT-induced liver disease (*table 2*). The patient was taking three hepatotoxic drugs as part of ATT, she was a woman of Oriental race and had a low body mass index. In addition, the initial dosage of 600 mg rifampin per day may have been too high in relation to her weight of 50 kg (110 lbs). This is the dosage advised for patients weighing ≥50 kg.[24,25] After resuming rifampin at 450 mg/day on day 89, a very high serum concentration was measured, indirectly indicating that the initial dosage had been too high.

Patient B had four risk factors (*table 2*). He was on three hepatotoxic drugs as part of ATT, was of Oriental race, was >35 years and he had pre-existing liver disease,

Table 2. *Risk factors for liver disease induced by antituberculosis treatment in patients A and B*

	Patient A	Patient B
Age >35 years	No	Yes
Female sex	Yes	No
Oriental race	Yes	Yes
Pre-existing liver disease	No	Yes*
Extensive tuberculosis	No	No
Alcohol consumption	No	No
Low body mass index	Yes	No
Hepatotoxic drugs**	Yes	Yes
High dosage in relation to body weight	Yes	No
Acetylator status	Not determined	Not determined
Risk factors present (total)	5	4

*This was not known at the start of treatment. **Hepatotoxic drugs as part of antituberculosis treatment (isoniazid, rifampin and pyrazinamide), prescribed drugs for other indications or self-administered drugs.

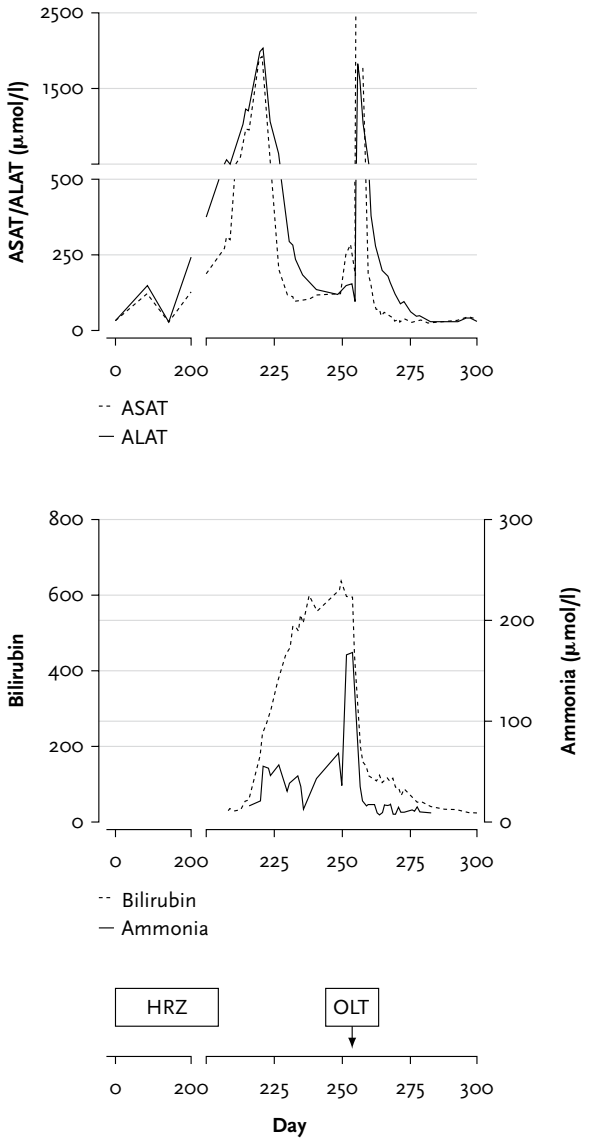
namely chronic HBV infection although the latter was first diagnosed later during ATT. He had been taking pyrazinamide for a relatively long time, considering the recommended therapeutic regimens in national and international guidelines advocate the use of this drug during the initial two months of treatment only.[1,17,18,26]

DISCUSSION

The diagnosis of acute liver failure caused by ATT was made in both the patients described above. Patient A did not have liver disease before starting ATT, while patient B suffered from chronic inactive hepatitis B virus (HBV) infection even though this was first diagnosed at a late stage during ATT and baseline liver functions had been normal. Another difference was the interval between starting ATT and onset of hepatic dysfunction, which was three weeks in patient A, while in patient B this was diagnosed after almost 30 weeks of ATT (*figures 1* and *2*). Rash is another side effect of isoniazid (2%), rifampin (0.8%) and ethambutol (0.5%). Patient A had a rash as well as liver failure but the relation to ATT-induced liver disease is unclear.[27] Patients A and B both underwent liver transplantation, temporary APOLT and orthotopic liver transplantation, respectively. The severity of liver damage precluded APOLT in patient B. The graft could be removed in patient A after regeneration of the native liver had occurred. In both patients, guidelines on the use of ATT were not strictly adhered to and this most likely contributed to the progression to fulminant liver failure. In patient A, all hepatotoxic drugs should have been stopped immediately after the symptoms had developed and liver function was significantly abnormal. In patient B, an evaluation of viral hepatitis at the time of the transient elevation of liver enzymes during ATT would have revealed the presence of HBV infection which should have led to more frequent monitoring of liver functions and to the discontinuation of pyrazinamide.

Prescribed drugs are responsible for 10 to 30% of cases of acute liver failure, and acetaminophen intoxication is the cause in the majority of these cases. ATT represents an important class of drugs that can cause acute liver failure when used in normal dosages, with an incidence of one out of every 10,000 patients taking ATT. The case fatality rate of ATT-induced hepatotoxicity has been estimated at 4.2 per 100,000 patients commencing ATT.[28] A wide disparity exists between the reported incidence of ATT-induced liver disease in India (8 to 39%) compared with reports from Western countries (2 to 3%).[6] The higher incidence in India has been attributed to various factors such as older age, higher alcohol intake, malnutrition, intestinal infections with intestinal parasites, past history of jaundice, high prevalence of chronic liver disease, indiscriminate use of drugs and concomitant viral hepatitis.[15]

Figure 2. *Liver function parameters in patient B*



The X-axis denotes days after starting antituberculosis treatment. HRZ = isoniazid (H), rifampin (R), pyrazinamide (Z); OLT = orthotopic liver transplantation.

Factors that have been associated with a higher risk of ATT-induced liver disease include female sex, age >35 years, oriental race, extent of tuberculosis, pre-existing liver disease, alcohol consumption, nutritional status defined by low body mass index and serum albumin level, certain antituberculosis drugs or combinations thereof and the dosage of drugs in relation to body weight.[7-16,29] Before starting ATT in a specific patient, apart from the measurement of baseline liver function, an assessment of all these known risk factors of ATT-induced liver disease could aid in determining the frequency of monitoring liver enzymes.

The drugs most frequently responsible for hepatotoxicity are isoniazid, rifampin and pyrazinamide.[1,4,17,18] The frequency of ATT-induced hepatotoxicity in the Netherlands is not known because this is not registered. The reported incidence of drug-induced liver disease in patients taking isoniazid or rifampin is 1.6 and 1.1%, respectively.[6] When used in combination, isoniazid and rifampin more frequently cause hepatotoxicity (2.6%) than either drug alone,[6] suggesting an additive but not a synergistic effect. The frequency of severe hepatotoxicity in patients treated with a combination of isoniazid, rifampin and pyrazinamide was 3.4%.[30]

The proposed mechanism of isoniazid toxicity is the production of a hepatotoxic metabolite in liver cells.[3,31] Isoniazid is acetylated to acetylisoniazid, which in turn is hydrolysed to yield the free hydrazine derivative that is the main cause of hepatocellular damage. Acetylator status seems to matter, with most evidence pointing towards slow acetylators having a higher risk of isoniazid-induced liver disease.[8-11,32] Large increases in transaminases were observed more often in slow acetylators (72%) than in rapid acetylators (27%),[10,15] reflecting hepatic exposure to higher drug concentrations, but the difference was only observed during the first weeks of treatment. After eight weeks of treatment the risk of ATT-induced liver disease was not different between slow and rapid acetylators.[10]

Patient B received pyrazinamide 2000 mg/day for almost seven months, which probably contributed significantly to the development of acute liver failure. Pyrazinamide hepatotoxicity is dose-dependent, liver disease rarely occurring with the current dosage of 30 mg/kg and when used for two months at the most.[4] The mechanism is unknown. Liver failure due to pyrazinamide usually occurs after long periods of ATT for tuberculosis disease. In contrast, rapidly progressive liver failure has been described during short-course treatment with a combination of rifampin and pyrazinamide (2RZ) for the treatment of latent tuberculosis infection.[30] For this reason, this regimen has now mostly been abandoned. Pyrazinamide coadministration is associated with an increased mortality in patients with (sub)fulminant liver failure due to ATT, compared with patients with the same condition who have not received pyrazinamide.[20] Pyrazinamide should be prescribed with caution to individuals with hepatic dysfunction,[27] and should not be used for longer than two months because pyrazinamide is only active during the intensive phase of treatment: see the review by Mitchison.[33] If used in patients with underlying liver disease, regular monitoring is indicated.[1]

Speculations have been made on how to distinguish which drug in an ATT regimen is responsible for a patient's ATT-induced liver disease. The interval between the start of ATT and the onset of the abnormalities in liver function can help to assess which drug is the most likely cause. Isoniazid-induced hepatotoxicity usually occurs soon after the start of ATT, as was the case in patient A, but can still occur at any later time point during treatment. Continuation of isoniazid despite symptoms has been associated with a severe clinical course and fatal outcome.[34] Pyrazinamide hepatotoxicity usually occurs after longer periods of treatment (patient B), but again this is not a rule. Isoniazid is associated with fulminant liver failure (patient A) while pyrazinamide more often leads to subfulminant liver failure (as occurred in patient B).[20] However, these parameters cannot be used in an individual patient to discriminate which drug was causative. In patients in whom liver function recovers after discontinuation of ATT, the drugs can often be restarted by sequential introduction followed by frequent monitoring of liver function parameters. This may reveal the causative drug, but liver functions more frequently remain normal or rise only insignificantly during re-challenge because the risk of recurrence of ATT-induced liver disease after resumption of ATT following normalisation of liver functions is low. There is no clear explanation for this phenomenon, but it argues against an idiosyncratic or allergic reaction as the cause of ATT-induced liver disease.

International guidelines issued by the American Thoracic Society, the British Thoracic Society and the European Respiratory Society Task Force all state that baseline determination of liver function tests should be carried out before ATT is started in patients with TB disease.[1,17,18] Notably, there are no general data to support the practice of routine measurement of liver function in patients with normal pretreatment liver function and without evidence of pre-existent liver disease, guidelines being based on clinical experience and expert opinion.[18] Elevated liver function tests are not necessarily a contraindication for ATT but alternative regimens with less or no hepatotoxic drugs are available.[1] Regular monitoring of liver functions is advocated in patients with pre-existent abnormalities or known risk factors and in patients developing symptoms.[1,17,18] In patients with latent TB infection, baseline monitoring of liver functions is only advised in selected cases with a history of liver disease, HIV infection, alcoholism or pregnancy or if the combination of rifampin and pyrazinamide is used.[1,35] Repeat measurements are advocated only if baseline values were abnormal.

So, it has not been definitively established whether liver function parameters should always be measured during ATT and how frequently, or whether this can be guided by the symptoms. However, it is generally agreed that liver parameters should be checked at regular intervals, e.g. monthly, in patients with known pre-existing liver disease, in those using comedication with a risk of interaction with ATT or if continued alcohol consumption is suspected. Guidelines for the clinical management of patients with a rise in liver function parameters during

ATT state that all drugs should be discontinued when serum transaminases exceed five times the upper level of normal.[1] In patient A, ATT was not stopped until a week after the high liver function tests were found. This delay may have contributed to the progressive deterioration as the prognosis is related to the time between onset of hepatic dysfunction and discontinuation of ATT.[9,27] Patient B was admitted to the hospital with symptoms suspicious of hepatitis and high liver enzyme values on day 207 after starting ATT. On day 136 his liver enzymes had been within the normal range. More frequent monitoring during this interval of 70 days could have revealed an elevation of liver enzymes at an earlier stage, before symptoms led to the detection of already severe abnormalities.

In patients requiring liver transplantation for ATT-induced liver failure, non-hepatotoxic drugs are preferred for the treatment of tuberculosis after transplantation in order to avoid toxicity and difficulties with interpretation of liver function parameters. In patient A, liver function parameters rose during the occurrence of partial portal vein thrombosis and later during primary CMV infection in the postoperative period. At that time, the non-hepatotoxic drugs levofloxacin and ethambutol were used. When liver function has stabilised, rifampin can generally be resumed under close monitoring. In patient A, this was done without affecting liver function and was tolerated well after adjustment of the dosage to serum levels.

The incidence of elevated liver enzymes was significantly higher in HBV carriers using ATT when compared with non-HBV carriers with such treatment, probably reflecting pre-existent liver disease.[2,30,36,37] Since coinfection with HBV is endemic in many parts of Asia, this could also contribute to the observed higher incidence of ATT-induced liver disease in India and in general to the increased susceptibility of patients from oriental origin to ATT-induced liver disease. The clinical and histological signs of ATT-induced liver disease often resemble viral hepatitis.[3,7,38] Efforts have been made to distinguish hepatitis B from ATT-induced liver disease histologically. Wong *et al*. developed a probability score to evaluate ATT as the cause of liver injury in HBV carriers and noncarriers with liver dysfunction while using ATT.[36] Except for the presence of fibrosis, which is a typical characteristic of (chronic) HBV infection, no marked difference in histopathological pattern could be observed between HBV carriers and noncarriers. It has previously been mentioned that virological tests to exclude coexistent viral hepatitis should be considered before starting ATT.[17]

In conclusion, acute liver failure is a serious complication of ATT. Monitoring of liver function parameters at regular intervals can help to prevent this condition by withdrawal of all hepatotoxic drugs when values of liver enzymes reach critical levels. An assessment of all risk factors for hepatotoxicity before starting ATT may help to determine the frequency of monitoring. Screening for chronic viral hepatitis in risk groups could contribute to the prevention of ATT-induced liver disease, especially in patients originating from regions where HBV and hepatitis C infection are endemic.

REFERENCES

1. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.
2. Scharer L, Smith JP. Serum transaminase elevations and other hepatic abnormalities in patients receiving isoniazid. Ann Intern Med 1969;71:1113-20.
3. Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. Gastroenterology 1975;69:289-302.
4. Girling DJ. Adverse effects of antituberculosis drugs. Drugs 1982;23:56-74.
5. Tost JR, Vidal R, Cayla J, Diaz-Cabanela D, Jimenez A, Broquetas JM. Severe hepatotoxicity due to anti-tuberculosis drugs in Spain. Int J Tuberc Lung Dis 2005;9:534-40.
6. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest 1991;99:465-71.
7. Kopanoff DE, Snider DEJ, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. Am Rev Respir Dis 1978;117:991-1001.
8. Farrell FJ, Keeffe EB, Man KM, Imperial JC, Esquivel CO. Treatment of hepatic failure secondary to isoniazid hepatitis with liver transplantation. Dig Dis Sci 1994;39:2255-9.
9. Mitchell I, Wendon J, Fitt S, Williams R. Anti-tuberculous therapy and acute liver failure. Lancet 1995;345:555-6.
10. Gronhagen-Riska C, Hellstrom PE, Froseth B. Predisposing factors in hepatitis induced by isoniazid-rifampin treatment of tuberculosis. Am Rev Respir Dis 1978;118:461-6.
11. Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. Ann Pharmacother 2004;38:1074-9.
12. Dossing M, Wilcke JT, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. Tuber Lung Dis 1996;77:335-40.
13. Burman WJ, Reves RR. Hepatotoxicity from rifampin plus pyrazinamide: lessons for policymakers and messages for care providers. Am J Respir Crit Care Med 2001;164:1112-3.
14. Fernandez-Villar A, Sopena B, Fernandez-Villar J, et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2004;8:1499-505.
15. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax 1996;51:132-6.
16. Singh J, Arora A, Garg PK, Thakur VS, Pande JN, Tandon RK. Antituberculosis treatment-induced hepatotoxicity: role of predictive factors. Postgrad Med J 1995;71:359-62.
17. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. Thorax 1998;53:536-48.
18. Migliori GB, Raviglione MC, Schaberg T, et al. Tuberculosis management in Europe. Task Force of the European Respiratory Society (ERS), the World Health Organisation (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) Europe Region. Eur Respir J 1999;14:978-92.

19. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002;35:716-21.

20. Durand F, Bernuau J, Pessayre D, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment including isoniazid. Hepatology 1995;21:929-32.

21. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439-45.

22. Nederlands Genootschap van Maag-Darm-Leverartsen. Richtlijn acuut leverfalen. http://nvh.ewise.nl/uploads/108/44/Richtlijn_Acuut_leverfalen_oktober_2005.pdf . 2005.

23. Nederlandse Vereniging voor Hepatologie. Protocol indicatiestelling en selectie voor levertransplantatie bij volwassen in Nederland. http://nvh.ewise.nl/uploads/108/30/protocol.indicatieselectieolt.final.pdf. 2002.

24. Munoz P, Rodriguez C, Bouza E. Mycobacterium tuberculosis infection in recipients of solid organ transplants. Clin Infect Dis 2005;40:581-7.

25. Tuberculosemiddelen. In: Farmacotherapeutisch Kompas. 2006:739-46.

26. Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT). Richtlijn medicamenteuze behandeling van tuberculose. 2005.

27. Petri WA Jr. Antimicrobial Agents (continued). In: Hardman JG, Limbird LE, Goodman Gilman A (eds). The Pharmacological Basis of Therapeutics. 10th ed. Columbus, OH: McGraw-Hill Companies, 2001:1273-83.

28. Sanyal AJ, Stravitz RT. Acute Liver Failure. In: Zakim D, Boyer TD (eds). Hepatology, a textbook of liver disease. 4th ed. Philadelphia: Saunders, 2003:445-96.

29. Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. Chest 2005;128:116-23.

30. Van Hest R, Baars H, Kik S, et al. Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. Clin Infect Dis 2004;39:488-96.

31. Hussain Z, Kar P, Husain SA. Antituberculosis drug-induced hepatitis: risk factors, prevention and management. Indian J Exp Biol 2003;41:1226-32.

32. Huang YS, Chern HD, Su WJ, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. Hepatology 2002;35:883-9.

33. Mitchison DA. The diagnosis and therapy of tuberculosis during the past 100 years. Am J Respir Crit Care Med. 2005;171:699-706.

34. Moulding TS, Redeker AG, Kanel GC. Twenty isoniazid-associated deaths in one state. Am Rev Respir Dis 1989;140:700-5.

35. Anonymous. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221-47

36. Wong WM, Wu PC, Yuen MF, et al. Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. Hepatology 2000;31:201-6.

37. Patel PA, Voigt MD. Prevalence and interaction of hepatitis B and latent tuberculosis in Vietnamese immigrants to the United States. Am J Gastroenterol 2002;97:1198-203.

38. Garibaldi RA, Drusin RE, Ferebee SH, Gregg MB. Isoniazid-associated hepatitis. Report of an outbreak. Am Rev Respir Dis 1972;106:357-65.

Netherlands
The Journal of Medicine

LETTER TO THE EDITOR

'Nutrothorax' due to misplacement of a nasogastric feeding tube

ABSTRACT

We report a serious complication of blind nasogastric feeding tube insertion in a 65-year-old female patient, which was overlooked and caused severe respiratory failure.

KEYWORDS

Chemical pleuritis, (hydro)pneumothorax, nasogastric feeding tube, thoracostomy tube

CASE REPORT

A nasogastric tube (18 Ch, Kendall-Argyle feeding tube) was inserted for nutritional support by a home care nurse. The patient suffered from malnutrition caused by a vital depression. Blind insertion of the tube was difficult but gurgling was heard over the epigastrium during air insufflation. Control chest X-ray was assessed by an on-call junior doctor who confirmed the correct position of the tube (figure 1). Enteral feeding was started through the nasogastric tube.

Next day, the patient presented to the emergency room with cough, tachypnoea and fever. Chest X-ray showed a significant right-sided pleural effusion and collapse of the right lower lobe (figure 2). Arterial blood gases showed a pH 7.17 (7.35 to 7.45), $PaCO_2$ 7.2 kPA (4.5 to 6.0 kPA), PaO_2 6.5 kPA (9.5 to 13.0 kPA), HCO_3 -15.5 mmol/l (22 to 26 mmol/l), BE –11 mmol/l (-2.0 to 2.0 mmol/l), and SaO_2 86% (92 to 99%) with 10 l/min O_2 through oxygen mask

The patient was immediately intubated and admitted to the intensive care unit. Laryngoscopy confirmed the endotracheal placement of the nasogatric tube. The tube could be removed without resistance. Control chest X-ray showed a massive pleural effusion and possible hydropneumothorax of the right lung. Revision of the initial chest X-ray revealed the malpositioned tube that was initially missed. A right-sided closed-tube thoracostomy was performed and returned approximately 900 ml of enteral nutrition (figure 3). Intercostal drainage did not resolve the pneumothorax even after insertion of a second thoracostomy tube. Computer tomography (CT) scan of the chest showed a right-sided anterior pneumothorax and a significant dorsal pleural effusion (figure 4). CT-guided insertion of an intercostal drain resulted in a complete resolution of the pneumothorax.

Figure 1. *Control chest X-ray after blind insertion of the nasogastric tube, showing malpositioning of the tube*

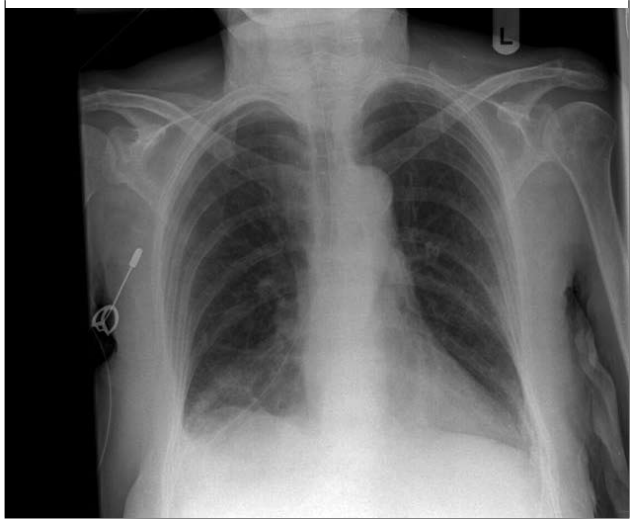
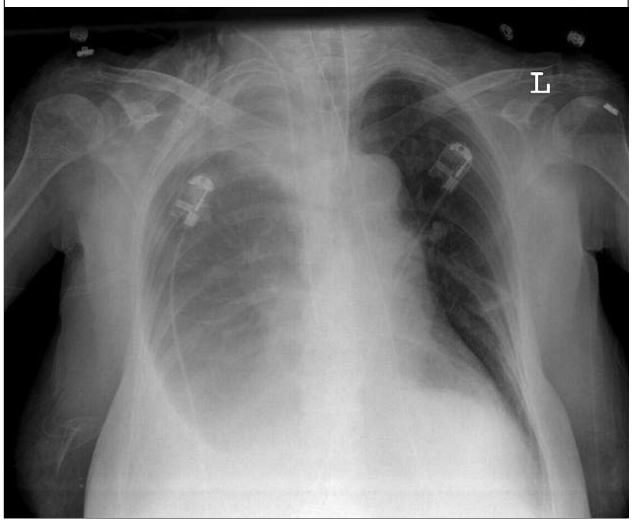


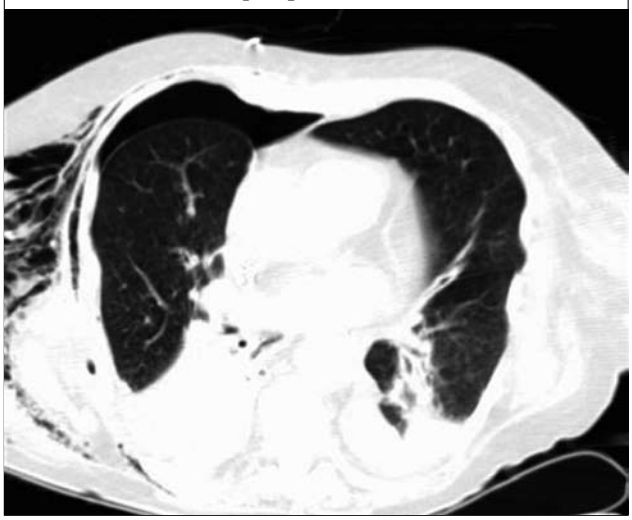
Figure 2. *Chest X-ray the next day, showing right sided pleural effusion and collapse of the right lower lobe*



© 2006 Van Zuiden Communications B.V. All rights reserved.

Figure 3. *Enteral nutrition that was drained after insertion of a right-sided thoracostomy tube*

Figure 4. *CT-scan of the chest, showing a right-sided pneumothorax and a significant dorsal pleural effusion, with the thoracostomy in place*



DISCUSSION

Nasogastric feeding tubes are frequently used in conscious patients. Introduction is performed blindly and is considered a safe procedure. However, complications do exist especially in patients with an altered mental status with decreased cough or gag reflex.[1] *Misplacement of a nasogastric tube is a well-known complication of a blind insertion technique.*[2]

The rate of inadvertent insertion of nasogastric tubes into the trachea and distal airways varies from 0.3 to 15%.[3] *Introduction of chemicals into the lungs and pleural spaces may cause severe aspiration pneumonia, hydrothorax, haemothorax, empyema, delayed pneumothorax and in our case a 'nutrothorax'.*[3]

Physical examination is a poor predictor of tube malpositioning. The placement of a nasogastric tube is usually evaluated by aspirating fluid from the proximal port or insufflating air while auscultating the epigastric area. However, both techniques may yield false-positive results. Penetration into the pleural cavity has been reported and is a potentially lethal complication. It is always necessary to be alert with respect to the tube position, especially if the patient develops respiratory symptoms after insertion. Radiological confirmation is the gold standard. However, as our case shows, correct interpretation of the chest radiograph is an essential final step in the proper confirmation of the position of the nasogastric tube.[4,5] *If this had been done correctly, our patient would not have experienced this rare complication.*

ACKNOWLEDGEMENT

We would like to express our gratitude to R.H.A.M. Kneepkens, radiologist, for his contribution.

L.E.M. Haas, D.H.T. Tjan*, A.R.H. van Zanten
Department of Intensive Care Medicine, Gelderse Vallei Hospital, Ede, the Netherlands, *corresponding author: tel.: +31 (0)318-43 41 15, fax: +31 (0)318-43 41 16, e-mail:icu@zgv.nl

REFERENCES

1. Kawati R, Rubertsson S. Malpositioning of fine bore feeding tube: a serious complication. Acta Anaesthesiol Scand 2005;49:58-61.
2. Marderstein EL, Simmons RL, Ochoa JB. Patient safety: effects of institutional protocols on adverse events related to feeding tube placement in the critically ill. J Am Coll Surg 2004;199:39-50.
3. Boyes RJ, Kruse JA. Nasogastric and nasoenteric intubation. Crit Care Clin 1992;8:865-78.
4. Torrington KG, Bowman MA. Fatal hydrothorax and empyema complicating a malpositioned nasogastric tube. Chest 1981;79:240-2.
5. Hendry PJ, Akyurekli Y, McIntyre R, Quarrington A, Keon J. Bronchopleural complications of nasogastric feeding tubes. Crit Care Med 1986;14:892-4.

LETTER TO THE EDITOR

Status epilepticus and Hashimoto's encephalopathy

Jansen et al. reported a patient with marked hypothyroidism who developed status epilepticus.[1] Although hypothyroidism in itself can lead to ataxia and cognitive dysfunction, we would like to propose the alternative diagnosis of Hashimoto's encephalopathy (HE).[2] This was first described by Brain in 1966; affected individuals present with neurological problems and autoimmune thyroid disease.[3] The lady in question had a combination of thyroid dysfunction with psychosis, ataxia, seizures progressing to status epilepticus and cognitive impairment which are well described in HE.[3-11] Other features of this condition include myoclonus, dementia and demyelinating peripheral neuropathy.[10] Her other clinical signs and symptoms, such as hoarseness and myopathy, can be attributed to the profound hypothyroidism. HE is an uncommon entity; based on a small number of patients, it has an estimated prevalence of 2.1/100,000.[8] Computed tomography of the brain and cerebrospinal fluid findings may be normal but levels of serum antithyroid antibodies, such as antithyroid microsomal, antithyroid peroxidase and antithyroglobulin antibodies are elevated. More recently autoantibodies against the amino terminal of α-enolase and intrathecal synthesis of antithyroid autoantibodies have been reported as useful markers.[8,9] Given its low incidence, there have been few pathological analyses but some autopsy cases have revealed focal inflammatory cell infiltrates within the stroma of the thyroid gland, lymphocytic infiltrates around venules and arterioles and gliosis of gray matter in the cortex, thalmai, basal ganglia and hippocampi.[6] The important point is that patients typically recover following corticosteroids and in some cases immunogloblins. It is worthwhile to determine antithyroid autoantibody levels in patients with unexplained encephalopathies or unexplained seizures with thyroid dysfunction.[12]

A.C.F. Hui*, B.L. Man, W.H. Leung
Division of Neurology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, *corresponding author: tel.: +852-2632 31 31/2632 31 33, fax: +852-2637 53 96/2637 38 52, e-mail: cfhui@cuhk.edu.hk

REFERENCES

1. Jansen HJ, Doebe SR, Louwerse ES, van der Linden JC, Netten PM. Status epilepticus caused by a myxoedema coma. Neth J Med 2006;64:202-5.
2. Dugbartey AT. Neurocognitive aspects of hypothyroidism. Arch Intern Med 1998;158:1413-8.
3. Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. Lancet 1966;2:512-4.
4. McGinley J, McCabe DJ, Fraser A, Casey E, Ryan T, Murphy R. Hashimoto's encephalopathy: an unusual cause of status epilepticus. Ir Med J 2000;93:118.
5. Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: syndrome or myth? Arch Neurol 2003;60:164-71.
6. Duffey P, Yee S, Reid IN, Bridges LR. Hashimoto's encephalopathy: Postmortem findings after fatal status epilepticus. Neurology 2003;61:1124-6.
7. Chaudhuri A, Behan P. The clinical spectrum, diagnosis, pathogenesis and treatment of hashimoto's encephalopathy (recurrent acute disseminated encephalomyelitis). Curr Med Chem 2003;10:1945-53.
8. Ferracci F, Bertiato G, Moretto G. Hashimoto's encephalopathy: epidemiologic data and pathogenetic considerations. J Neurol Sci 2004;15;217:165-8.
9. Fujii A, Yoneda M, Ito T. Autoantibodies against the amino terminal of alpha-enolase are a useful diagnostic marker of Hashimoto's encephalopathy. J Neuroimmunol 2005;162(1-2):130-6.
10. Sheng B, Lau KK, Li HL, Cheng LF. A case of Hashimoto's encephalopathy with demyelinating peripheral neuropathy. Eur Neurol 2005;53:84-5.
11. Marshall GA, Doyle JJ. Long-term treatment of Hashimoto's encephalopathy. J Neuropsychiatry Clin Neurosci 2006;18:14-20.
12. Creutzfeldt CJ, Haberl RL. Hashimoto encephalopathy: a do-not-miss in the differential diagnosis of dementia. J Neurol 2005;252:1285-7.

Response from the authors

We thank Hui et al. for their comment. We agree that Hashimoto's encephalopathy (HE) should be in the differential diagnosis. HE refers to a syndrome of persisting or fluctuating neurological and neuropsychological deficits associated with elevated blood concentrations of antithyroid antibodies. Affected individuals are usually euthyroid or mildly hypothyroid[1,2] and respond well to corticosteroid therapy.[2,3] Furthermore, Hashimoto's thyroiditis can be associated with other autoimmune diseases, such as Addison disease, autoimmune gastritis (pernicious anaemia), rheumatoid arthritis, systemic lupus erythematosus, celiac disease, and diabetes mellitus type 1.

© 2006 Van Zuiden Communications B.V. All rights reserved.

We think that some findings argue against HE, namely: 1) Our patient presented with extreme hypothyroidism, 2) Autopsy of the brain showed no abnormalities, and 3) there was no clinical response to corticosteroid therapy.
In addition, there was no associated autoimmune disease present. Cerebrospinal fluid examination revealed no abnormalities, although a normal cerebrospinal fluid may be present in up to 25% of HE cases.
Unfortunately, we did not measure any thyroid autoantibodies. We agree that thyroid autoantibodies should be determined in every patient with unexplained encephalopathy or unexplained seizures with thyroid dysfunction.

H.J. Jansen*, **P.M. Netten**
Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands, *corresponding author: tel.: +31 (0)73-699 30 81, e-mail: h.jansen@aig.umcn.nl

REFERENCES

1. Henderson LM, Behan PO, Aarli J, et al. Hashimoto's encephalopathy: A new neuroimmunological syndrome. Ann Neurol 1987;22:140-1.
2. Kothbauer-Margreiter I, Sturzenegger M, Komor J, et al. Encephalopathy associated with Hashimoto's thyroiditis. Diagnosis and treatment. J Neurol 1996;243:585-93.
3. Hartmann M, Schaner B, Schelgmann K, Bucking A, et al. Hashimoto's-Enzephalopathie. Steroidsensitive Enzephalopathie bei Hashimoto-Thyroiditis. Nervenartz 2000;71:489-94.

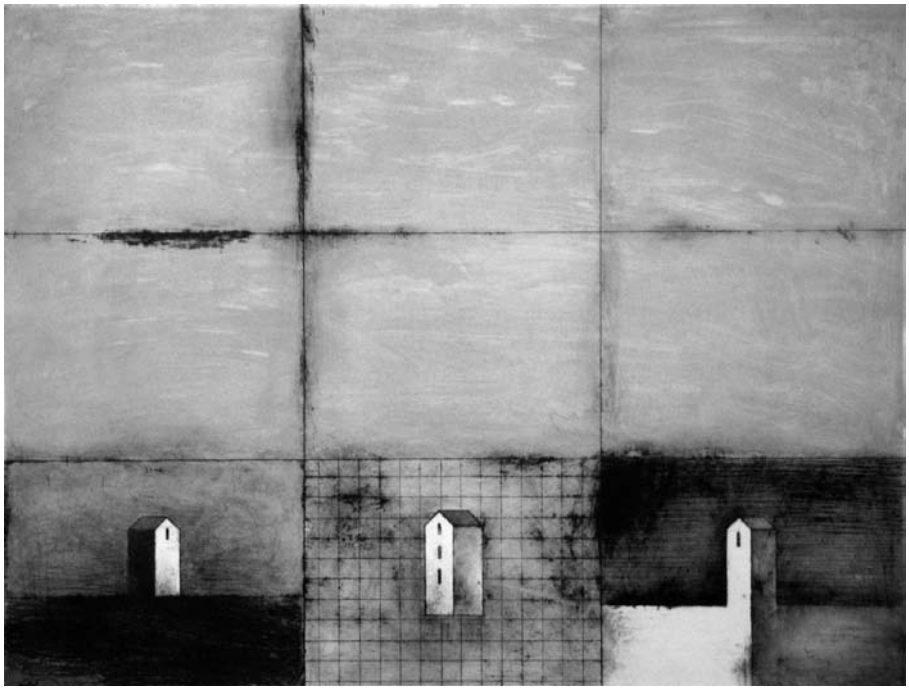
© 2006 Van Zuiden Communications B.V. All rights reserved.

Netherlands
The Journal of Medicine

ABOUT THE COVER

'Drie Huizen'

Jurjen Ravenhorst



Jurjen Ravenhorst was born in Utrecht in 1958 and studied at the Royal Academy of Fine Arts in The Hague, where he graduated cum laude.

Since 1989 he has been supervisor and master printer at Graphic Arts Studio 'Prints' in The Hague. He has won several prices, including the Dutch Graphic Arts Award and Sponsor Prize, and the second International Print Biennial Sapporo in Japan.

His work – paintings, sculptures and graphics – has been shown in many solo exhibitions in the Netherlands and also abroad, where he has participated in various international art exhibitions, such as in Poland, Malaysia, USA and Brazil.

All the different materials that can be used on lithographic stones offer endless possibilities, each with its own consequences. By respecting the basic principals and playing with the unexpected, Ravenhurst comes to new solutions. The image of his prints is usually built up from abstract forms and flats. Small recognisable details, like a house, a moon, an arch or a pillar transfer it into a world of its own.

You can order an original lithography (size 65 x 50 cm) at a price of € 320 from Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands, e-mail: Galerie-Unita@planet.nl, www.galerie-unita.com.

© 2006 Van Zuiden Communications B.V. All rights reserved.

Netherlands
The Journal of Medicine

CT colonography to visualise the whole colon can be complementary to incomplete colonoscopy

T.M. Bisseling[1*], H.M. Dekker[2], B. Cools[1], F.M. Nagengast[3]

Departments of [1]General Internal Medicine, [2]Radiology and [3]Gastroenterology,
Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, the Netherlands,
[*]corresponding author: tel.: +31 (0)24-361 88 19, fax: +31 (0)24-354 17 34

CASE REPORT

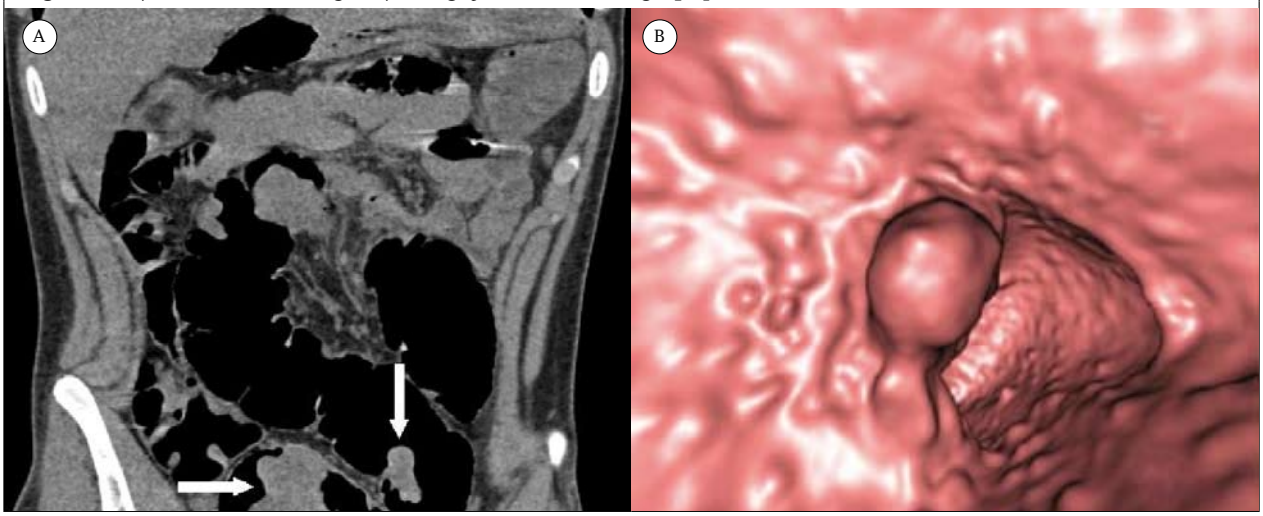
A 20-year-old man was referred to the outpatient clinic with anaemia. Two weeks before presentation he developed a vague pain in the lower abdomen. Bowel motions had always been three times a day, without diarrhoea or constipation. Once he observed rectal blood loss. However, his father told us this had been a daily matter for several weeks. There was no relationship between the abdominal pain and defecation, urination, food products, or physical activity. His appetite was normal, his weight was stable, and he had no fever or night sweats. Family history was negative for inflammatory bowel disease, polyps and malignancy in the gastrointestinal tract.

Physical examination revealed a pale young man with a blood pressure of 124/58 mmHg, a pulse rate of 68 beats/min, a length of 197 cm, and a weight of 81 kg (BMI 20.9 kg/m^2). Examination of the abdomen showed normal bowel sounds, liver and spleen were not enlarged, there was no tenderness and no palpable mass. Rectal examination revealed clear blood. Blood tests showed a haemoglobin of 4.0 mmol/l, MCV 55 fl, leucocytes 5.2 x10^9/l (normal differentiation), iron 1 µmol/l, iron binding capacity 66 µmol/l, iron saturation 1.7%, ESR 8 mm/h, creatinine 65 µmol/l, potassium 3.8 mmol/l, alkaline phosphatase 59 U/l, alanine aminotransferase 9 U/l, lactate dehydrogenase 288 U/l, and albumin 36 g/l. During a colonoscopy the ascending colon could not be visualised. An additional computed tomography (CT) colonography was performed. In *figure 1* an image of this CT colonography is presented.

WHAT IS YOUR DIAGNOSIS?

See page 390, for the answer to this photo quiz.

Figure 1. *A) Coronal CT image, B) Image from CT colonography*



© 2006 Van Zuiden Communications B.V. All rights reserved.

ANSWER TO PHOTO QUIZ (ON PAGE 389)

CT COLONOGRAPHY TO VISUALISE THE WHOLE COLON CAN BE COMPLEMENTARY TO INCOMPLETE COLONOSCOPY

During colonoscopy multiple large polyps were seen in the colon (*figure 2*). Histology showed multiple tubulovillous adenomas with high-grade dysplasia. Unfortunately, the ascending colon could not be visualised during colonoscopy. To visualise the complete colon a CT colonography was performed.[1] This is a technique for which bowel preparation is required, as for a barium enema. Colonic distention is achieved by means of air insufflation through a rectal tube. Nonenhanced supine and prone images were obtained at a multidectector CT scanner (Sensation 64, Siemens, Germany). The interpretation strategy includes two-dimensional and three-dimensional (fly-through) review. CT colonography showed polypoid lesions in varying diameters (*figure 1*).

The prevalence of polyps on colonoscopy in young individuals without a genetic predisposition has not been studied often. In a retrospective analysis de Jong *et al*. observed an incidence of colonic polyps of 4.1% in individuals between 20 and 30 years of age without a gene mutation.[2] Persons who have colonic adenomas are known to have an increased risk of developing colorectal cancer. For this reason surveillance colonoscopies should be performed every three to six years (depending on the number of adenomas). Sometimes it is not possible to visualise the complete colon. Recently the CT colonography has proven to be a good alternative diagnostic procedure as compared with a conventional colonoscopy.[3] However, colonoscopy has the advantage of being both diagnostic and therapeutic.

In our case, a large number of tubolovillous adenomas were found throughout the whole colon. For this reason the patient was referred to the surgical department for a total colectomy with ileo-anal pouch anastomosis. The most likely differential diagnosis is a spontaneous APC mutation on chromosome 5 or a biallelic MYH mutation on chromosome 1.[4] Genetic analysis will follow.

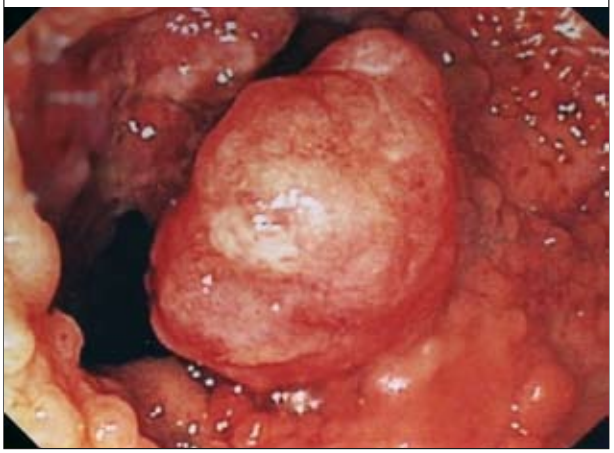
DIAGNOSIS

Adenomatous polyposis coli.

REFERENCES

1. Pickhardt PJ. Differential diagnosis of polypoid lesions seen at CT colonography (Virtual colonoscopy). Radiographics 2004;24:1535-59.
2. De Jong AE, Morreau H, Nagengast FM, et al. Prevalence of adenomas among young individuals at average risk for colorectal cancer. Am J Gastroenterol 2005;100:139-43.
3. Summers RM, Yao Y, Pickhardt PJ, et al. Computed tomographic virtual colonoscopy Computer-Aided Polyp detection in a Screening Population. Gastroenterology 2005;129:1832-44.
4. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis Am J Gastroenterol 2006;101:385-98.

Figure 2. *The polyps as observed during colonoscopy*



© 2006 Van Zuiden Communications B.V. All rights reserved.

INFORMATION FOR AUTHORS

Aims and scope
The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the editor are welcomed.

Manuscripts
Manuscripts submitted to the Journal should report original research not previously published or being considered for publication elsewhere. Submission of a manuscript to this Journal gives the publisher the right to publish the paper if it is accepted. Manuscripts may be edited to improve clarity and expression.

Language
The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

Submission
All submissions to the *Netherlands Journal of Medicine* should be submitted online through Manuscript Central at http://mc.manuscriptcentral.com/nethjmed. Authors should create an account and follow the instructions. If you are unable to submit through Manuscript Central contact the editorial office at g.derksen@aig.umcn.nl, tel.: +31 (0)24-361 04 59 or fax: +31 (0) 24-354 17 34.

Preparation of manuscripts
Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process, number the lines in the margin and the pages.
Subheadings should not exceed 55 characters, including spaces.
Abbreviations: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for generic names of substances and materials.
A *Covering letter* should accompany the manuscript, identifying the corresponding person (with the address, telephone number, fax number and e-mail address). Conflicts of interest, commercial affiliations, consultations, stock or equity interests should be specified. In the letter one to three sentences should be dedicated to what this study adds. The letter should make it clear that the final manuscript has been seen and approved by all authors. All authors should sign the letter. The letter should either be submitted through http://mc.manuscriptcentral.com/nethjmed or faxed to the editorial office (+31 (0)24-354 17 34).

Divide the manuscript into the following sections: Title page, Abstract, Keywords, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

The *Title page* should include authors' names, degrees, academic addresses, correspondence address, including telephone number, fax number, e-mail address and grant support. Also the contribution of each author should be specified.
The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

The *Abstract*, not exceeding 250 words, should be written in a structured manner and with particular care. In original articles, the Abstract should consist of the following paragraphs: Background, Methods, Results and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

Keywords: Include three to five keywords.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

The *Results* should be presented precisely, without discussion.

The *Discussion* should directly relate to the study being reported. Do not include a general review of the topic, but discuss the pertinent literature.

Acknowledgement: All funding sources should be credited here. Also a statement of conflicts of interest should be mentioned.

© 2006 Van Zuiden Communications B.V. All rights reserved.

References should be numbered consecutively as they appear in the text (after the punctuation and in square brackets). Type the reference list with double spacing on a separate page. References should be in the language they are published in, conform the 'Vancouver' style for biomedical journals (N Engl J Med 1991;324:424-8).

Journal abbreviations should conform to the style used in the Cumulated Index Medicus. Examples:

1. Smilde TJ, van Wissen S, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184-95.
2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

Please note that all authors should be listed when six or less; when seven or more, list only the first three and add et al. Do not include references to personal communications, unpublished data or manuscripts either 'in preparation' or 'submitted for publication'. If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against the reference list after your manuscript has been revised.
The use of bibliographic software programmes that are designed to generate reference lists such as Reference Manager© or Endnote© is highly encouraged. Authors can use the predefined output 'Vancouver' style from these programmes.

Tables should be typed with double spacing each on a separate page, numbered consecutively with Arabic numerals, and should contain only horizontal lines. Provide a short descriptive heading above each table with footnotes and/or explanation underneath.

Figures must be suitable for high-quality reproduction (>300 DPI). Submit line drawings made in Word or other computer programmes but not in a PowerPoint file. Colour figures are occasionally possible and will be charged to the authors.
Legends for figures should be typed, with double spacing, on a separate page.

Case reports
Case reports containing concise reports on original work will be considered for publication. Case reports which are relevant for understanding the pathophysiology or clinical presentation of disease may also be accepted under this heading. Selection of case reports will be based on criteria as outlined in a special report by the editors (Drenth et al. The case for case reports in the Netherlands Journal of Medicine. Neth J Med 2006;64(7):262-4). We advise potential authors to take notice of the instructions in this report. Articles published in this section should be no longer than 1000 words, and supplied with a summary of about 60 words, preferably no more than two figures and/or tables, and no more than 15 references.

Mini reviews
Mini reviews are concise notes that bring the reader up to date with the recent developments in the field under discussion. The review article should mention any previous important reviews in the field and contain a comprehensive discussion starting with the general background of the field. It should then go on to discuss the salient features of recent developments. The authors should avoid presenting material which has already been published in a previous review. The manuscript should be divided as follows: title page, abstract and main text. The text may be subdivided further according to the areas to be discussed. The text should not exceed 2500 words.

Letters to the editor (correspondence)
Letters to the editor will be considered by the editorial board. Letters should be no more than 400 words. Please use SI units for measurements and provide the references conform the Vancouver style (N Engl J Med 1991;324:424-8). No more than one figure is allowed. For letters referring to articles previously published in the Journal, the referred article should be quoted in the list of references.

Photo quiz
A photo quiz should not exceed 500 words and include no more than two figures and four references conform the Vancouver style. Abbreviations of measurements should be quoted in SI units.

Book reviews
The editorial board will consider articles reviewing books.

Reviewing process
After external and editorial review of the manuscript the authors will be informed about acceptance, rejection or revision. We require revision as stated in our letter.

Proofs
Proofs will be sent to the authors to be carefully checked for printer's errors. Changes or additions to the edited manuscript cannot be allowed at this stage. Corrected proofs should be returned to the editorial office within two days of receipt.

Offprints
These are not available. The first author receives a sample copy of the Journal with the published article.

© 2006 Van Zuiden Communications B.V. All rights reserved.