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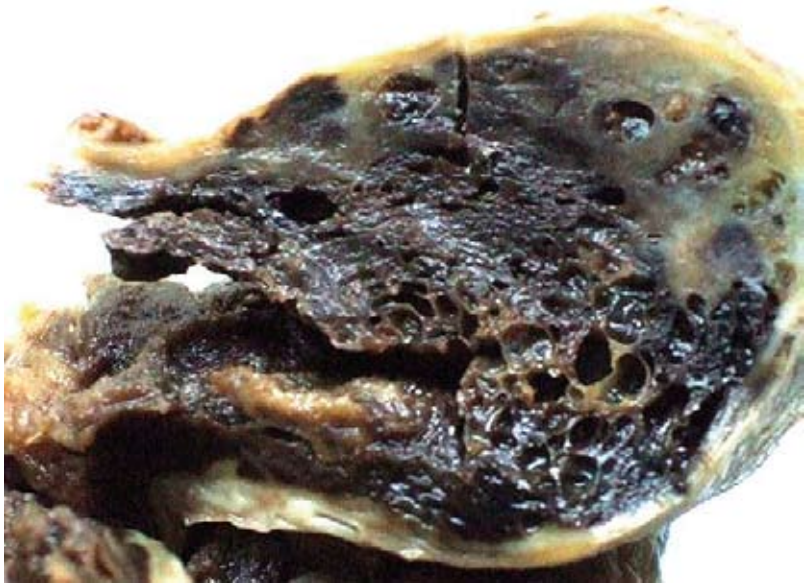

PHOTO QUIZ: A patient with a neck mass, see page 38

Hepatitis C

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Focal segmental glomerulosclerosis

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Gastrointestinal symptoms

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EDITORIAL

The hepatitis C virus burden: a Dutch point of view

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The hepatitis C virus (HCV) infection is one of the leading causes of liver fibrosis and cirrhosis with more than 2.2% of the world population infected. The major routes of transmission are intravenous drug abuse and blood transfusion prior to 1992.[1] The absence of an effective HCV vaccination and the slow progression towards liver cirrhosis may pose a serious health problem in the near future. HCV can be effectively eradicated in a moderate (genotype 1, 4, 5 and 6) to substantial (genotype 2 and 3) number of patients using a combined treatment of pegylated interferon alpha 2a or 2b and ribavirin.

At the moment, newer molecules (e.g. telaprevir, boceprevir) in association with the standard of care could result in a higher HCV eradication percentage. However, in a substantial number of patients the infection is not detected before the occurrence of liver-related complications (decompensated cirrhosis, hepatocellular carcinoma) or extrahepatic manifestations (mixed cryoglobulinaemia, membranoproliferative glomerulonephritis, lichen planus, porphyria cutanea tarda, diabetes, non-Hodgkin's lymphoma). This results in HCV being a major indication for orthotopic liver transplantation.[2]

In the absence of HCV eradication, recurrent HCV after liver transplantation ranges from minimal damage to cirrhosis developing within a few months or years in a substantial proportion of transplant recipients. Therapeutic strategies can be utilised in the pre-, peri- or post-transplantation setting. Antiviral therapy using interferon and ribavirin and modifying immune suppression are the main strategies to prevent progressive disease. Current sustained virological response rates (SVR) are approximately 28%, far below the SVR rates in the non-transplant setting.[2]

The approach to limit HCV-related complications and to lower the costs associated with the disease is multifactorial: prevent infection, identify the population at risk, estimate the seroprevalence, ameliorate treatment outcome, identify difficult/easy to treat populations and increase organ donors. In this issue of the Netherlands Journal of Medicine, two articles and two letter to the editor focus on one or more of these factors.[3-6]

The article by Slavenburg *et al.*[3] could demonstrate a low seroprevalence of HCV (0.2%) in a Dutch population. When combined with data from an earlier trial, a seroprevalence of 0.1% (95% CI 0.039 to 0.17%) was found. One can question if the collected data are from a cohort representative for the entire population. A total of 2200 persons visiting general practitioners (GP) from the urbanised region of Arnhem/Nijmegen were included. No data are included on how many more patients were invited to participate but refused, opening a possibility for a selection bias. Also, by including persons visiting a GP an overrepresentation of HCV-risk groups could be possible (e.g. a higher number of patients who had received blood transfusions or blood products prior to 1992). On the other hand, patients more concerned about their health status and therefore avoiding risk behaviour for blood-borne infections and more frequently seeking medical advice to reassure their good health status could be overrepresented. Regarding the low seroprevalence, overpresentation of high-risk groups seems unlikely. Another flaw is the age distribution (mean age of 60 years) which is not the age distribution of the entire population. Although all those objections are valid, the figures obtained were tested on robustness by comparing them with data from a previously studied population. This resulted in similar figures.

What does this seroprevalence of 0.1% (CI 0.039 to 0.17%) show us? As the authors state, this prevalence is lower than that in other European countries (e.g. Belgium has a seroprevalence of 0.9 %).[7] However, recent screening data in unselected cohorts in Belgium demonstrated a far lower prevalence (unpublished data).

As prevalence is low, this confirms that mass screening can not be cost-effective. Screening should be limited to risk groups (such as intravenous drug abusers, patients receiving blood products prior to 1992, and haemophiliacs).

The Letter to the Editor from de Vries *et al.*[4] can help in identifying 'new' risk groups. They found that intravenous drug abuse remains the major risk behaviour for HCV (45% of the infected patients). Unknown aetiology is the second risk factor (17% of the patients) which illustrates that more epidemiological and virological research is needed to clarify the real cause(s) in this subcohort. Although the authors state that a minority of patients come from outside the Netherlands, this 'minority' is in fact four out of ten patients! The mode of transmission in this 'foreign' cohort seems similar to the entire population. In the perspective of new treatment options (e.g. more resistance and mutations are seen in genotype 1a patients *vs* genotype 1b patients treated with telaprevir), it would have been interesting to know if there was an increase/decrease of these subtypes over time. In a recent Belgian paper, a significant decrease in genotype 1b was counterbalanced by a genotype 1a increase.[8] These new Dutch epidemiological data on seroprevalence and genotype distribution can help the medical community and government in predicting the impact of this disease on the health economy of the country.

In a third contribution on HCV in this issue of the Journal, Korte *et al.*[5] present a case report describing the management of an extrahepatic HCV manifestation after liver transplantation (cryoglobulinaemia-associated glomerulonephritis).

In the seminal paper by Ojo *et al.*[9] 9% of the liver transplant patients have end-stage renal disease necessitating renal replacement therapies such as haemodialysis and kidney transplantation. In the majority of them, this is related to calcinurin inhibitory treatment.

However, patients undergoing liver transplantation for cirrhosis due to HCV infection have a greater frequency of renal insufficiency compared with patients without HCV. It is speculated that there is a higher prevalence of glomerulonephritis at the time of transplantation. In a recent American Association for the Study of Liver Diseases (AASLD) abstract,[10] it was reported that 29 of 34 patients (85%) with HCV and end-stage cirrhosis had histologically recognisable glomerular disease. In contrast, the percentage of clinical nephrotic syndrome after liver transplantation for HCV seems lower. The best way to avoid HCV-related liver and extrahepatic disease after liver transplantation is to get rid of the virus prior to transplantation. However, this is seldom achieved.

What is peculiar in this case report is the occurrence of cryoglobulinaemia associated glomerulonephritis (an immune-mediated disease) after liver transplantation (in an immunosuppressed patient). Immunosuppressive drugs used in transplantation target T cells, whereas cryoglobulinaemia associated glomerolonephritis is a B cell/antibody mediated disease. If antiviral treatment is ineffective, alternative therapies (high-dose steroids, plasmapheresis) need to be used. The effectiveness of these treatments is limited and potential side effects are severe (e.g. infections). Again, a recent AASLD abstract[11] demonstrated the risk of death to be independently associated with central nervous system involvement and the use of immunosuppressors.

Rituximab, an effective depleting monoclonal antibody for circulating CD20 bearing B lymphocytes, seemed effective in the presented case report and is possibly not linked with a higher risk of infections. However, this needs to be proven in an larger cohort.

As a conclusion, these good Dutch papers on HCV in this issue of the Journal contribute to a better understanding of HCV seroprevalence and genotype distribution in the Netherlands, and open new treatment options in the management of HCV-related extrahepatic disease post liver transplantation. However, there is still a long way to go before definitive eradication of the HCV virus is achieved.

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REVIEW

Review on diagnosis and treatment of focal segmental glomerulosclerosis

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ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is one the most important causes of the nephrotic syndrome in adult patients. FSGS is not a disease entity. The identification of underlying causes of FSGS (secondary FSGS) has increased our insight into the pathogenesis of FSGS. Moreover, differentiating between primary (idiopathic) and secondary forms of FSGS is important to allow appropriate treatment. Recently a new pathological classification of FSGS was proposed, expanding FSGS to include nonsclerotic lesions. In this review we discuss the current diagnostic and therapeutic options in patients with FSGS.

KEYWORDS

Diagnosis, focal segmental glomerulosclerosis, nephrotic syndrome, treatment

INTRODUCTION

In 1957, Rich provided the first detailed pathological description of focal segmental glomerulosclerosis (FSGS).[1] However, it was not until the 1970s that FSGS emerged as a separate clinico-pathological entity.[2] Currently, FSGS is one of the most common patterns of glomerular injury encountered in human renal biopsies.[3] For a long period of time FSGS in adults has been considered to be prednisone resistant.[4] However, over the last 25 years the results of treatment have improved. Furthermore, new underlying causes of FSGS have been identified and improved our understanding of the pathogenesis of FSGS. Moreover, a recently proposed pathology classification has pointed to the existence of new, nonsclerotic forms of FSGS. In this review, we provide an update on the diagnosis and treatment of FSGS.

Aetiology and pathogenesis of FSGS

According to the classical description, FSGS is characterised by the presence of a scarring lesion in a portion (segment) of some (focal), but not all glomeruli. The scar comprises increased mesangial matrix with collapsed glomerular capillaries, an adhesion between the tuft and Bowman's capsule, and hyaline deposits.[5] The glomerular scar can be accompanied by features such as mesangial hypercellularity and foam cells. Progressive lesions are characterised by periglomerular and tubulo-interstitial fibrosis.

It has been recognised for many years that FSGS is a merely descriptive diagnosis and not a single disease entity. FSGS can be idiopathic (primary; unknown cause) or secondary (with underlying cause). Secondary forms of FSGS were generally considered to result from maladaptive responses that occurred due to the loss of functioning nephrons, hyperfiltration or increased glomerular pressure. Based on studies in experimental animal models such as the remnant kidney model in the rat, Kriz *et al*. demonstrated that loss of podocytes was pivotal in FSGS resulting from these maladaptive responses.[6] Of note, all animal models used had evidence of glomerular hyperfiltration, hypertrophy or increased glomerular pressure. Based on these studies Kriz proposed that the following sequence of events results in FSGS: there is initial injury to the podocyte, the damaged podocytes detach from the glomerular basement membrane (GBM), ultimately followed by loss of the entire cell into Bowman's space. Because podocytes are incapable of regenerative replication, loss of podocytes cannot be replaced, which leads to areas of 'bare' GBM. Next, parietal epithelial cells covering Bowman's capsule attach to the bare GBM, leading to the formation of an adhesion between the capillary tuft and Bowman's capsule. At the site of the adhesion, a gap forms in the parietal epithelium. If the

attached capillary is still functioning, fluid leaks into the gap in the parietal epithelium (misdirected filtration), leading to the formation of a fluid-rich periglomerular space. Then fibroblasts are stimulated, which results in periglomerular and tubulointerstitial fibrosis. The continuing misdirected filtration and podocyte loss results in a further expansion of the adhesion. Inside an adhesion capillaries eventually collapse or become occluded either by deposition of hyaline material or microthrombosis.

In recent years the list of secondary causes has steadily grown and now also includes FSGS not related to glomerular hyperfiltration (*table 1*). FSGS may result from direct injury to the podocytes due to viral infections (HIV) or the use of drugs (pamidronate/alendronate).[7,8] Even more important, and instrumental in our knowledge of the role of the podocyte in proteinuria and FSGS, was the discovery that Finnish type congenital nephrotic syndrome was caused by mutations in nephrin, a podocytic protein and important constituent of the slit diaphragm.[9] Meanwhile, mutations in other podocytic proteins have been discovered in other familial forms of FSGS (*table 1*). A special form of inheritable FSGS is caused by podocytic mitochondrial DNA mutations.[10]

Still, for most patients with FSGS the pathogenesis is still unknown. There is strong evidence that this idiopathic FSGS may be the result of a circulating factor that alters the permeability of glomeruli.[11,12] The best evidence supporting the presence of a circulating factor comes from recurrent FSGS after renal transplantation. Proteinuria may develop within days after transplantation, and plasma exchange instituted early in the course of recurrent disease removes the putative factor and results in a remission of proteinuria.[13] More recent data paint a more complicated picture, suggesting that the increased permeability may be due to the absence or loss of an inhibitor for the permeability factor.[14]

Damage to the podocyte also plays a central role in the pathogenesis of idiopathic FSGS.[15] However, the subsequent events differ from secondary FSGS due to maladaptive responses.

Based on studies in animals and humans we proposed the following sequence of events in idiopathic FSGS.[16-18] Initially injury of the podocytes results in foot process effacement, proteinuria and microvillous transformation without podocyte detachment or podocyte loss. Parietal epithelial cells (PECs) are injured, start to proliferate and cover the glomerular tuft. The proliferating PECs produce and deposit newly formed extracellular matrix that leads to scarring. The stimulus for PEC proliferation is not clear. Possibly, the interaction between activated/injured podocytes and activated/injured PECs or denuded areas of Bowman's capsule plays a role.[19]

Table 1. *Aetiological classification of focal segmental glomerulosclerosis (FSGS)*[101]

Idiopathic (primary) FSGS
Secondary FSGS:
1. Familial
   - A. Mutations in α-actinin 4
   - B. Mutations in nephrin
   - C. Mutations in podocin
   - D. Mutations in WT-1
   - E. Mutations in CD2-associated protein
   - F. Mitochondrial cytopathies
2. Virus associated
   - A. HIV-associated nephropathy
   - B. Parvovirus B19
3. Medication
   - A. Heroin nephropathy
   - B. Interferon-α
   - C. Lithium
   - D. Pamidronate / alendronate
4. Adaptive structural-functional responses likely mediated by glomerular hypertrophy or hyperfiltration
   - 4.1 Reduced renal mass
     - A. Oligomeganephronia
     - B. Unilateral renal agenesis
     - C. Renal dysplasia
     - D. Cortical necrosis
     - E. Reflux nephropathy
     - F. Surgical renal ablation
     - G. Chronic allograft nephropathy
     - H. Any advanced renal disease with reduction in functioning nephrons
   - 4.2 Initially normal renal mass
     - A. Diabetes mellitus
     - B. Hypertension
     - C. Obesity
     - D. Cyanotic congenital heart disease
     - E. Sickle cell anaemia
5. Malignancy (lymphoma)

Nonspecific pattern of FSGS caused by renal scarring in glomerular disease
- A. Focal proliferative glomerulonephritis (IgA nephropathy, lupus nephritis, pauci-immune focal necrotising and crescentic glomerulonephritis)
- B. Hereditary nephritis (Alport syndrome)
- C. Membranous glomerulopathy
- D. Thrombotic microangiopathy

DIAGNOSIS OF IDIOPATHIC AND SECONDARY FSGS

Distinguishing between idiopathic and secondary forms is not merely semantic, but has important therapeutic implications as discussed below. Generally, the distinction can be made from the history (with special attention to secondary causes) and some additional laboratory (serum albumin) and radiological (chest X-ray and kidney ultrasound) studies.

In patients with nephrotic range proteinuria (≥3 g/day), serum albumin is an important clinical parameter to distinguish between FSGS secondary to hyperfiltration and other forms of FSGS. In a study of 37 patients with nephrotic range proteinuria due to biopsy-proven FSGS, Praga *et al.* showed that serum albumin was significantly lower in patients with presumed idiopathic FSGS (serum albumin <30 g/l) compared with FSGS

secondary to massive obesity, vesicoureteral reflux, or renal mass reduction (serum albumin >35 g/l).[20] In contrast to hyperfiltration-associated FSGS, other forms of secondary FGSG such as viral-associated FSGS, drug-induced FSGS and familial FSGS may also present with a low serum albumin. Especially the last-mentioned form cannot be differentiated from idiopathic FSGS on clinical grounds.

Although clinical data and serum albumin levels often allow differentiation between idiopathic FSGS and FSGS secondary to hyperfiltration, discussion sometimes remains, especially in patients with a serum albumin between 30 g/l and 35 g/l. It has been suggested that these forms could be differentiated by evaluation of foot process effacement in electron microscopy, with mild effacement occurring in secondary FSGS and complete effacement in idiopathic FSGS.[21,22] In a recent study of podocyte alterations we noted that the mean foot process width was significantly greater in patients with idiopathic FSGS compared with secondary FSGS mediated by adaptive structural-functional responses.[23] The association between foot process width and type of FSGS was independent of proteinuria. Furthermore, the degree of overlap in foot process width between idiopathic and secondary FSGS was low, suggesting that quantitative assessment of foot processes may provide a means for distinguishing between idiopathic and secondary FSGS. Electron microscopy can also help in determining other underlying causes of FSGS. Special attention should be paid to the presence of tubulo-reticular inclusions in endothelial cells (HIV), viral particles, or the presence of abnormal mitochondria in the podocyte (mitochondrial DNA mutation).

A positive family history identifies patients with FSGS based on mutations in podocytic proteins.[24-26] Obviously, it is important to consider whether patients with FSGS need genetic testing to evaluate spontaneous mutations. In contrast to children, spontaneous mutations in adults with FSGS are rare, with a reported prevalence of 1.5 to 5%.[27-29] He *et al.* screened 78 adult patients with nonfamilial FSGS (15 steroid-sensitive and 63 steroid-resistant) for known mutations in the podocin gene. Compound heterozygous mutations were detected in only one patient with steroid-sensitive FSGS; no homozygous mutations were found. These results are consistent with the findings by Caridi *et al.,* who discovered only three heterozygous mutations in a cohort of 64 patients with steroid-resistant nephrotic syndrome.[28] The study by He *et al.* also identified eight patients with heterozygous R229Q, a podocin polymorphism. The allele frequency of this variant did not differ from normal controls. The significance of the R229Q variant as a disease-causing mutation in FSGS is currently unknown.[30] Similarly, mutations in the gene encoding α-actinin-4 are also rare. Aucella *et al.* found no α-actinin-4 gene mutations in 33 adults with nonfamilial FSGS.[29] In view of the low incidence of spontaneous mutations, we do not recommend mutation screening in adult patients with nonfamilial FSGS.

CLINICAL PRESENTATION, PROGNOSIS AND TREATMENT

The data on the clinical characteristics and natural history of patients with FSGS are biased by variable inclusion criteria of the reported studies. Patients with secondary FSGS due to hyperfiltration injury will not be biopsied and are often not included in these studies. Search for aetiological causes has been limited, especially in the older studies. In most studies patients with idiopathic FSGS will predominate.

Clinical presentation

FSGS can occur at any age. In adults the mean age at onset varies between 40 and 50 years.[31-33] The number of affected males and females is roughly similar with a male-to-female ratio of 1:1. Patients with idiopathic FSGS and patients with FSGS secondary to infections, medication or genetic mutations typically present with a nephrotic syndrome.[20] By comparison, patients with FSGS secondary to adaptive structural-functional responses (hyperfiltration-associated FSGS) usually present with a more indolent course without hypoalbuminaemia or oedema, even when proteinuria exceeds 3 to 4 g/day.[20,22] In addition to proteinuria, microscopic haematuria and hypertension are common presenting features of both idiopathic and secondary FSGS.

Prognosis

Important clinical features predicting the clinical course of FSGS are the amount of proteinuria and the level of plasma creatinine. Half of the patients presenting with a proteinuria >3 g/day or a serum creatinine over 115 μmol/l progress to end-stage renal disease within five to ten years.[34-36] Renal survival is even worse if proteinuria exceeds 10 g/day, with end-stage renal disease (ESRD) occurring in the majority of patients within five years after presentation. In contrast, non-nephrotic proteinuria portends a much better prognosis, with a renal survival of >80% after ten years. Still, the single best predictor of a favourable outcome is attainment of a complete or partial remission of proteinuria. Less than 15% of patients attaining a remission progress to ESRD.[33,37,38] Most reported remissions were induced by steroid therapy and it is generally suggested that spontaneous remissions occur infrequently in patients with FSGS. However, we have recently shown a high spontaneous remission rate of 60% in patients with idiopathic FSGS who present with a normal renal function and a selective proteinuria (selectivity index <0.2). In addition these patients were characterised by a serum albumin >20 g/l and a proteinuria <8 g/day at three months after renal biopsy.[39]

Other authors have attempted to determine whether prognosis in patients with FSGS can be predicted. Bazzi

et al. showed that a fractional excretion (FE) of IgG <0.14% was associated with a high remission rate after immunosuppressive therapy.[40] In contrast, patients with an FE of IgG >0.14% had a dismal prognosis even with immunosuppressive therapy. Recently, we also reported on the predictive value of FE IgG in 32 patients with idiopathic FSGS.[41] Our data do not support Bazzi's conclusion that FE IgG predicts resistance to immunosuppressive medication. Although an FE IgG >0.14% was associated with worse baseline characteristics, remission rate was high (59%) and not different from patients with FE IgG <0.14%. Therefore, until more data become available, FE IgG should not be used to guide treatment in patients with FSGS.

Approximately 50% of patients who develop a remission after prednisone therapy will develop recurrent proteinuria during tapering of the prednisone (steroid dependent) or after stopping treatment (relapse). Patients who do not develop a remission after a minimum of eight to 16 weeks of prednisone therapy are called steroid resistant. However, this definition is subject to debate (see below).

Treatment

In patients with secondary FSGS, therapy should obviously be directed at the underlying disorder or removal of the inciting drug. In patients with severe obesity, weight loss (>10% of body mass index) induces a significant decrease of proteinuria, which is almost similar to the effect of ACE inhibitors.[42] However, maintaining the weight loss is often difficult and many patients relapse.[43] Small cohort studies suggest that antiretroviral therapy improves renal survival in patients with HIV-associated FSGS.[44,45] Case reports also provide support for the use of antiretroviral therapy, with recovery of dialysis-dependent renal failure after initiation of antiretroviral therapy.[46] FSGS associated with haematological conditions such as multiple myeloma and (non) Hodgkin's lymphomas often responds with a resolution of the proteinuria after successful treatment of the underlying haematological condition.[47,48] Familial forms of FSGS are known to be steroid resistant.[25,49-51] A possible exception are patients with a nonfamilial (sporadic) heterozygous podocin mutation.[52]

It is well known that blood pressure control and reduction of proteinuria significantly slows the progression of renal insufficiency in patients with proteinuric nondiabetic renal disease.[53-57] Proteinuria should be reduced to <0.5 g/day. Target blood pressures are ≤130/80 mmHg in patients with proteinuria ≤1 g/day and ≤125/75 mmHg in patients with proteinuria >1 g/day.[55,58] ACE inhibitors (ACE-i) or in case of side effects angiotensin receptor blockers (ARB) are preferred because they are more effective than other antihypertensive agents in slowing the progression of most nondiabetic kidney diseases.[53,58,59] Despite the recognised beneficial effect of ACE-i in patients with chronic kidney disease, little is known about the efficacy of ACE-i in patients with idiopathic FSGS. Although ACE-i reduce proteinuria in idiopathic FSGS, the few available studies suggest that ACE-i rarely induce a complete remission and development of end-stage renal disease is not prevented.[60,61] However, there is some evidence that ACE-i slow the progression to ESRD.[62] Furthermore, treatment with ACE-i also improves the hypoalbuminaemia and hyperlipidaemia that is associated with idiopathic FSGS.[63] Therefore, treatment with ACE-i is recommended for all patients with FSGS. The antiproteinuric effect of ACE-i is most prominent in patients who are on a low sodium diet (50 to 100 mmol/day) or who are treated with diuretics, since relative volume depletion results in greater angiotensin II dependence of the glomerular microcirculation. Other antihypertensive drugs should be added if the goals for blood pressure and proteinuria are not reached with ACE-i, a low sodium diet and diuretics.

An abnormal lipid metabolism usually accompanies a nephrotic syndrome. Most prominent are an increased LDL cholesterol, hypertriglyceridaemia and an increased lipoprotein A (LP(a)).[64,65] This combination is highly atherogenic.[66,67] HMG CoA reductase inhibitors (statins) are very effective in lowering total and LDL cholesterol and to a lesser degree triglycerides and LP(a), also in patients with a nephrotic syndrome.[68-72] Although a cardioprotective effect of statins has never been proven in patients with a nephrotic syndrome, prevention studies in the general population with similar lipid disorders have shown a marked reduction of cardiovascular diseases.[73,74] Notably, recent studies have also suggested that the use of statins in patients with proteinuria attenuates the deterioration of renal function.[75,76]

Immunosuppressive therapy should be considered in patients with idiopathic FSGS and a proteinuria ≥3 g/day. Current recommendations for the initial treatment of idiopathic FSGS are almost entirely based on retrospective studies.[38] Data from these studies show that corticosteroids remain the mainstay of treatment in idiopathic FSGS. Remission rates do not improve if cytotoxic agents are added to the initial treatment of FSGS with corticosteroids.[77] To attain a remission both the duration and dose of corticosteroid therapy are important factors. The median time until a remission is attained is three to four months, with the majority of patients entering a remission within six months.[34,35,77-82] In addition, studies reporting higher remission rates are also characterised by a longer duration (two to four months) of high-dose treatment.[35] FSGS is often considered to be steroid resistant if no remission has occurred after two to four months of treatment with high-dose prednisone.[83] However, a significant number of patients do attain a remission four to six months after initiation of treatment with high-dose prednisone. It is our experience that patients who will

eventually develop a remission show some reduction in proteinuria within the first months of treatment. Therefore, one could argue that patients who respond to treatment with a significant reduction of proteinuria (>50%) should be treated for a total of six months before considering them resistant to corticosteroids.[84,85]

Few studies have addressed the best therapeutic approach for relapsing or corticosteroid-dependent FSGS. The most important goal is to achieve a stable remission without the need for long-term prednisone. Both cyclophosphamide and cyclosporine appear to be beneficial, inducing a new remission in 78 and 73% of patients, respectively.[38] However, despite similar remission rates, a new relapse is more common after cessation of cyclosporine. In contrast, cyclophosphamide induces more stable remissions.[86] Cyclophosphamide is usually given in a dose of 2 mg/kg/day for two to three months.

Several studies have evaluated the effect of cytotoxic agents and cyclosporine in patients with corticosteroid resistant FSGS. The definition of steroid resistance was quite variable in these studies, ranging from four to 16 weeks of treatment with prednisone. Alkylating agents do not seem to benefit patients with steroid-resistant FSGS. Retrospective studies in adults report low remission rates for alkylating agents compared with cyclosporine (11 *vs* 40%).[78-80,87-96] Two prospective trials have been conducted in adults, comparing six to 12 months of treatment with cyclosporine with placebo.[91,92] Remission rate was significantly higher in patients treated with cyclosporine (60 to 69%) compared with placebo (4 to 33%). However, within one year after discontinuation of cyclosporine, 60 to 80% of the patients had relapsed.

The high relapse rate may decrease with prolonged use of cyclosporine. A study by Meyrier *et al*. suggests that continuing treatment with cyclosporine for one year in case of a remission followed by a slow tapering of the dose results in a more durable remission.[83] However, this study included a small number of patients with FSGS with relatively mild FSGS lesions on the first renal biopsy. Therefore, the results should be interpreted with caution.

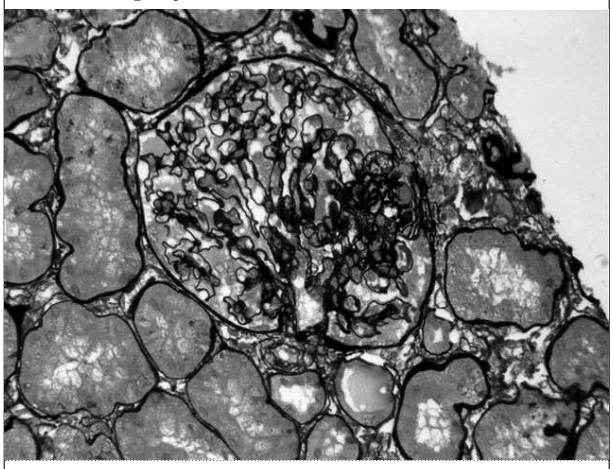
A major concern is the nephrotoxicity of cyclosporine. Continuous use for more than 12 months is associated with a significant increase in tubulointerstitial fibrosis. In most cases serum creatinine does not significantly change despite the aggravation of fibrosis.[83] In addition, cyclosporine may accelerate the progression of FSGS. The number of glomeruli with sclerotic lesions increases significantly during treatment with cyclosporine, even in patients with a partial or complete remission. Cyclosporine nephrotoxicity is associated with higher doses of cyclosporine (>5.5 mg/kg/day), a higher percentage of glomeruli with FSGS lesions and renal insufficiency prior to treatment. Therefore, the cyclosporine dose should not exceed 5.5 mg/kg/day and treatment with cyclosporine should be limited to patients with a creatinine clearance >60 ml/min/1.73 m^2).[83]

Uncontrolled studies have demonstrated an improvement in both renal function and proteinuria for patients with HIV-associated FSGS treated with corticosteroids.[97-99] The data from these studies are conflicting regarding increased risk for serious infections and hospitalisation. Nevertheless, a recent guideline for the management of chronic kidney disease in HIV-infected patients advised considering prednisone therapy at 1 mg/kg/day (maximum dose 80 mg/day) for two months, followed by two to four months taper in patients with HIV-associated FSGS whose kidney function is deteriorating despite use of antiretroviral therapy.[100] Before considering corticosteroids active infection and active illicit intravenous drug use should be excluded. In patients with obesity, treatment with corticosteroids can even be detrimental, because of a further increase in body weight.

A NEW PATHOLOGICAL CLASSIFICATION OF FSGS

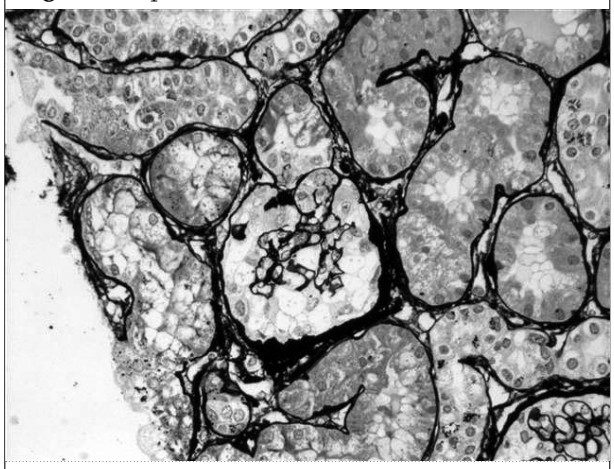
Over the years, the pathological description of FSGS has evolved, and in addition to the classical form other variants have been described. Recently, a group of pathologists proposed a new pathological classification for FSGS based on an assessment of glomerular light microscopic features (Columbia classification; *table 2*; *figures 1* to 5). This classification presumes exclusion of FSGS caused by glomerular scarring in the

Figure 1. *Focal segmental glomerulosclerosis not otherwise specified*



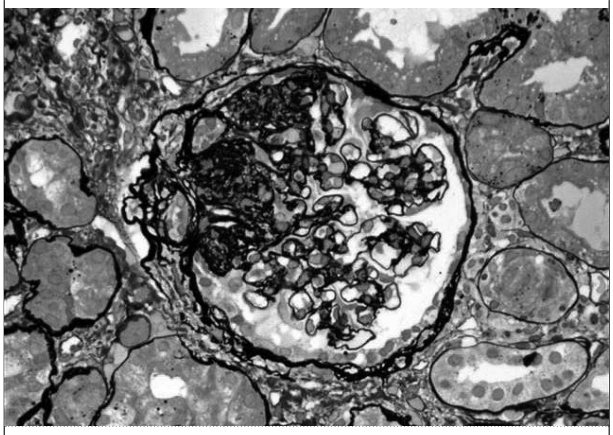
Segmental obliteration of capillary lumina by accumulation of matrix and hyalinosis. Features of collapse, glomerular tip lesion or endocapillary hypercellularity are not seen.

Figure 2. *Tip variant*



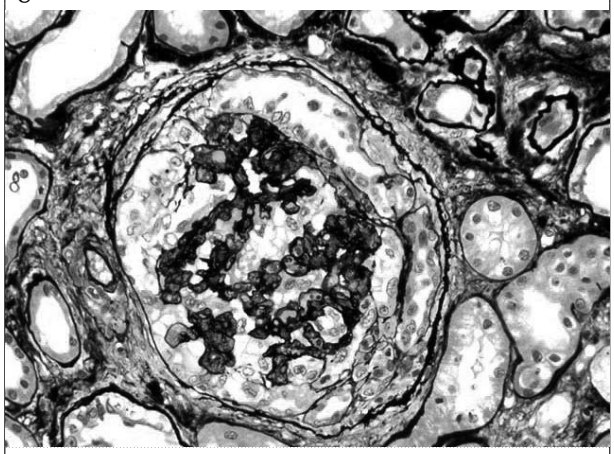
Adhesion between glomerular tuft and Bowman's capsule at the tubular pole, adjacent to the origin of the proximal tubule. No collapse of the capillary tuft.

Figure 3. *Perihilar focal segmental glomerulosclerosis*



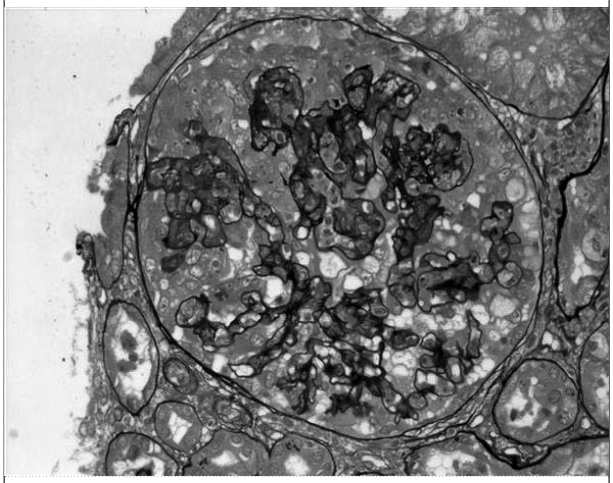
A lesion of segmental sclerosis and hyalinosis located at the glomerular vascular pole. Features of collapse, glomerular tip lesion or endocapillary hypercellularity are not present.

Figure 4. *Collapsing focal segmental glomerulosclerosis*



Global collapse of the capillary tuft, with hypertrophy and hyperplasia of glomerular epithelial cells.

Figure 5. *Cellular focal segmental glomerulosclerosis*



Segmental endocapillary hypercellularity. Features of collapse or glomerular tip lesion are not present.

Table 2. *Morphological variants of focal segmental glomerulosclerosis*[101]

Subtype	Characteristics	Exclusion criteria
Not otherwise specified variant	At least one glomerulus with segmental increase in matrix obliterating the capillary lumen There may be segmental glomerular basement membrane collapse without overlying podocyte hyperplasia	Exclude perihilar, cellular, tip and collapsing variant
Perihilar variant	At least one glomerulus with perihilar hyalinosis, with or without sclerosis >50% of glomeruli with segmental lesions must have perihilar sclerosis and/or hyalinosis	Exclude cellular, tip and collapsing variant
Cellular variant	At least one glomerulus with segmental endocapillary hypercellularity occluding lumina, with or without foam cells and karyorrhexis	Exclude tip and collapsing variant
Tip variant	At least one segmental lesion involving the tip domain (outer 25% of tuft next to origin of proximal tubule) The tubular pole must be identified in the defining lesion The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck The tip lesion may be cellular or sclerosing	Exclude collapsing variant
Collapsing variant	At least one glomerulus with segmental or global collapse and overlying podocyte hyperplasia	None

course of other idiopathic glomerular diseases (*table 1*).[101] The classification defines five main light microscopic variants: FSGS not otherwise specified (NOS), tip variant, perihilar variant, cellular variant, and collapsing variant. It is important to notice that the presence of sclerosis is no longer obligatory for the diagnosis of FSGS since sclerosis is often absent, particularly in the tip variant and the collapsing variant.

Although the different variants may reflect different diseases (with different causes and differences in pathogenesis), this has not been proven. The different variants may be just a reflection of a different stage of FSGS, dependent on the activity and time of onset of the disease.

Some pathological variants are more likely to occur in relation to certain causes. The perihilar variant of FSGS is associated with hyperfiltration, whereas HIV typically results in collapsing FSGS. However, there is a clear overlap, and patients with idiopathic FSGS may present with either variant.

Clinical presentation and sociodemographic findings differ between the FSGS variants (*table 3*).[32,41,102] Collapsing FSGS has a predilection for black people originating from Africa and typically presents with a severe nephrotic syndrome and substantial renal insufficiency. The tip variant has a low proportion of black people originating from Africa. The majority of these patients also present with a severe nephrotic syndrome (>90%). Renal function is usually preserved in patients with the tip variant. Perihilar FSGS has the lowest frequency of nephrotic syndrome. Patients with FSGS NOS tend to have clinical parameters intermediate between the tip variant and perihilar FSGS, whereas cellular FSGS had clinical parameters intermediate between the tip variant and collapsing FSGS.

Several retrospective studies have reported on the prognostic utility of the Columbia classification. A recent study by Chun *et al*. was unable to detect a significant difference in remission rate among patients with collapsing FSGS, FSGS NOS and the tip variant.[33] However, the statistical power of this study to detect a clinically significant difference was low due to the small number of patients with the tip variant. In contrast, two other studies reported a lower remission rate and worse renal survival among patients with the collapsing variant compared with the tip variant and FSGS NOS.[32,102] Patients with the cellular variant had remission rates between those of patients with the tip variant and collapsing FSGS.[102] A study by our group showed a significantly better renal survival in patients with the tip variant compared with FSGS NOS and perihilar FSGS.[103] These studies suggest that the tip variant has a higher remission rate and a better renal survival compared with other FSGS variants. At present classification of FSGS should not influence therapeutic decisions.

GUIDELINES FOR DIAGNOSIS AND TREATMENT OF FSGS

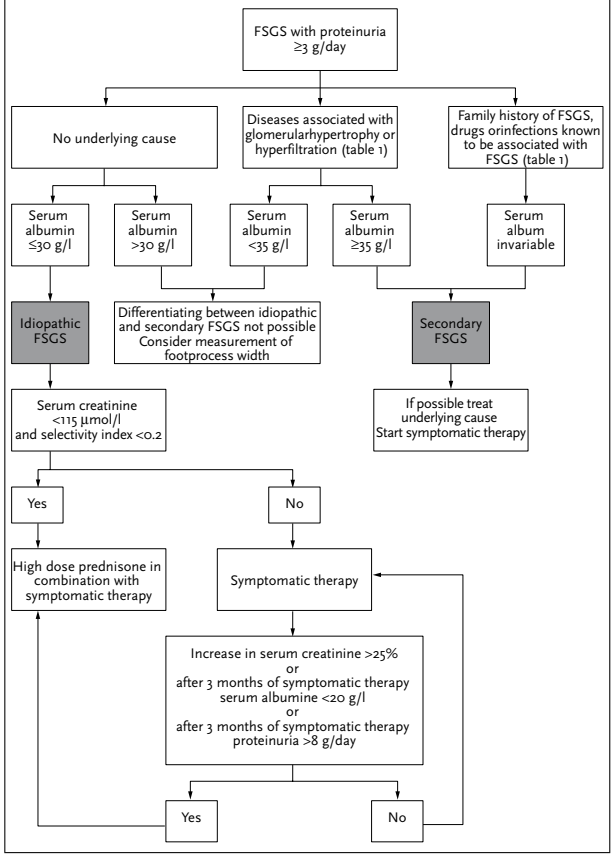
The Dutch Federation of Nephrology recently published guidelines for the diagnosis and treatment of patients with FSGS. An outline of the most important diagnostic steps is given in *figure 6*. Medical history and family history are important to rule out secondary causes of FSGS. We do not advocate routine use of mutational screening. In patients with proteinuria in the nephrotic range (≥3 g/day), serum albumin is an important clinical parameter to distinguish between idiopathic FSGS and FSGS secondary to maladaptive responses. If serum albumin is inconclusive, electron microscopy examination can also help to distinguish between idiopathic FSGS and FSGS secondary to maladaptive responses. Although the use of the Columbia classification is advised for comparative studies, this should

Table 3. *Clinical characteristics of focal segmental glomerulosclerosis variants as reported in two North American and one West-European study*[32,102,103]

	Not otherwise specified (n=200)	Tip (n=128)	Perihilar (n=76)	Collapsing (n=83)	Cellular (n=28)
Male (%)	55%	57%	55%	47%	61%
Age at biopsy (years)	43 ± 5	48 ± 7	50 ± 6	35 ± 4	48 ± 7
Black people	30%	11%	20%	60%	32%
Serum creatinine concentration (μmol/l)	177 ± 91	129 ± 46	166 ± 113	317 ± 133	179 ± 53
Renal insufficiency*	49%	35%	38%	75%	57%
Serum albumin concentration (g/l)	31 ± 5	22 ± 5	37 ± 6	22 ± 5	23 ± 4
Proteinuria (g/24 hours)	5.5 ± 2.9	8.9 ± 3.7	4.7 ± 3.1	9.2 ± 2.7	10.9 ± 4.2
Serum cholesterol	7.3 ± 2.0	8.2 ± 2.1	6.7 ± 1.8	7.7 ± 1.6	6.3 ± 2
Nephrotic syndrome (%)	60%	94%	46%	85%	84%
Mean arterial blood pressure (mmHg)	108 ± 14	111 ± 14	107 ± 13	106 ± 14	110 ± 10
Hypertension (%)	69%	62%	80%	68%	70%

*The definition of renal insufficiency varied between studies, either a serum creatinine >106 μmol/l or >135 μmol/l.

Figure 6. *Flowchart of diagnosis and treatment of focal segmental glomerulosclerosis (FSGS)*



not influence treatment decisions. Immunosuppressive therapy should be limited to patients with idiopathic FSGS. Since spontaneous remissions occur frequently in patients with idiopathic FSGS, normal renal function and a selective proteinuria, a wait-and-see approach should be considered in such patients (*figure 6*). Otherwise, patients with idiopathic FSGS and a nephrotic syndrome should initially be treated with high-dose prednisone for four to six months. To induce a remission, the initial immunosuppressive therapy should consist of high-dose prednisone (1 mg/kg/day, up to 80 mg/day) for four months. In the elderly (>65 years) an alternate day regimen (2 mg/kg/day) is also effective with less complications.[82]

In patients with steroid-dependent or frequently relapsing FSGS, cyclophosphamide 2 mg/kg/day for two to three months in combination with prednisone results in more stable remissions. In steroid-resistant FSGS, the most effective treatment consists of cyclosporine (3-5 mg/kg/day, in two divided doses) for six months. Treatment should be limited to patients with a relatively well-preserved renal function, to prevent nephrotoxicity. If a remission occurs, cyclosporine treatment should be continued for one year and then slowly tapered off to prevent a relapse. In the absence of a remission cyclosporine should be stopped after six months.

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ORIGINAL ARTICLE

Prevalence of hepatitis C in the general population in the Netherlands

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ABSTRACT

Background: Chronic hepatitis C virus (HCV) is transmitted by blood-blood contact and this leads to high HCV prevalence in risk populations such as haemophilia patients and intravenous drug users. The prevalence in the general Dutch population is unknown, although it appears to be very low in screened blood donors (0.0169%).
Aim: The objective of this study is to estimate the prevalence of HCV in a general population sample living in an urbanised region in the Netherlands.
Methods: We randomly selected 2200 EDTA blood samples that had been submitted for analysis of biochemical parameters to a regional servicing laboratory for general practitioners (SHO, Arnhem/Nijmegen, the Netherlands). HCV antibody testing was performed using a three-step approach. For initial screening, an enzyme immunoassay (Bioelisa HCV 4.0, Biokit, Spain) was used. Positive samples were subjected to a second, microparticle enzyme-linked immunoassay (AxSYM HCV version 3.0, Abbott laboratories, IL, USA). Genotypes were determined by Line Probe Assay.
Results: A total of four persons (two females, two males) (0.2%) tested positive for HCV antibodies. The average OD/cut-off ratio of the screening assay was 2.9 (range 1.0 to 7.3) and serological findings were confirmed using a specific second immunoassay. HCV RNA (genotype 1b) was found in the sera of two persons.
Conclusion: The HCV prevalence in our sample of the Dutch population was 0.2% which accords with earlier estimates from prevalence studies in the Netherlands.

KEYWORDS

Hepatitis C, prevalence, the Netherlands

BACKGROUND

Hepatitis C virus (HCV) is mainly transmitted through contact with blood and blood products. The majority of HCV-seropositive individuals will have persistent viraemia. More than half of all patients will develop chronic hepatitis, and in 20% infection will lead to cirrhosis with all the subsequent complications, such as ascites, encephalopathy, variceal bleeding and hepatocellular carcinoma.[1] Chronic HCV infection often runs an asymptomatic course and only 25 to 30% of infected persons seek medical attention for symptoms attributable to HCV infection.[2] Early detection is of key importance in order to prevent complications of HCV-related liver disease. The WHO estimates that 3% of the world's population is HCV-infected and in the USA it is a leading cause of liver transplantations.[3,4] It is thus a significant clinical problem. However, there is wide variation in HCV prevalence in different parts of the world. For example, the prevalence in Scandinavia is less than 0.5%, whereas the prevalence in Egypt is over 20%.[5]
In the UK, the number of new HCV diagnoses rose from 2116 in 1996 to 7580 in 2005. Hospital admissions, transplants, and deaths related to HCV increased, and deaths from end-stage liver disease rose from 76 in 1997-8 to 216 in 2004-5. These results suggest that the number of people at risk for HCV-associated morbidity or mortality will double over the next decade in the UK.[6,7]
In the Netherlands there have been only a few studies that focus on the prevalence of HCV. These studies were generally limited to high-risk populations, such as intravenous drug users and haemophilia patients. Some 54% of Dutch haemophilia patients are HCV carriers, and up to 74% of iv drug users are infected.[8] In 2000, two nationwide prospective surveys among 2281 and 2286 dialysis patients resulted in an HCV prevalence of 2.9 and 3.4%, respectively.[9]

The prevalence in the general population is estimated to be much lower (0.1 to 0.4%). However, this is a crude estimation based on extrapolation of the prevalence among selected high- and low-risk groups.[10,11] Thus, the actual prevalence in the population at large is unknown, hence the need for population-based serological studies. These data are desirable because they allow medical professionals and policymakers to develop and evaluate efforts with respect to treatment and prevention.

Therefore, the aim of this study is to determine the prevalence of HCV infection and the distribution of genotypes in the general Dutch population in urbanised regions of the East-Netherlands.

MATERIALS AND METHODS

Patients and setting

Data for the present study were collected prospectively from 2200 persons visiting general practices in the urbanised regions of Arnhem/Nijmegen in June 2006.

Patients had been referred to a servicing laboratory (SHO) by the general practitioner for analysis of biochemical parameters. After determination of the desired parameters, the remaining blood samples were stored at 4°C until transport to the laboratory of Radboud University Medical Centre in Nijmegen. All aspects of the protocol were reviewed and approved by the local medical ethical committee (CMO) Arnhem/Nijmegen, the Netherlands.

Laboratory methods

Immediately after arrival to the laboratory, samples were centrifuged. Sera were then stored in aliquots at -80°C.

Antibody testing

HCV antibody testing was performed using a three-step approach. For initial screening, an enzyme immunoassay (bioelisa HCV 4.0, Biokit, Barcelona, Spain) was used. Microtitre plates are coated with recombinant HCV antigens including core, NS3, NS4 and NS5. The cut-off value was determined by multiplying the mean optical density (OD) value of the low positive control by 0.9. Ratios of sample OD value and cut-off value of >1 were considered positive. Positive samples were further tested by a second, commonly used microparticle enzyme-linked immunoassay (AxSYM HCV version 3.0, Abbott Laboratories, IL, USA), because the Biokit assay is considered as sensitive as the AxSYM but somewhat less specific according to the information supplied by the manufacturer. Positive results in the AxSYM assay were then further tested using a recombinant immunoblot assay (INNO-LIA HCV™ Score, Innogenetics NV, Gent, Belgium).

Hepatitis C RNA detection and genotyping

Antibody positive samples were tested for the presence of viral RNA and the HCV genotype. For isolation of HCV RNA the COBAS® AmpliPrep (Roche Molecular Systems, Branchburg, USA) was used according to the manufacturer's instructions. Isolated HCV RNA was detected using the COBAS® TaqMan® HCV Analyzer real time PCR. Results are given in IU/ml. The detection range lies between 15 and 7 x 10^7 IU/ml. Hepatitis C genotype was determined using a Line Probe Assay LiPA, based on sequence variations found in the 5' untranslated region of the different HCV genotypes (VERSANT HCV Genotype Assay, Bayer HealthCare LLC, USA) as described before.[12] All assays were performed according to the manufacturer's instructions.

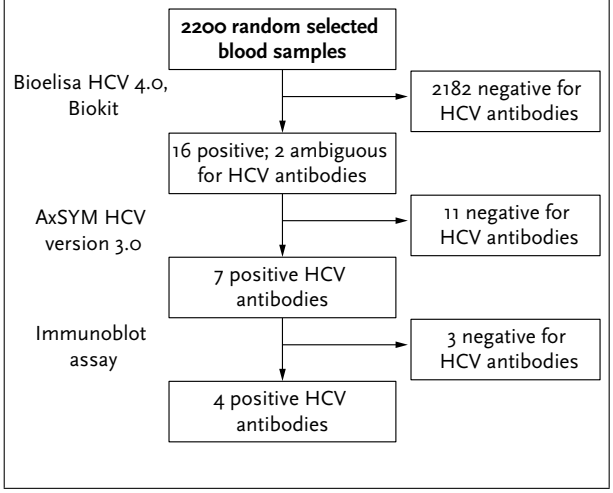
Statistical analysis

Quantitative results are reported as the mean ± standard deviation, and qualitative results are given as percentages. For comparison of proportions between groups, χ^2, Fisher tests and independent T-tests were used. If a p value was below 0.05, the difference between proportions was considered statistically significant.

RESULTS

In total 2200 subjects were tested on HCV antibodies. This group consisted of 1254 (57%) females and 928 (42.2%) males with a mean age of 60.4 years (SD = 16.6). Demographical data on 18 patients were lacking, but they tested HCV negative using our testing strategy. *Figure 1* shows the strategy we followed to determine the HCV positivity.

Figure 1. *Flowchart of strategy to determine hepatitis C virus (HCV) positivity*



In the initial screening using the Biokit assay, 16 out of 2200 (0.7%) subjects had a positive test result with OD values varying from 1.016 to 8.466. Results from two additional samples were ambiguous with values of 0.919 and 0.949. There were no significant differences with respect to age and gender of subjects between those with a positive and those with a negative ELISA (p=ns) (*table 1*).

Table 1. *Anti-hepatitis C virus (HCV) prevalence tests according to gender and age*

	HCV test 1		HCV test 2	
	Negative (n=2166)	**Positive (n=16)**	**Negative (n=2178)**	**Positive (n=4)**
Age* (mean/SD)	60.4 (16.6)	61.4 (17)	60.4 (16.6)	60.0 (16.1)
n% females**	1244 (57.1)	10 (0.8)	1252 (57.5)	2 (50)
n% males**	922 (42.3)	6 (0.6)	926 (42.5)	2 (50)

*No age information about zeven subjects, **no gender information about 11 subjects.

These 16 positive and two ambiguous samples were subjected to further testing using an AxSYM assay. This established the presence of HCV antibodies in seven out of 16 positive samples (OD values of 37.36 to 82.82). Next we performed an immunoblot assay to confirm the HCV infection and were able to confirm the presence of specific anti-HCV antibodies in these four samples (two males, two females). Thus, the HCV prevalence in this sample can be estimated at 0.2%. Lastly, we searched for HCV RNA in these samples and detected viral RNA in two out of four samples. Both samples contained genotype 1b.

In order to test the robustness of our findings, we designed a novel study using our cohort and the dataset of an earlier study as a replication cohort.[15,16] We detected a positivity rate of 4/2200 while the other study found 6/7373 positive.[15,16] Next we calculated whether both datasets were statistically different. Using Fisher's exact test we found that they were not (p=0.2). Subsequently we combined the datasets which yield a much larger cohort of 9573, containing ten HCV-positive patients. The new prevalence was 0.10%, with a calculated 95% confidence interval of 0.039 to 0.17%.

DISCUSSION

We performed a cross-sectional study to assess the epidemiology of HCV infection and we were able to estimate the prevalence at 0.2% among the general population residing in the eastern part of the Netherlands. Most of the previous research in this field had been conducted in high-risk groups or in blood donors, which may over- or under-estimate the actual burden of HCV infection in the general population. How do these data compare with other studies in this field?

The prevalence (0.2%) from this study is appreciably higher compared with healthy blood donors from the Netherlands. In 2001 approximately 0.0169% of new blood donors tested positive for HCV antibodies.[13] In comparison, the HCV prevalence rates among healthy blood donors range from 0.01 to 0.02% in the North-Western Europe, to 1 to 5% in Southern Europe.[14]

While interpreting these results, it is important to realise that blood donors are a self-selected group of individuals who have lower rates of blood-borne infections compared with the general population. Many of the people with risk factors for infection due to HCV (parenteral drug addiction, previous history of hepatitis) are rejected as blood donors. Therefore, these prevalence rates probably underestimate the actual HCV carrier rate.

To this end, in another Dutch study a nationwide call was sent out for volunteers to give sera. The general public was invited by postal request to donate blood samples and the study went to great lengths to obtain a well-balanced age mix among the different geographic regions. This study measured HCV antibodies among a sample of 7373 volunteers and found that only six tested anti-HCV positive (0.08%).[15,16] When we combined this dataset with our own data, the cohort now encompasses a sample of 9573 patients and yields an HCV prevalence of 0.10% (95% CI 0.039 to 0.17%).

In our study, we analysed sera obtained from subjects who underwent blood analysis for various reasons requested by their general practitioners in the Arnhem/Nijmegen region. This is a potential source of bias as we selected subjects who had a reason to go to their general practitioner and have blood taken. However, blood analysis in primary care is a common procedure, often used for the exclusion of severe disorders or for the reassurance of the physician or the patient that there is no severe pathology of underlying symptoms.

As the incidence of serious diseases is low in the general practice population, it can be assumed that the observed prevalence of HCV is representative for the general population.[17-19]

This study was performed in the eastern part of the Netherlands, which is an urban region with a smaller immigration population of 13.7% in Gelderland compared with 25.1% in the Utrecht/North-Holland/South-Holland regions, which may affect the findings.[20]

Anti-HCV testing is performed in different settings, including hospitals, other healthcare facilities and also for screening purposes. Therefore the most desirable HCV screening is the test that has a very high specificity.

Consequently, this might lead to a lower sensitivity. Therefore in line with recommendations published elsewhere we decided to perform a second confirmatory ELISA in the positive samples.[21] Indeed, this was beneficial as it led to exclusion of the suspicion of HCV infection in nine of the 16 samples (56%).

It is possible that a larger sample would have led to different results but in view of the abovementioned studies it is probable that the real HCV prevalence in the Netherlands is well below 0.5%, though we cannot exclude that there is a wide region-region variation.
Other possible limitations include the absence of detailed information on whether these patients were aware of their infection and whether they had had treatment. In addition, HCV RNA could not be detected in two of the four subjects with HCV-positive antibodies. This can be explained by a decline in viral load during storage of the tubes or because the two subjects had cleared the HCV. It is known that around 20% of patients spontaneously clear HCV.[4]
The genotypes detected in our sample (1b) is the most common genotype in the Netherlands. A recent study performed by de Vries *et al.* showed that genotype 1 is found in approximately 50% of HCV patients in the Netherlands.[22]

How does this prevalence compare with other countries? In the USA, the prevalence of HCV infection is estimated at 1.6%.[3] Various studies performed throughout Europe on the prevalence of HCV in general population indicate prevalences from 0.63% in Germany, 0.9% in Belgium to 1.2% in France.[23-25] In Southern Europe the prevalence varies from 1.6% in Spain to 4.8 to 26.0% in Italy.[26,27] The HCV prevalence is higher in Southern Italy compared with Northern Italy. The large variation is most probably due to differences in the quality of the healthcare system. In the recent past, healthcare facilities in Southern Italy made extensive use of glass syringes, and/or non-sterile syringe use facilitating nosocomial HCV transmission.[28]
Our results show lower HCV infection rates in the Dutch population compared with those found in other countries in Europe. Further, this accords with a North-South gradient in HCV prevalence in Europe.

CONCLUSION

The current study provides information on HCV prevalence in the general population. We found an HCV prevalence of 0.2% in the general population. Combining our data with other observations provides a point estimate of 0.10%, with a 95% confidence interval of 0.039 to 0.17%, which is clearly lower than in other European countries.

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New developments in the treatment of systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is the prototype of a systemic autoimmune disease. Many organ systems can be affected and a multitude of autoantibodies can be present. Although the aetiopathogenesis of the disease has not been fully elucidated yet, there is increasing evidence that genetic factors, next to environmental influences, play a major role. Certain polymorphisms in genes that are involved in immune responsiveness appear to be skewed in lupus. In recent years particular attention has been given to the role of apoptosis in lupus. Defective clearance of apoptotic cells leads to accumulation of these cells. In addition, intracellular antigens are, whether or not in modified form, expressed on the surface of these apoptotic cells. Handling of these (antigenetically modified) apoptotic cells by macrophages/dendritic cells may result in (auto)immune responses to these intracellular antigens. Thus, together with other developments, new insights have been gained into the pathogenesis of SLE.

Besides these breakthroughs in pathogenesis, new treatment modalities have become available for SLE. Although corticosteroids and immunosuppressives are still the mainstay of treatment in SLE, biologicals are now being tested with great promise for the future. As mentioned, aberrant B-cell activity with production of numerous autoantibodies appears to underlie many clinical characteristics of lupus. B-cell targeting via monoclonal antibodies in various forms is now a realistic goal in SLE. Interference in co-stimulation by small molecules or blocking B-cell activating factors is another way of inhibiting (autoreactive) B-cells. So, the horizon is open for many new exciting clinical trials in SLE.

All of these new developments in pathogenesis and treatment of SLE will be discussed in depth during the Seventh European Lupus Meeting that will be held in Amsterdam, 7-10 May 2008. The programme promises exciting news on autoimmunity in general and SLE in particular. For more information: www.lupus2008.nl.

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ORIGINAL ARTICLE

Gastrointestinal symptoms are still common in a general Western population

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ABSTRACT

Background: Results from studies conducted in the late 1980s and early 1990s showed that gastrointestinal symptoms were common among the general population. Meanwhile, lifestyle habits have changed and important treatment options have been introduced. This might have influenced symptom prevalence.

Methods: This study aimed to describe the current prevalence of upper and lower gastrointestinal symptoms within the general population. For this purpose, a demographically representative sample of the Dutch population within the city of Nijmegen and surrounding areas was selected after careful comparison with demographic figures from a government demographic database. Participants were invited to fill in a valid self-report questionnaire about gastrointestinal symptoms and prevalence figures were calculated.

Results: A total of 5000 questionnaires was sent and 1616 (32%) were returned. Of these, 839 (52%) subjects reported having had upper (43%) or lower (38%) gastrointestinal symptoms in the past four weeks. The most prevalent individual symptoms reported were flatulence (47%), abdominal rumbling (40%), bloating (37%), alternating solid and loose stools (31%), belching (25%) and postprandial fullness (25%). People who smoked or used a proton pump inhibitor had an increased risk for reporting upper as well as lower gastrointestinal symptoms (OR 1.99; 95% CI 1.56 to 2.55, and OR 1.37; 95% CI 1.01 to 1.75, respectively for smoking; and OR 3.17; 95% CI 2.17 to 4.72, and OR 2.14; 95% CI 1.49 to 3.08, respectively for PPIs).

Conclusion: Both upper and lower gastrointestinal symptoms are very common in a representative sample of a general Western population.

KEYWORDS

Dyspepsia, epidemiology, gastrointestinal diseases, gastrointestinal symptoms

INTRODUCTION

Gastrointestinal symptoms are very common in the general population and a frequent reason for consulting a healthcare professional.[1] In 1989, it was shown that 38% of an English population reported dyspeptic symptoms.[2] When this study was expanded over five other regions in England and Scotland, prevalence of dyspepsia over a six-month period was 41%.[3] In another random sample of older (aged 65-93 years) Minnesota inhabitants, studied in 1992, similar results were obtained.[4] In addition, a prevalence ranging from 10 to 25% was observed for lower abdominal symptoms, such as constipation and diarrhoea.

No recent data on the prevalence of gastrointestinal symptoms in a general population are available. Since these studies were conducted, there have been significant changes in lifestyle habits, treatment options, and socioeconomic and cultural factors, influencing upper as well as lower gastrointestinal symptoms. The most prominent changes were probably the introduction of proton pump inhibitors (PPIs) and strategies to eradicate *Helicobacter pylori* in national and international guidelines for the treatment of patients with upper gastrointestinal symptoms. Subsequently, infection rates of *H. pylori* have decreased, whereas the number of prescriptions for PPIs has increased dramatically.[5,6] Secondly, the use of gastro-toxic drugs, such as NSAIDs, has risen and gastrointestinal symptoms induced by these drugs are increasing.[7] Thirdly, the prevalence of overweight and obesity is increasing. A high body mass index, and the lifestyle habits that precede that, are associated with the development of both upper and lower gastrointestinal symptoms, such as regurgitation, gastro-oesophageal reflux and altered bowel movements.[8]

These developments strengthened the need for data on the current prevalence of gastrointestinal symptoms in the general population. Indeed, a more recent study has shown

that, although there is great inter-country variability (46% in Mexico, 10% in Japan), abdominal cramping and pain are still common in a general population.[9] Similar results were obtained in the Kalixanda study from Northern Sweden, in which the prevalence of predominantly reflux symptoms over a three-month period was found to be about 40%.[10,11]

Although both studies indicate that upper gastrointestinal symptoms are still a frequent phenomenon among the general population, they were conducted in specific populations and investigated specific symptom complexes. This study aims to investigate the prevalence of a broad range of both upper and lower gastrointestinal symptoms in a representative sample of the general population.

PATIENTS AND METHODS

Subjects

Questionnaires were spread door-to-door in the city of Nijmegen and the Nijmegen area. Data from Statistics Netherlands (CBS) were used to select neighbourhoods that matched the general Dutch population for social economic status, age, property value, racial configuration and household configuration. One person over the age of 18 per household was asked to fill in the questionnaire and return it by mail. It was specifically mentioned that the questionnaire should also be completed if gastrointestinal symptoms were absent.

Questionnaire

The questionnaire contained items on demographics, lifestyle habits and current medication use. Severity of gastrointestinal symptoms in the past four weeks was assessed using a valid self-report questionnaire. This questionnaire has been extensively used before[12-15] and symptoms include upper abdominal pain, epigastric pain, heartburn, regurgitation, abdominal rumbling, bloating, nausea, empty feeling in the stomach, early satiety, postprandial fullness, belching, flatulence, haematemesis, dysphagia, questions on defecation and foetor ex ore. Subjects were asked to rate the severity of gastrointestinal symptoms on a seven-point Likert scale (0 = absent; 1 = hardly any; 2 = mild; 3 = moderate; 4 = moderately severe; 5 = severe and 6 = very severe). In analysis a score of 2 or higher was defined as symptom presence. Questionnaires returned without any of the questions answered were not taken into further analysis.

Statistical analysis

Statistical analysis was performed using SAS statistical software (version 8.2). Data on symptom frequencies were summarised using descriptive statistics. Participants reporting three or more of the following symptoms: epigastric pain, heartburn, regurgitation, abdominal rumbling, bloating, empty feeling, nausea, vomiting, early satiety, postprandial fullness, belching, haematemesis, dysphagia and foetor ex ore, were defined as having upper gastrointestinal symptoms. Having three or more of these symptoms was defined as having lower gastrointestinal symptoms. Alcohol abuse was defined as drinking ≥14 units/week for women and ≥21 units/week for men (National Drug Monitor Netherlands/Trimbos Institute), and coffee abuse was defined as the consumption of ≥6 units/day.[16] Any consumption of cigarettes or cigars was defined as current smoking. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in metres (kg/m^2), classifications were made according to WHO standards: a BMI ≤18.5 = underweight, a BMI 18.5 to 25 = normal and a BMI ≥25 = overweight.[17] Comparison of symptom frequencies between genders was done using Pearson's χ^2 analysis, and Pearson's correlation coefficient was calculated to assess the correlation between age and number of symptoms. To adjust for multiple testing, a p value <0.01 was considered statistically significant. Logistic regression analysis was used to assess adjusted odds ratios in order to identify risk factors for upper or lower gastrointestinal symptoms.

RESULTS

A total of 5000 questionnaires were distributed and 1616 were returned (32%). Mean age of the responders was 52.3 years (±17.2) and 34% of the responders were male (*table 1*). Eighty percent of all subjects reported having had at least one gastrointestinal symptom in the past four weeks. The most frequently reported upper gastrointestinal symptoms were bloating (37%), belching (25%), postprandial fullness (25%) and heartburn (21%). Lower gastrointestinal symptoms most frequently reported were flatulence (47%),

Table 1. *Population demographics (n=1616)*

Mean age ±SD	52.3 ± 17.2
Male gender, n (%)	549 (34%)
Non-Western European origin, n (%)	104 (6.4)
BMI, n (%):	
• <18.5	33 (2.0)
• (18.5-25)	814 (50.4)
• ≥25	704 (43.6)
Smoking, n (%)	385 (24.0)
Alcohol abuse, n (%)	102 (6.3)
Excessive coffee consumption, n (%)	383 (23.7)
Current medication, n (%):	
• Proton pump inhibitor	134 (8)
• Aspirin	165 (10)
• H2-receptor antagonist	17 (1)
• NSAID	66 (4)

abdominal rumbling (40%), alternating solid and loose faeces (31%) and strong urgency (24%) (*figures 1* and *2*). Women statistically significantly more often reported abdominal pain in general (27 *vs* 16%), abdominal rumbling (42 *vs* 35%), bloating (41 *vs* 30%), nausea (20 *vs* 9%), early satiety (15 *vs* 9%), postprandial fullness (27 *vs* 20%), constipation (7 *vs* 18%) and defecation frequently with pain (13 *vs* 7%) than men (all p values <0.01).

In general, 43% of participants reported having had at least three upper gastrointestinal symptoms in the past four weeks and 38% reported having had at least three lower gastrointestinal symptoms. Although proportions of subjects with upper and lower gastrointestinal symptoms seemed to decrease with increasing age in both men and women (*figure 3*), no correlation could be shown (r = -0.22 in men, and r = -0.21 in women for age and upper abdominal symptoms; r = -0.19 in men, and r = -0.24 in women for age and lower abdominal symptoms; all p values <0.01).

Of all subjects taking either a PPI or an H2-receptor antagonist, 68% reported upper gastrointestinal symptoms and 55% reported lower gastrointestinal symptoms. Smoking and PPI use were associated with an increased risk for both upper and lower gastrointestinal symptoms (OR 1.99; 95% CI 1.56 to 2.55, and OR 1.37; 95% CI 1.01 to 1.75, respectively for smoking; and OR 3.17; 95% CI 2.17 to 4.72, and OR 2.14; 95% CI 1.49 to 3.08, respectively for PPIs). Excessive coffee consumption was associated with a decreased risk for upper and lower gastrointestinal symptoms (OR 0.75; 95% CI 0.59 to 0.96, and OR 0.72; 95% CI 0.56 to 0.93, respectively).

Figure 1. *Prevalence of upper gastrointestinal symptoms*

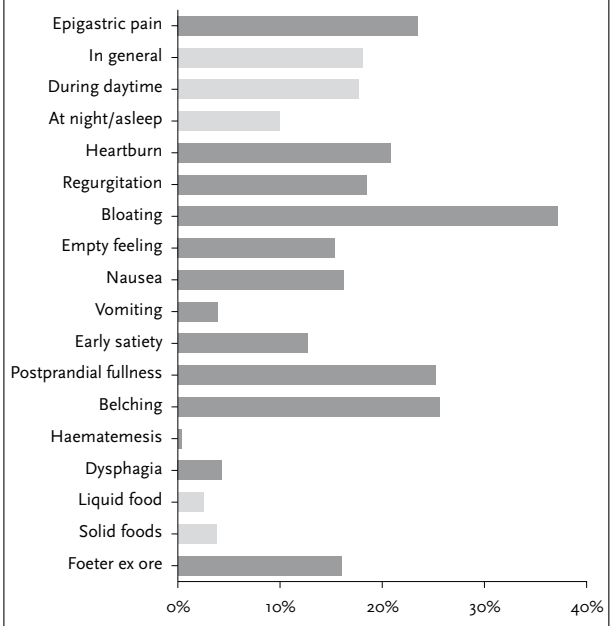

Figure 2. *Prevalence of lower gastrointestinal symptoms*

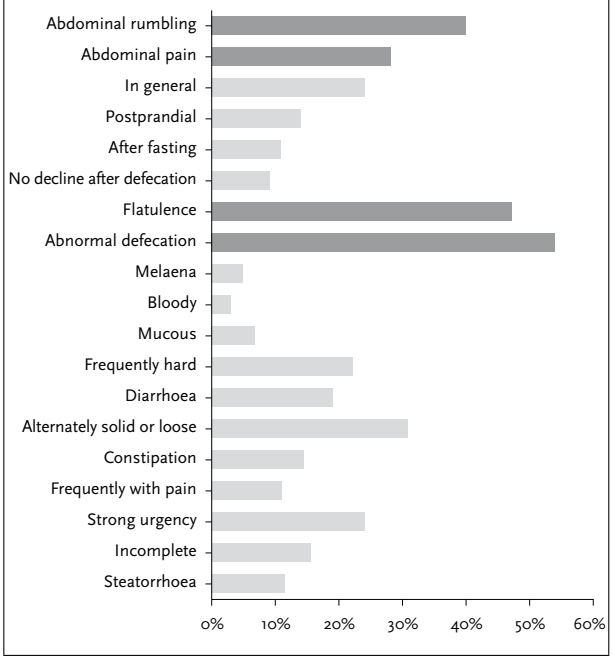

Figure 3. *Prevalence of upper and lower gastrointestinal symptoms in men and women with increasing age*

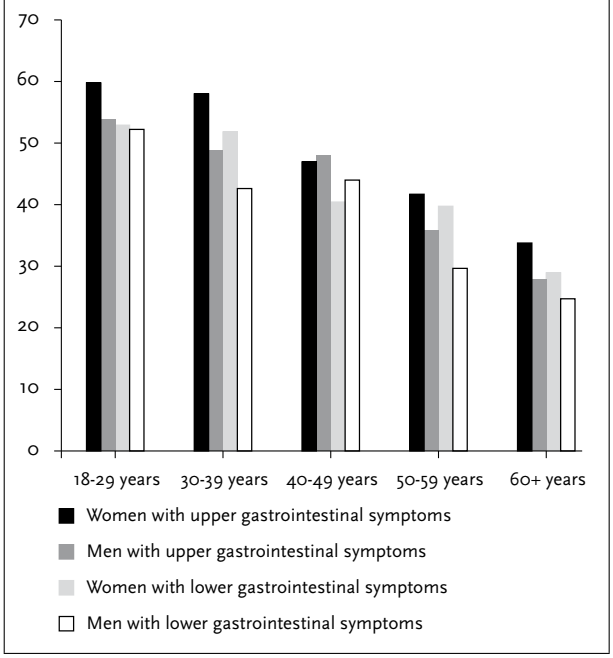

Table 2. *Prevalence of specific characteristics among subjects with and without upper and lower gastrointestinal symptoms*

	Upper gastrointestinal symptoms			Lower gastrointestinal symptoms		
	Present n=690 (43%)	Not present n (%)	Adjusted* OR (95% CI)	Present n=616 (38%)	Not present n (%)	Adjusted* OR (95% CI)
Alcohol abuse	37 (5.4)	65 (7.0)	0.66 (0.43-1.02)	36 (5.8)	66 (6.6)	0.85 (0.55-1.30)
Excessive coffee consumption	156 (22.6)	227 (24.5)	0.75 (0.59-0.96)	130 (21.1)	253 (25.3)	0.72 (0.56-0.93)
Smoking	207 (30.0)	178 (19.4)	1.99 (1.56-2.55)	164 (26.6)	221 (22.3)	1.37 (1.01-1.75)
Medication						
Aspirin	65 (9.4)	100 (10.8)	0.85 (0.60-1.19)	57 (9.3)	108 (10.8)	0.84 (0.59-1.18)
NSAID	36 (5.2)	30 (3.2)	1.37 (0.82-2.30)	28 (4.6)	38 (3.8)	1.05 (0.62-1.74)
Proton pump inhibitor	92 (13.3)	42 (4.5)	3.17 (2.17-4.72)	74 (12.0)	60 (6.0)	2.14 (1.49-3.08)
H2-receptor antagonist	11 (1.6)	6 (0.7)	2.63 (0.97-7.84)	10 (1.6)	7 (0.7)	2.52 (0.95-7.06)
BMI (kg/m²):						
• <18.5	20 (2.9)	13 (1.4)	1.54 (0.64-3.80)	19 (3.1)	14 (1.4)	1.97 (0.83-4.78)
• 18.5-25	326 (47.3)	488 (52.7)	0.65 (0.38-1.09)	297 (48.2)	517 (51.7)	0.81 (0.48-1.36)
• 25>	310 (44.9)	394 (42.6)	0.74 (0.44-1.26)	272 (44.2)	432 (43.2)	0.87 (0.52-1.48)

*Adjusted for all other variables. Alcohol abuse: ≥14 units/week for women and ≥21 units/week for men. Excessive coffee consumption: ≥6 units/day. Smoking: any consumption of cigarettes or cigars. NSAID = non-steroid anti-inflammatory drug.

DISCUSSION

The results of this large-sample study show that upper and lower gastrointestinal symptoms are very common in a general Western population. The vast majority of subjects experienced at least one gastrointestinal symptom in the past four weeks. Women reported more symptoms than men, and the number of symptoms seems to decrease with increasing age, regardless of gender. Smoking and use of PPIs were associated with the presence of gastrointestinal symptoms, and there was a negative association with excessive coffee consumption.

Other studies have investigated the prevalence of dyspeptic and irritable bowel syndrome-related symptoms before. These studies, performed since 1951, reported a prevalence ranging from 25 up to 40%, depending on the study population and symptom definition.[2,4,18-20] Since these first data, several changes in factors associated with the treatment and development of gastrointestinal symptoms have taken place, such as altered treatment options, increasing bodyweight and altered lifestyle habits. It might be expected that this has influenced gastrointestinal symptom aetiology and, with that, prevalence. Indeed, in a recent study we showed that the prevalence of upper gastrointestinal disorders found at endoscopy had changed significantly over time compared with 15 years previously.[21] Unfortunately, the current data do not allow us to draw any conclusions on diagnoses, and there is no data available on these symptoms in a comparable population. Nevertheless, proportions of patients with symptoms are in concordance with proportions described in the earlier studies, and although aetiology and the prevalence of certain disorders may have changed, gastrointestinal symptoms are still a common phenomenon in the general population.

PPIs and smoking were associated with an increased risk for both upper and lower gastrointestinal symptoms. Smoking has previously been associated with the development of gastrointestinal disorders,[22,23] and our results show once again how important it is for healthcare workers to emphasise the importance of quitting for the prevention and control of symptoms. PPIs are currently among the most frequently prescribed drugs in the Netherlands and numbers are still increasing (source: GIP databank; 01-05-2007). Currently, a common approach in Western countries is to prescribe acid-suppressive drugs for upper gastrointestinal tract symptoms without suspicion of a malignancy.[24] A large proportion of patients with upper gastrointestinal symptoms have no acid-related disorder underlying symptoms and it is therefore likely that a group of patients are taking acid-inhibiting medication without the expected effect on gastrointestinal symptoms.[25] It is very probable that the observed increased risk is a reflection of the large number of people using this medication without obtaining the desired effect, rather than a true association between the use of PPIs and symptom development. The association with lower gastrointestinal symptoms might be the result of common side effects of PPIs on the lower gastrointestinal tract, such as diarrhoea, constipation and flatulence.[26] On the other hand, it is known that gastrointestinal symptoms are often hard to locate, and that upper and lower gastrointestinal symptoms often coexist.[27] It is quite possible that many patients received a PPI for their upper gastrointestinal symptoms, while their lower gastrointestinal symptoms persisted. Regarding the inversed association with excessive coffee consumption, it is imaginable that subjects with gastrointestinal symptoms consume less coffee in order

to avoid symptoms, rather than that coffee itself has a protective effect for symptom development.

The response rate to the self-report questionnaire was rather low, compared with the previously mentioned studies investigating symptom prevalence. The low response rate is most probably due to the voluntary, anonymous nature of this study: questionnaires were spread door-to-door, whereas other studies often used a clinical or outpatient setting to approach potential participants. This last method leads to higher response rates since people are more likely to fill in a questionnaire if asked to by a healthcare worker. Our purpose was to obtain insight into a general population, regardless of medical background or healthcare seeking behaviour. Therefore, response was dependent on individual willingness to complete the questionnaire, and response bias might have influenced our results. The investigated sample matched the general Dutch population for several demographic and socioeconomic factors (data from Statistics Netherlands (CBS)). However, the mean age of the responders was slightly higher, and there were more women than men. This would mean that our results could in fact represent an underestimation of prevalence because younger people report more symptoms, or that the higher proportion of women has caused an overestimation because women tend to report more symptoms. The truth probably lies somewhere in the middle; considering these contradicting influences on symptoms, the large sample size and the resemblance of our sample to the general Dutch population for other factors, it might be assumed that data about the prevalence of symptoms are representative for the general population as well.

In summary, over the past decades, several changes in factors associated with the development and treatment of gastrointestinal disorders have taken place. The results of this study show that although these changes might have altered the aetiology and prevalence of underlying disorders, gastrointestinal symptoms are still very common in the general population.

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CASE REPORT

Hairy cell leukaemia presenting with ascites, pleural effusion and increased CA 125 serum level

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ABSTRACT

The body cavities are rarely involved in hairy cell leukaemia. Here we report a patient who had pancytopenia, hepatosplenomegaly, massive haemorrhagic ascites, pleural effusion at the left hemithorax and increased CA 125 serum level at the time of initial diagnosis. Laparoscopy showed multiple nodular white, opaque lesions on the omentum and on the parietal peritoneum. Laparoscopic biopsy of these lesions, and a bone marrow biopsy revealed a diffuse cellular infiltrate of tartrate-resistant acid phosphatase staining mononuclear cells. These mononuclear cells with irregular cytoplasmic protrusions were also found in the peripheral blood, in the ascites fluid and in the pleural effusion. The patient was treated with cladribine 0.1 mg/kg/day with continuous infusion for seven days. Three months after the treatment, the patient achieved a complete remission with normalisation of the peripheral blood count, bone marrow findings, CA 125 serum level, with no detectable ascites and/or pleural effusion.

KEYWORDS

Ascites, CA 125, hairy cell leukaemia, peritoneal hairy cell infiltration

INTRODUCTION

Hairy cell leukaemia (HCL) is a chronic lymphoproliferative disorder characterised by splenomegaly, cytopenia and the presence of malignant B-cells with hair-like protrusions in peripheral blood, bone marrow, spleen and liver.[1] Rarely the patients may present with marked leucocytosis, spontaneous rupture of the spleen, cryptococcal meningitis, massive splenomegaly due to hairy cell infiltration but with normal peripheral blood and bone marrow findings at the time of initial diagnosis,[2-4] but not with massive ascites and pleural effusion. The occurrence of massive ascites and pleural effusion in HCL has been reported as a complication during the course of the disease.[4,5]

Here, we report a patient who presented with massive haemorrhagic ascites and haemorrhagic pleural effusion at the left hemithorax, an elevated CA 125 serum level and a multiple nodular infiltration of the peritoneum with hairy cells at the time of initial diagnosis. To our knowledge, haemorrhagic ascites and pleural effusion with elevated CA 125 level have not been reported previously as initial findings in this disorder.

CASE REPORT

A 49-year-old man was referred to our department because of pancytopenia and ascites. Three months prior to admission he started to experience easy fatigue, abdominal swelling and slight shortness of breath. On examination, the spleen and the liver were palpable 10 cm and 6 cm below the costal margins, respectively. In addition to these findings, he had massive ascites and pleural effusion at the left hemithorax. No superficial lymph node enlargements were noted. An X-ray of the chest showed elevation of the diaphragm and pleural effusion at the left hemithorax. A computed tomography confirmed the presence of hepatosplenomegaly, ascites and pleural effusion. There was no lymphadenopathy.

Peripheral blood count revealed haemoglobin (Hb) 4.6 mmol/l, platelets 86 x 10^9/l, and white blood cell count (WBC) 4.1 x 10^9/l. The differential showed 36% neutrophils, 20% lymphocytes and 44% mononuclear cells with irregular cytoplasmic protrusions. The bone marrow was aspirated with difficulty, and the sample showed typical hairy cells. A bone marrow biopsy revealed a diffuse cellular infiltrate of tartrate-resistant acid phosphatase (TRAP) stained mononuclear cells. These cells were B cells, staining with the pan B-cell marker CD20 (*figures 1A-C*).

Figure 1A. *Neoplastic infiltration in bone marrow trephine biopsy, haematoxylin and eosin x 20*

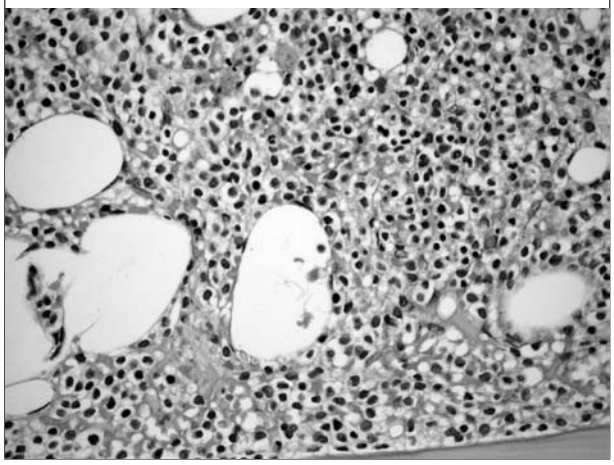


Figure 1B. *Neoplastic infiltration in the bone marrow with CD20 immune reactivity, anti-CD20 primary antibody (L 26), aminoethylcarbasol (AEC) chromogen x 20*

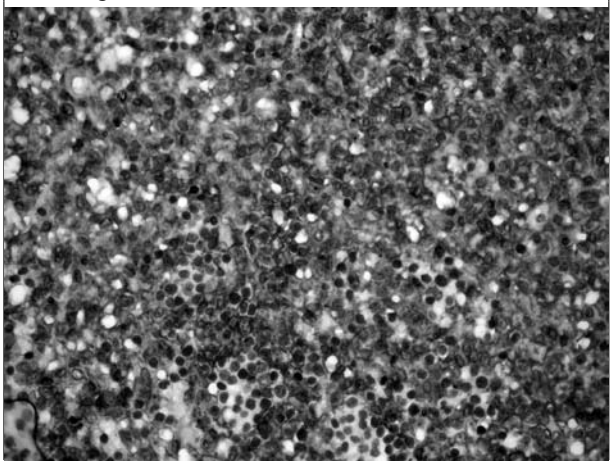
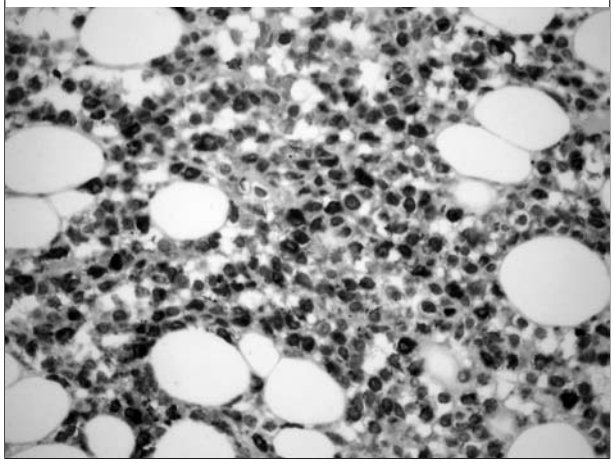


Figure 1C. *Neoplastic infiltration in the bone marrow biopsy with TRAP immune reactivity, AEC chromogen x 40*



Immunophenotyping of the peripheral blood demonstrated the presence of HCL-specific antigen expression (CD19 89%, CD20 60%, $CD11^c$ 84%, CD25 88% and CD103 78%).

In the haemorrhagic ascites, total protein was 3.6 g/l with 1.9 g/l albumin, Hb 0.6 g/l, WBC 0.9 x 10^9/l, with 60% typical hairy cells using Wright's stain. Pleural effusion was similar in appearance and in chemistry to the ascites fluid. Bacterial culture of both fluid samples remained sterile. The liver function studies were normal except for an elevated polyclonal γ-globulin level (1.6 g/l). Serum total protein and albumin levels were normal (5.5 g/l and 2.6 g/l, respectively). The CA 125 serum level was found to be elevated (272 IU/ml; normal 0 to <30 IU/ml).

The laparoscopic examination showed multiple nodular white, opaque lesions on the omentum and on the parietal peritoneum (*figure 2*). Laparoscopic peritoneal biopsy of these lesions revealed a dense infiltration with TRAP positive hairy cells. These cells were positive for the B-cell marker CD20 (*figures 3A-C*).

The patient was treated with cladribine 0.1 mg/kg/day with continuous infusion for seven days. The result obtained with this treatment was very satisfactory. The ascites and pleural effusion subsided with cladribine therapy. The patient is still asymptomatic and has no detectable hepatosplenomegaly, ascites and/or pleural effusion with a normal CA 125 serum level, normal bone marrow findings and peripheral blood levels (Hb 9.6 g/l, platelets 310 x 10^9/l, WBC 5.8 x 10^9/l) after three months of therapy.

Figure 2. *Multiple nodular lesions on the peritoneum as seen in laparoscopy*

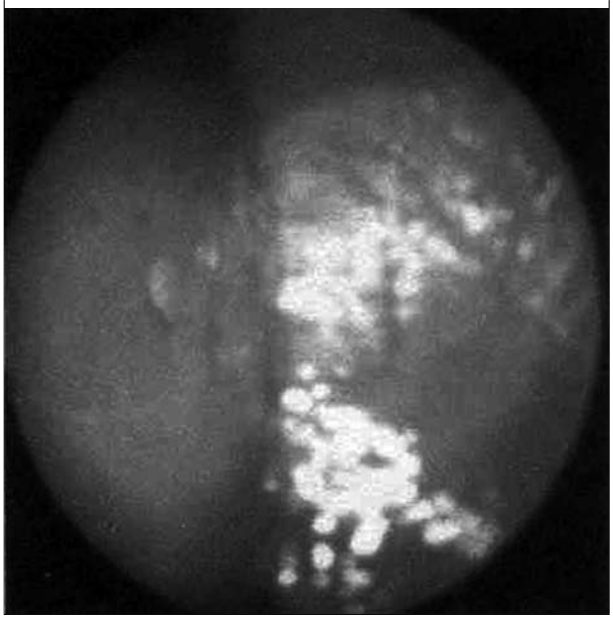


Figure 3A. *Peritoneal biopsy: Mesothelial surface and neoplastic lymphoid infiltration, haematoxylin and eosin x 40*

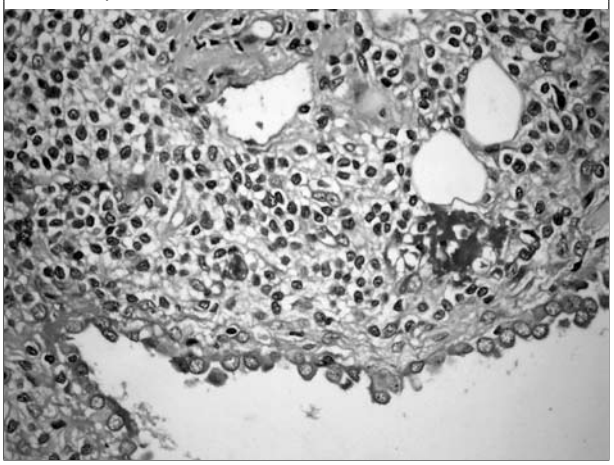


Figure 3B. *CD20 positive neoplastic lymphoid infiltrations in the same biopsy as in figure 3A, AEC chromogen x 40*

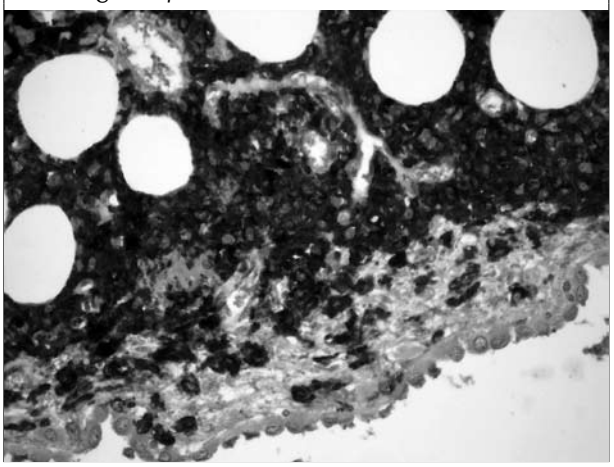
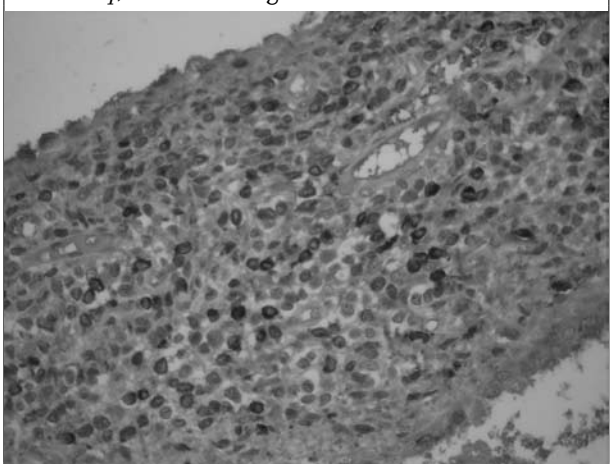


Figure 3C. *Neoplastic cells with TRAP immune reactivity, AEC chromogen x 20*



DISCUSSION

This report describes a case of HCL. Clinically, the patient presented with massive ascites, pleural effusion at the left hemithorax and hepatosplenomegaly. Ascites and pleural effusion are unusual manifestations of HCL at the time of initial diagnosis. Several case reports of HCL describe ascites, but in each, there was histologically proven cirrhosis of the liver.[6,7] Only three patients with HCL have been reported in the literature who developed ascites during the course of their illness.[4,5] In one of these patients, chylous ascites appeared 16 months after the diagnosis of hairy cell leukaemia.[5] In the other two patients, massive ascites and pleural effusion developed 10 and 13 months after the diagnosis.[4] Ascites was not chylous. All of the patients had massive retroperitoneal and abdominal lymphadenopathy. According to the authors, the cause of the massive ascites in these patients showed a similarity to that seen in lymphomas and was most likely related to the extensive lymphadenopathy.

To our knowledge, massive ascites and pleural effusion, in association with elevated CA 125 serum levels, as the initial manifestation of HCL, has not been reported previously. In our experience, this is the first patient in whom the multiple nodular peritoneal infiltration was documented by laparoscopy, and the diagnosis of HCL was confirmed by laparoscopic biopsy.

CA 125 is a glycoprotein antigen expressed in the celomic epithelium. It is a tumour marker used for the diagnosis and monitoring of epithelial ovarian carcinoma.[8,9] This marker has also been found to be increased in patients with serosal effusions, derived from non-neoplastic inflammatory disease,[10,11] in advanced non-Hodgkin's lymphoma,[12,13] and in acute leukaemia[14] with serosal involvement. Serial CA 125 measurements may be of value in monitoring response to chemotherapy in these patients.

CA 125 elevation in our patient is most likely to be due to a serosal reaction caused by the leukaemic infiltration. After the cladribine treatment, our patient showed a complete haematological and clinical response with normalisation of the peripheral blood cell count, the CA 125 serum level, disappearance of the ascites, the pleural effusion and, hepatosplenomegaly.

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CASE REPORT

Rituximab for the treatment of glomerulonephritis in hepatitis C associated cryoglobulinaemia

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ABSTRACT

Mixed-type cryoglobulins are strongly associated with hepatitis C virus (HCV) infection and may lead to vasculitis with renal involvement. The treatment of this condition is antiviral therapy for HCV, but this may be ineffective or not tolerated because of side effects. Alternative strategies such as immunosuppressive drugs and plasmapheresis are of limited use, especially in patients after liver transplantation (LTx). We describe an LTx patient with cryoglobulinaemia-associated glomerulonephritis, who was treated successfully with the B cell depleting monoclonal antibody rituximab.

KEYWORDS

Cryoglobulinaemia, glomerulonephritis, hepatitis C, liver transplantation, rituximab

INTRODUCTION

Cryoglobulins are plasma proteins that precipitate below 37°C, and consist of immunoglobulins with or without complement components.[1] Type 2 and 3 cryoglobulins are immunoglobulin G (IgG) complexed with monoclonal immunoglobulins (type 2), or polyclonal immunoglobulins (type 3). Usually, immunoglobulin M (IgM) is found as the complexing immunoglobulin. The type 2 and 3 cryoglobulins are together known as mixed-type cryoglobulins.

The immune complexes arise as a consequence of oligoclonal proliferation of B lymphocytes that produce autoantibodies against IgG.[2] The IgG binding property of these IgM antibodies is known as rheumatoid factor activity. An infection with hepatitis C virus (HCV) usually underlies the presence of mixed-type cryoglobulins and HCV antigens may be found within the circulating and precipitated immune complexes.[3,4] The immune complexes may precipitate within the glomeruli, thereby leading to glomerulonephritis with the typical histological appearance of membrano-proliferative glomerulonephritis (MPGN) type I.[4] This glomerulonephritis leads to progressive loss of renal function and an unfavourable prognosis for the survival of the patient.[5] The treatment of HCV-associated cryoglobulinaemia should be individualised and based on the severity of the symptoms. It consists of supportive care and antiviral or immunosuppressive therapy. Antiviral treatment may not be effective in clearing HCV and is sometimes poorly tolerated,[1] especially after LTx. Also, this strategy is of course not an option for the small group of patients with a non-HCV-related cryoglobulinaemia. To reduce the concentration of cryoglobulins and the related inflammation, high doses of corticosteroids with additional plasmapheresis or cyclophosphamide have been given. The efficacy of these treatment regimens is rather poor, with a risk of severe infections and an increase in HCV viral load.[6,7] Because of concomitant immunosuppressive treatment, the higher risk of serious infections and problems regarding graft rejection, the treatment options after LTx are limited even further. Alternative treatments with a greater efficacy and less toxicity are therefore needed. Rituximab may be such an alternative. Rituximab is a monoclonal antibody against the CD20 antigen on the cell surface of B lymphocytes. Recently, it has been reported that depletion of B lymphocytes by rituximab may lead to a complete remission of mixed-type cryoglobulinaemia-associated glomerulonephritis.[5] We describe a patient with mixed-type cryoglobulinaemia-associated MPGN type 1, who was successfully treated with rituximab, and review the current literature on this subject.

CASE REPORT

A 51-year-old male was admitted for clinical evaluation of oedema of the legs and progressive shortness of breath on physical exercise, which developed seven months after a

liver transplantation. His medical history showed a chronic hepatitis C (HVC genotype 1) viral infection, for which he had been treated with PEG interferon and ribavirin in the past, with relapse after the therapy was withdrawn. Finally, he developed decompensated liver cirrhosis and underwent orthoptic liver transplantation from a hepatitis B surface antigen-positive donor. The immunosuppressive medication consisted of cyclosporine and prednisone. In addition, he received lamivudin as antiviral medication to prevent hepatitis B reactivation. Six months postoperatively, routine liver biopsy showed recurrence of HCV infection with mild inflammation. He had documented type 2 diabetes mellitus, for which he used insulin subcutaneously. His renal function had previously been normal, without the presence of proteinuria.

At physical examination, obesity was noted with a weight of 125 km (height 190 cm), blood pressure 205/110 mmHg, heart rate 74 beats/min and an increased respiratory rate of 24/min. Remarkable findings included the presence of inspiratory crackles at the base of the lungs and pitting oedema at both lower extremities, extending to the knees. The examination of skin and joints was unremarkable.

The results of the laboratory examination of blood and urine are shown in *table 1*. Rituximab treatment was started two weeks after admission, during which time no significant change in renal function and proteinuria occurred. Hepatitis B DNA was not detectable in the serum by polymerase chain reaction. Ultrasonography showed kidneys of a normal size and appearance. A renal biopsy procedure was performed subsequently.

Microscopic examination of the renal biopsy showed 23 glomeruli in total, three of which were globally sclerosed. The intact glomeruli showed an increase in mesangial matrix and cells with splicing of the glomerular basement membrane. Microthrombi were observed in a few small vessels. In addition, diffuse tubulo-interstitial fibrosis with tubulus atrophy was noted. By immunofluorescence, a strong granular pattern of IgM (3+), C3 (3+), IgA (2+), IgG (+), and C1Q (+) was noted, following the contours of the basal membrane. Electron microscopy revealed deposits within the basement membrane and subendothelially, confirming the light microscopic diagnosis of MPGN type 1.

Clinical course

The patient showed a severely compromised renal function with a nephrotic syndrome at presentation. The presence of cryoglobulins and high levels of serum IgM rheumatoid factor activity in a patient with chronic HCV infection made the diagnosis of mixed-type cryoglobulinaemia-associated glomerulonephritis most likely. This diagnosis was confirmed by renal biopsy. Despite maximal supportive therapy with diuretics, angiotensin-converting enzyme inhibiting medication and increasing the dose of corticosteroids, blood pressure and renal function did not improve and the clinical condition of the patient worsened. Therefore, treatment with anti-CD20 (rituximab) monoclonal antibody was started at a dose of 375 mg/m^2 at weekly intervals for four weeks. Corticosteroids were tapered to a dose of 2.5 mg daily. Two weeks after the first dose of rituximab the clinical symptoms improved, with a decrease in the proteinuria and serum cryoglobulin concentration. No side effects were noted during this treatment. Despite the disappearance of the clinical symptoms of the nephrotic syndrome, renal function did not improve within the first weeks. The tubulo-interstitial abnormalities suggested the possibility of cyclosporine nephrotoxicity. Therefore, this medication was substituted by mycophenolate mofetil. The outcomes of the laboratory tests are shown in *table 1*. During one year of follow-up, a significant improvement in renal function was observed with a decrease in proteinuria. The serum concentration of total IgM and IgM rheumatoid factor activity declined

Table 1. *Biochemical results after 3, 6 and 12 months after the first gift of rituximab*

	Starting rituximab	+3 months	+6 months	+12 months
Plasma creatinine (40-90 µmol/l)	221	139	154	133
Plasma albumin (35-45 g/l)	27	35	39	37
Plasma complement C3 (0.84-1.68 g/l)	0.72	1.20	1.15	1.13
Plasma complement C4 (0.16-0.42 g/l)	0.04	0.11	0.16	0.18
IgM rheumatoid factor activity (<12 IE/l)	800	100	25	25
Plasma cryoglobulins g/l	0.81	0.18	0.05	ND
Plasma IgG (7.0-16.0 g/l)	6.1	6.4	6,6	6.3
Plasma IgM (0.45-2.30 g/l)	3.0	1.95	0.83	1.04
B lymphocytes (x 10^9/l)	-	0	0	0
Protein in 24-hour urine (g)	11.7	3.72	4.14	3.51
Active urine sediment*	Yes	Yes	Yes	No
ALAT (0-40 U/l)	86	97	299	71
Viral load HCV (10^7 c/ml)	4.37	0.14	3.35	-

ND = not detectable. Reference values are between brackets. *Urine sediment containing >5 leucocytes or 2 erythrocytes per high power field (400 x).

steeply within the first three months, while the total IgG concentration remained constant. After six months, cryoglobulins could no longer be detected and the levels of complement C3 and C4 had normalised. During the year of follow-up, no infections were seen and the HCV viral load decreased to the pre-existent level. However, after one year and with cryoglobulinaemia still in remission, active viral hepatitis was diagnosed by liver biopsy.

DISCUSSION

Mixed-type cryoglobulinaemia is highly associated with chronic HCV infection.[3] The circulating immune complexes may precipitate within the kidney, preferentially in the mesangium and in the subendothelial space. Splicing of the glomerular basement membrane is characteristic and caused by the ingrowth of mesangial cells. This can be visualised by light microscopy and is called the 'tram-track' phenomenon. These histological findings in the renal biopsy are characteristic for the diagnosis of membrano-proliferative glomerulonephritis (MPGN) type I. The presence of microthrombi in the small vessels, as was seen in our case, establishes the diagnosis of cryoglobulinaemia-associated MPGN with near certainty. MPGN type I is a rare diagnosis and the relation with a concomitant HCV infection is strong.[4,7] If not treated progressive renal failure will ensue. Glomerulonephritis is part of a spectrum of organ involvement in cryoglobulinaemic vasculitis, and other commonly observed manifestations are purpura, neuropathy, skin ulcera and arthralgias.[1]

Treatment options

The treatment of HCV-associated cryoglobulinaemia is based on elimination of HCV by the standard antiviral medication, PEG-interferon-alpha (IFN) combined with ribavirin.[1,6,8,9] Although effective (sustained viral response in 67 to 77% and a clinical response in 88%), this therapy is limited for several reasons. Despite effective antiviral treatment, cryoglobulinaemia may persist. Interferon may worsen or even induce symptoms of neuropathy, skin ulcers and renal insufficiency. With rapidly progressive or life-threatening disease the effect of antiviral treatment is too slow. Finally, IFN is contraindicated in advanced liver cirrhosis with risk of acute decompensation.[9] After LTx, antiviral therapy is less effective (sustained viral response 24 to 36%), poorly tolerated (severe haematological side effects in 36 to 60%) and may cause acute rejection of the graft in 5%.[10-14] If elimination of HCV is not possible, alternative strategies have been described, aiming at reducing the concentration of circulating immune complexes. The strategies include plasmapheresis and high-dose corticosteroids with or without cyclophosphamide. The effectiveness of these treatments is limited and potential side effects are severe infections – especially in the already immunocompromised LTx patients – and increase of viral load with hepatocellular damage.[6,7]

In recent years the concept of anti-CD20 for mixed-type cryoglobulinaemia has emerged as an effective and safe treatment, inducing a rapid remission of disease activity.[15,16] In the groundbreaking studies by Zaja *et al.* and Sansonno *et al.*, two series of patients with mixed-type cryoglobulinaemia were treated with rituximab. Patients in the study by Sansonno *et al.* had a follow-up of 12 months and 80% showed a complete remission without recurrence of disease. Only one of the 20 patients had nephritis that did not respond to treatment. In the study by Zaja *et al.* 15 patients were treated with rituximab with a follow-up of 9 to 31 months. Within the study, two patients were present with renal involvement, of which one did not respond to therapy and the other patient showed a complete remission. These studies were followed by two reports[5,17] of a series of patients with cryoglobulin-associated nephritis who were treated successfully with anti-CD20 monoclonal antibody infusion, and a number of case reports thereafter.[18-21] In the study by Rocatello *et al.*,[17] all five patients with cryoglobulin-associated nephritis showed a partial or complete response after rituximab treatment. In the follow-up period of 12 to 18 months no recurrence was noted. In the study by Quartuccio *et al.* also five out of five patients with cryoglobulin-associated nephritis responded to rituximab treatment but at follow-up (9 to 21 months), three out of five patients showed a recurrence of disease at five, seven and 12 months. A repeated cycle of rituximab infusion again induced remission of disease activity.[5] Of note is that in all studies the initial treatment schedule is based on the original non-Hodgkin's lymphoma study and consists of four weekly infusions of rituximab 375 mg/m^2.[22] It is not known whether lower or less frequent dosing may be equally effective.

Mechanism of action

Rituximab is an effective depleting monoclonal antibody for circulating CD20 bearing B lymphocytes, although in the secondary lymphoid organs a large number of the B lymphocytes remain present. Months (on average 6 to 9 months) after the last infusion, the B lymphocytes reappear in the circulation.[5,15,16] The IgM autoantibody producing B lymphocytes appears to be depleted preferentially, which may explain the efficacy of rituximab in the treatment of mixed-type cryoglobulinaemia and rheumatoid arthritis.[5] Also in our patient there was a clear decrease in the concentration of IgM rheumatoid factor activity, which correlated with the decrease of total serum IgM and cryoglobulin concentration. The observed improvement of creatinine clearance may in part be related to the withdrawal of cyclosporine in this specific case. However, the decrease in proteinuria and disappearance of an active urine sediment suggests the resolution of ongoing nephritis, by

limiting the deposition of newly formed cryoglobulins. The persistence of proteinuria in our patient, although reduced by 70% one year after rituximab treatment, may indicate permanent damage to the glomeruli.

Side effects of rituximab

Expression of the CD20 antigen is limited to immature and mature B lymphocytes. The long-lived plasma cells do not carry the CD20 antigen on their cell surface and are therefore not deleted. This probably explains why serum IgG concentration remains unchanged after anti-CD20 therapy. This leaves the humoral immunity intact and there is no necessity for prophylactic infusion with immunoglobulins. However, infections with human parvovirus B19 and reactivation of a hepatitis B viral infection have been described in association with rituximab.[23,24] The frequency of infectious complications seems low. Possibly, the risk for infectious complications is increased in already immunocompromised patients, such as patients taking immunosuppressive drugs (for instance transplant patients) or suffering from an HIV infection. Serious infectious complications have been reported in renal transplant patients receiving rituximab. However, these data are anecdotal.[25,26]

Patients with chronic HCV have received rituximab without an increase in HCV disease activity.[5,15,16] Of course, it cannot be excluded that the increase in HCV hepatitis disease activity in our patient, who was also taking immunosuppressive medication, was related to the rituximab treatment. The immediate side effects after infusion of rituximab are usually few and mild.[5,15-17] However, the side effects of anti-CD20 therapy in the long term, especially in relation to the function of the immune system, are not known.

CONCLUSION

Cryoglobulinaemia is a current clinical problem in HCV-infected patients, even after liver transplantation for HCV cirrhosis. Depletion of B lymphocytes by infusion of the monoclonal antibody rituximab appears to be a rapid, effective and non-toxic treatment for mixed cryoglobulinaemia-associated glomerulonephritis. Rituximab has emerged as an important new drug for the treatment of this condition, especially in selective cases in which the current therapeutic options are limited.

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CASE REPORT

Extrapulmonary lymphangioleiomyomatosis: an unusual cause of biliary tract obstruction

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ABSTRACT

We present a patient who was diagnosed with retroperitoneal lymphangioleiomyomatosis (LAM) and who developed biliary tract obstruction caused by LAM in the papilla of Vater. After endoscopic retrograde cholangiopancreatography (ERCP) and papillotomy, the patient's liver enzymes normalised. Disease progression was slowed down with gosereline and interferon alpha 2b (IFN-α2b). In patients with LAM and signs of biliary tract obstruction, disseminated LAM should be considered. IFN-α2b can be a useful treatment in patients with widespread LAM.

KEYWORDS

Biliary tract obstruction, extrapulmonary, lymphangioleiomyomatosis

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is characterised by non-neoplastic proliferation of abnormal smooth muscle cells (LAM cells) that almost exclusively affects women in their reproductive years. LAM is a rare systemic disease and the main manifestations are pulmonary.[1,2] Although LAM can occur in subjects with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous syndrome, most patients have sporadic LAM.[1]

Due to the rarity of this disease, many clinicians are unfamiliar with LAM. Hence, clinical management represents a great challenge, occasionally resulting in a delayed or missed diagnosis, unnecessary operative intervention, and inappropriate therapy. We report a case of a woman who was initially diagnosed with retroperitoneal LAM and subsequently developed pulmonary LAM in combination with elevated liver enzymes. This is the first case describing LAM of the papilla of Vater and it provides novel insights into the treatment of this rare disease.

CASE REPORT

This 23-year-old, otherwise healthy, woman presented with progressive abdominal pain. There was no significant family history. She did not have dyspnoea or chest discomfort. On physical examination no abnormalities were found and haematological tests were normal. On transvaginal ultrasonography, the ovaries were normal. A computed tomography (CT) scan of the abdomen showed a large retroperitoneal mass, 13 x 7 x 16 cm, with cystic and solid components in the lower right abdomen which extended around the abdominal aorta and inferior vena cava. A high resolution (HR) CT scan of the thorax was normal. Upon laparotomy, the mass was irresectable. Histology was highly characteristic of LAM and showed proliferation of smooth muscle tissue surrounding dilated lymph and blood vessels. These smooth muscle cells contained monomorphic oval nuclei with blunt-ended nuclei. Immunohistochemistry was positive for actin but negative for desmin. These findings are highly characteristic of LAM.

She started on a gonadoreline (GnRH) agonist (gosereline) 3.6 mg monthly and tamoxifen 40 mg daily. However, because of disease progression the tamoxifen was stopped and replaced by monthly medroxyprogesterone 500 mg in combination with thalidomide 50 mg daily (which has antiangiogenic and immunomodulating effects). Nevertheless, the disease progressed and HRCT of the thorax one year after diagnosis demonstrated pulmonary LAM. Subsequently, the medroxyprogesterone and thalidomide were stopped. Based on a case report describing

successful treatment of LAM with systemically applied interferon alpha 2b (IFN-α2b)[3] she was started on IFN-α2b 3 x 10^6 U three times a week. Abdominal and thoracic CT scans showed stable disease. However, liver enzymes became elevated (reference values are given in parenthesis): alkaline phosphatase (ALP) 111 U/l (<100), gamma-glutamyl transferase (γGT) 183 U/l (<25), aspartate aminotransferase (AST) 29 U/l (<30), alanine aminotransferase (ALT) 37 U/l (<30) and bilirubin 5 μmol/l (<5). This was attributed to the IFN-α2b but since the liver enzymes were only mildly elevated, treatment was continued. In the course of seven years, follow-up abdominal and thoracic CT scans showed stable disease under IFN-α2b but the liver enzymes kept increasing (ALP 215 U/l, γGT 520 U/l, AST 28 U/l, ALT 39 U/l, and bilirubin 10 μmol/l after seven years). Eventually, an abdominal CT scan showed dilated bile ducts without evidence of bile stones. On endoscopic retrograde cholangiopancreatography (ERCP) a hypertrophic papilla of Vater was seen (*figures 1* and *2*). After biopsy and papillotomy, bile drainage was good. Liver function returned to normal (ALP 103 U/l, γGT 55 U/l, AST 26 U/l, ALT 17 U/l, and bilirubin 3 μmol/l). Histology revealed lymphangiectasis in the lamina propria of the papilla of Vater concordant with the diagnosis of LAM (*figure 3*). Currently, almost ten years after diagnosis, the patient remains in follow-up with radiologically stable disease on treatment with gosereline and IFN-α2b. Clinical evidence of TSC was not present in this case, therefore evaluation for the TSC gene was not performed.

Figure 1. *Papilla of Vater after precut, which proved to contain lymphangioleiomyomatosis*

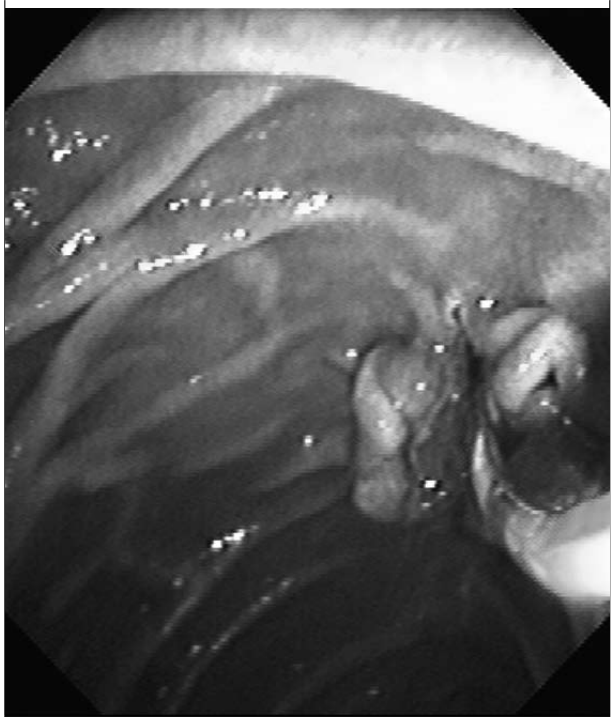


Figure 2. *Dilated bile ducts due to lymphangioleiomyomatosis of the papilla of Vater*

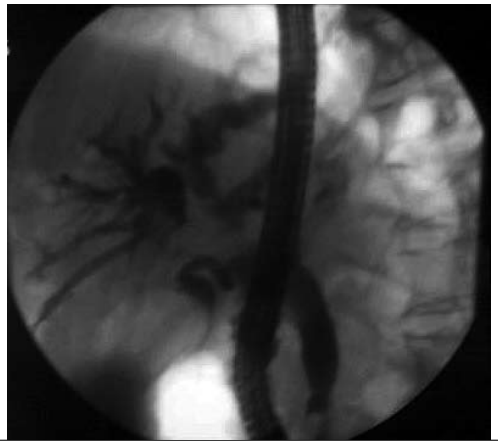
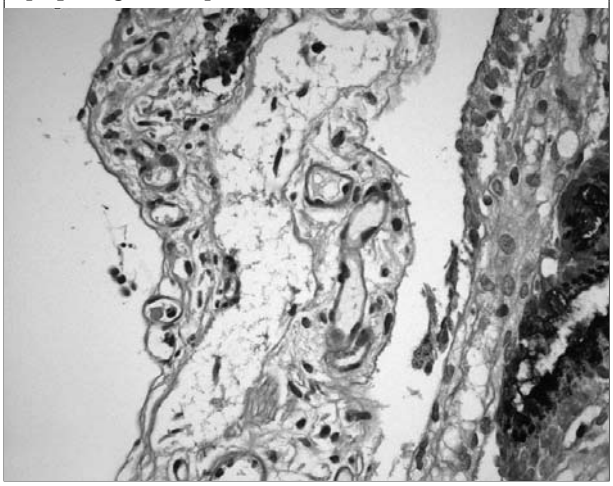


Figure 3. *Biopsy of the papilla of Vater demonstrating focal lymphangiectasis concordant with lymphangioleiomyomatosis*



DISCUSSION

This case demonstrates that LAM can occur at unexpected sites. In case of elevations of liver enzymes in patients with LAM, disseminated LAM should be considered in the differential diagnosis.

Much is still unknown regarding the natural behaviour of LAM. Patients with (sporadic) LAM generally develop progressive airflow obstruction, intermittent pneumothoraces, chylous collections or other complications. Although there are no prospective studies on survival, recent data have suggested that ten-year survival is in the order of 55 to 71%.[1] This case demonstrates that disease progression can be slowed down with a combined treatment of a GnRH agonist and IFN-α2b.

Patients who present with extrapulmonary LAM are rare. In a pathological analysis of 188 cases, extrapulmonary LAM without coexisting lung involvement was identified in only three patients (2%).[2] After reviewing the literature, we identified 24 patients who did not have lung involvement at the time of diagnosis; however, as our patient, many of these patients were later diagnosed with pulmonary LAM, usually within two years (*table 1*).[2,4-10]

The precise molecular mechanisms that modulate LAM cell growth remain unknown. LAM typically exacerbates after hormone replacement, pregnancy or oestrogen replacement and oestrogen and progesterone receptors are identified at histopathological examination.[11] These observations suggest that hormone metabolism plays a key role in LAM and most treatment concepts are now based on this suggestion. Different treatments have been tried, including oophorectomy, tamoxifen, GnRH analogues, progesterone and combinations. Radiation therapy, corticosteroids, and chemotherapy have shown little benefit.[1,12] Early institution of medroxyprogesterone is the most accepted medical treatment nowadays, although solid clinical evidence of its effectiveness is lacking. Hormonal treatment alone could not prevent disease progression in our patient. It was only when IFN-α2b was added to the treatment that the patient reached more or less stable disease (although she did develop LAM in the papilla of Vater). This case may, therefore, support the use of IFN-α2b in addition to hormonal treatment. IFN-α2b, a cytokine with antiproliferative and antiangiogenic properties, could theoretically have a place in the treatment of LAM, which is a proliferative disorder. Furthermore, recent research has demonstrated that IFN-α (which induces apoptosis) is downregulated in TSC-related and sporadic LAM providing a possible rationale for IFN-α2b treatment.[13] Recently it has been demonstrated that LAM lesions are generated by the proliferation of LAM cells with mutations leading to loss of TSC gene activity resulting in overexpression of the kinase mammalian target of rapamycin (mTOR).[12] Inhibitors of mTOR may therefore provide new treatment options.

In conclusion, we present a patient with biliary tract obstruction caused by LAM of the papilla of Vater. In patients with elevated liver enzymes and evidence of dilated bile ducts, disseminated LAM should be considered and symptoms of ampullary LAM can be treated by ERCP and papillotomy. Furthermore, our findings support the use of gosereline and IFN-α2b in patients with rapidly progressive disease and widespread lesions.

Table 1. *Cases of extrapulmonary lymphangioleiomyomatosis at diagnosis*

Reference	Age	Site	Size (cm)	Clinical features	pLAM	Follow-up (years)
Matsui *et al.*(2)	30	Pelvis	1	NA	No	5
	45	Retroperitoneal	2	Adenopathy	No	Not assessed
	53	Pelvis	NA	NA	No	36
	35	Retroperitoneal	NA	NA	No	Not assessed
	30	Pelvis	12	Pain	Afterwards*	11
	53	Retroperitoneal	2.5	NA	Afterwards*	3.5
	45	Retroperitoneal	2.5	Adenopathy	Afterwards*	5
	49	Retroperitoneal	5	Mass	Afterwards*	13
	34	Renal hilum	1	Mass	Afterwards*	7
	37	Retroperitoneal	1	NA	Afterwards*	3
	37	Retroperitoneal	20	NA	Afterwards*	6
	32	Retroperitoneal	2	Chylous ascites	Afterwards*	Not assessed
	Not known	Pelvis	NA	Mass	Not assessed	Not assessed
	Not known	Pelvis	NA	Mass	Not assessed	Not assessed
	31	Pancreas	9	Pain, diarrhoea	Afterwards*	1
	33	Perirenal	NA	Distension	Afterwards*	0.8
	29	Pelvis	5	Pain	Afterwards*	1
Jaiswal *et al.*(4)	51	Retroperitoneal	12	Radiculopathy	No	6, NED
Wong *et al.*(5)	32	Pelvis	NA	Pain	Not assessed	Not assessed
Lam *et al.*(6)	35	Pelvis	11	Leg oedema	Afterwards*	Not assessed
Kim *et al.*(7)	21	Pelvis	10	Pain	Afterwards*	6, died (pLAM)
Wan *et al.*(8)	31	Retroperitoneal	5	Mass	No	2
Atallah *et al.*(9)	44	Pelvis	22	Distension	No	NA
Kebria *et al.*(10)	59	Retroperitoneal	5.5	Vaginal bleeding	No	0.5

NED = no evidence of disease, pLAM = pulmonary lymphangioleiomyomatosis. *Patient presented with extrapulmonary lymphangioleiomyomatosis and subsequently diagnosed with pulmonary lymphangioleiomyomatosis.

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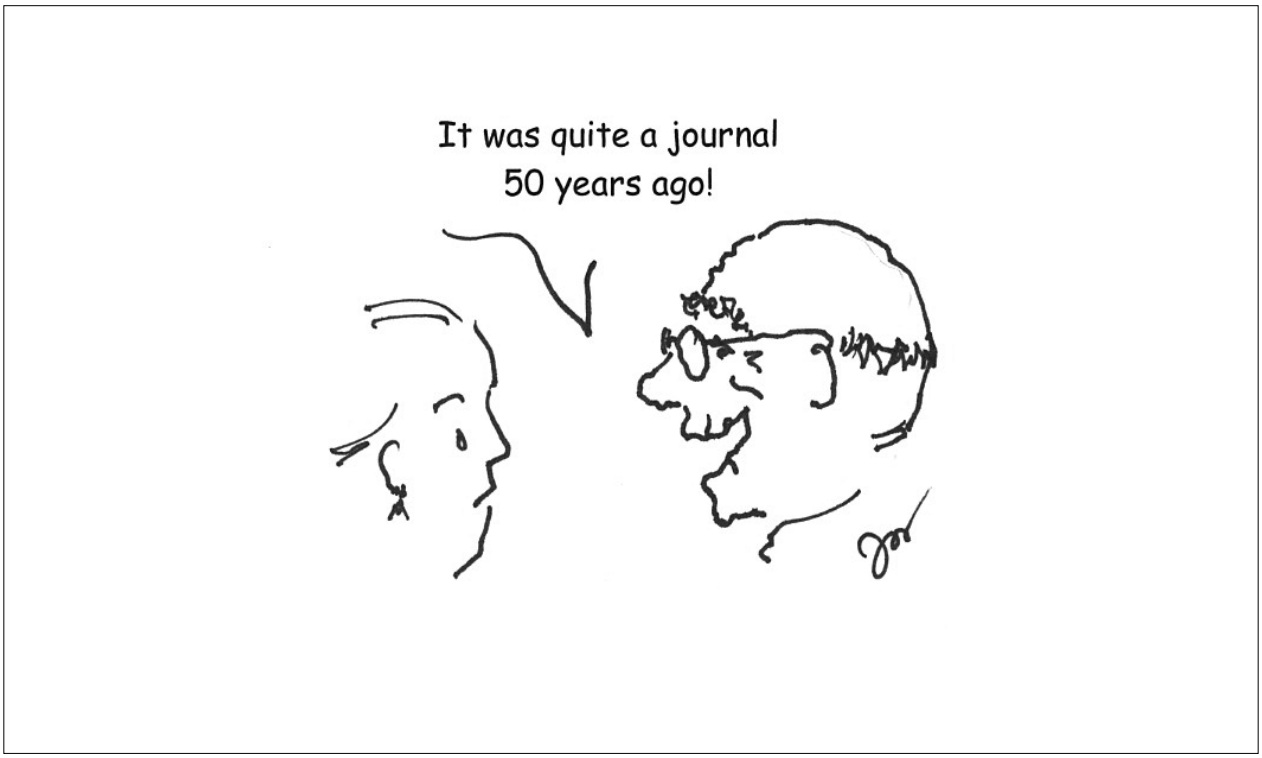

De Groot, et al. Extrapulmonary lymphangioleiomyomatosis.

SPECIAL REPORT

50 years Netherlands Journal of Medicine

Reminiscences of three successive editors

Transition from Folia Medica Neerlandica to the Netherlands Journal of Medicine as a fully fledged international medical monthly journal

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THE EARLY YEARS

After the end of the Second World War in 1945, most large hospitals and academic institutions were left in an impoverished condition and largely devoid of funds, proper laboratory instruments and accordingly trained research personnel. Hospitals and research facilities were out-of-date, often primitive and neglected. Nevertheless, medical research quite rapidly recovered; projects were set up and results reported at meetings.

Resourcefulness was quite remarkable, and accurate instruments were often constructed out of old spare parts. Although the local medical newspaper, the *Nederlands Tijdschrift voor Geneeskunde,* had almost succeeded in continuing publication throughout the war years, the influx of foreign medical journals showed a need to have the efforts of Dutch medical research workers published for a wider auditorium, possibly even in the UK or the USA.

The initiative to promote foreign contacts originally started from a small group of university teachers who had established excellent relations with colleagues in foreign countries because of their courageous attitude during the German occupation, and such friends were particularly found in the Scandinavian countries. As a result, some leading Dutch internists were invited to join the board of the old and prestigious English-language journal *Acta Medica Scandinavica* as associate members. For a number of years this was a profitable cooperative effort, and the opportunity to have one's thesis printed as supplement to the *Acta,* used by many Scandinavian students, was eagerly accepted, and not only because printing expenses in the Netherlands were often prohibitive.

Unfortunately, in the long run, Dutch physicians and medical research workers were unable to meet the very high standards imposed by their Scandinavian colleagues, and the Dutch editors were kindly requested to step down and leave the board of the *Acta*. Understandably, this was a dramatic setback and everyone found it quite humiliating. It took some years to overcome the loss and start a new initiative.

Lindeboom, then Professor of Medicine at the Free University in Amsterdam and a well-known medical historian, started a new journal of internal medicine in 1957. Its somewhat pompous Latin title, *Folia Medica Neerlandica,* was probably chosen because of the past links with the *Acta*. But the language of publication was Dutch, the set-up remained modest, and issues appeared irregularly.[1] The board of the Netherlands Association of Internal Medicine (Nederlandsche Internisten Vereeniging, NIV) came to the conclusion that the *Folia* should change its character and with this in mind Van Leeuwen (Binnengasthuis, Amsterdam) was asked to become the new managing editor in 1965. An editorial board was formed representing all the university hospitals and a few affiliated hospitals. Its aim was to make the *Folia* into an internationally accepted platform for clinical research from the Netherlands with English as the predominant language. It took a few years to achieve this goal. In the early days, publication of original work in English was actively solicited and when accepted rewarded with 50 free copies of the journal. However, by 1970, when Geerling succeeded Van Leeuwen, all original articles and reviews were published in the English language and both quantity and quality had satisfactorily increased. Finally, in 1973 the journal was completely issued in English and accordingly its name changed to *The Netherlands Journal of Medicine*. The publishing house succeeded in obtaining a quotation in Current Contents/Clinical Sciences. The subscription was linked to membership of the NIV, which also became responsible for the financial management.

The journal thus gradually changed into a semi-professionally run periodical issued on a monthly basis with a varied and interesting content. The cover was attractively redesigned – the well-known yellow/green one which was maintained until 1986. The technical arrangements were quite conservative and would now be regarded as slightly amateurish: the Journal shared the publishing firm – Bohn, an old family business – with the general medical journal, the *Nederlands Tijdschrift voor Geneeskunde*, and sometimes the finished manuscripts were brought to the printers on the back of a bicycle. Correspondence was either handwritten or typed. In the same style the editorial work remained very much a 'labour of love'. This was partly compensated for by the social aspects. The monthly meetings of the editorial board were informal, and held at the home of the managing editor with coffee and cake. After exchanging the latest news from the various departments, the real work began with the invaluable assistance of Mrs Stijger, the one and only freelance secretary. She took care of archiving and layout, maintained daily contact with the authors and the publisher and, if necessary, corrected the English language. She played an essential role in the development of the Journal.
Her salary was paid by the publisher, but all other expenses were the responsibility of the treasurer of the NIV, which was also the main financier, the number of paid subscriptions (mainly libraries) being quite low. The only other source of income was the publication of advertisements of pharmaceutical products, but this mainly covered the publisher's deficit. Proofs were circulated by mail; publishing delays therefore tended to be rather long.
Nevertheless, all these changes were appreciated by the members of the NIV and other subscribers, and there was rarely a shortage of manuscripts. The arrangement that the managing editor was also a member of the board of the NIV guaranteed a regular input. However, it has to be admitted that the rejection rate was low and standards had not yet reached an internationally acceptable level.
When Van Leeuwen handed the job of managing editor over to his successor, Geerling, in 1970 the position of the Journal was stable and the future looked bright. But the overall economic situation had worsened, and the financial resources of the Journal and its main sponsor, the NIV, were no longer as rosy as in the past. Geerling had a solid reputation as editor of the 'Referaten' section (Short summaries of articles from foreign medical journals, published regularly, originally as reports written for a journal club in the department of internal medicine in the Amsterdam) in the *Nederlands Tijdschrift voor Geneeskunde,* and he also had an excellent network in the world of Dutch internal medicine, both outside and inside university departments. Moreover, he was blessed with an almost photographic memory. Van Leeuwen's management model – including the homely aspects and the simple methods used – was carefully maintained.
Unfortunately, the initial enthusiasm had waned because Dutch clinicians increasingly tried to have their reports published in prestigious English-language journals, which enhanced their reputation and produced a higher number of quotations. This happened at a time when funding of clinical and research departments was not so much decided by local quality or practicability, but predominantly by international quotation rates – and these in turn were decided by one single institution, the International Scientific Institute or ISI. Repeated attempts at obtaining quotation in Current Contents/Life Sciences failed in that period. Despite doubling the effort to solicit papers both input quantity and quality suffered and the number of issues had to gradually be reduced. This also meant a drop in advertising income and the increasing scrutiny of the NIV's treasurer. Nevertheless the Journal survived the lean years to meet newer challenges and greater upheaval.

ANTICIPATING NEWER DEVELOPMENTS

In the present era, publishing a scientific journal without the resources of electronic media, the Internet, word processing and the use of databases would be unthinkable. But when guards changed in 1981 and Offerhaus took over from Geerling, such notions still sounded like futuristic fantasies. The only immediate change was the purchase of a voluminous file indexing system copied from the secretariat of the *Nederlands Tijdschrift voor Geneeskunde*. There they were already aware of the possibilities offered by desktop computing systems, but these were still quite expensive. Mainframe systems were difficult to handle and not especially suited for this kind of work. However, by pure chance some funds were made available from one of the Dutch drug bulletins and for the hefty price of *f* 5000 (approx. € 2250) an Apple IIe system was purchased (*figure 1*), two years before the appearance of

Figure 1. *The antediluvian 'personal' computer used to start computerisation of the Journal. See text for a description*

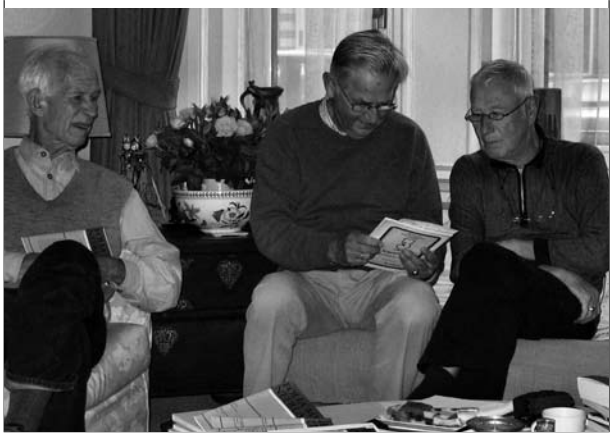
the IBM PC on the European market. The Apple IIe was an impressive machine with an internal memory of 1028 kB, a clock speed of 1 MHz (!), two floppy disk drives each 320 kB and even a large box harbouring a hard disk of 20 MB; it could connect to the outside world at a maximum speed of 1.2 kB/min. But it could also write letters, maintain a simple database and consult Medline all the way to the USA. Because institutional secretarial assistance was not available, the use of a computer was a necessity.[2]

Although both the editors and the publisher were quite happy, many authors and referees had difficulty in adjusting to modern times. Printed standard letters, submitting texts on diskette etc. were felt to be unfriendly and impersonal. It took some time before these changes were accepted. And to his dismay, the NIV's treasurer discovered that a 'paperless' office can be quite expensive. On the other hand, publishing speed was considerably enhanced, and consequently the number of submissions increased. It became possible to fill twelve issues per year and even to raise standards and reject some substandard material.

All went smoothly until the NIV's treasury started questioning the publishing expenses and discovered that most of the income from advertising had been spirited away. The contract with the original publisher had to be cancelled and a new one found. This proved to be quite difficult. An attempt to merge with the British *Quarterly Journal of Medicine* utterly failed because their editors felt far superior to any journal from 'on the continent', even though their publisher, Blackwell's, was sympathetic. A second attempt through the German publisher Springer looked much more promising, but the proposed merger with the German internists' journal *Klinische Wochenschrift* and the Belgian *Acta Clinica Belgica* ended in total failure because our Southern neighbours refused to give up their independence – even though the Germans were willing to make concessions on a new name and abandon the German language in favour of English. In the end, in 1985 it remained up to Offerhaus's successor De Leeuw to cut off all old ties and start with a new publishing house, this time Elsevier. This proved to be an unhappy marriage and it also meant the involuntary retirement of Mrs Stijger, who had acted as the heart and soul of the enterprise for so many years. However, the transition did not harm the Journal. But it was the beginning of a totally new era in which freelance assistants were replaced by academic office staff, mailings and postage stamps by word processing and e-mail, and coffee and cake at the managing editor's home replaced by the mobile phone. Despite entering the electronic age. the Journal survived quite well.

On 23 October 2006 there was a final meeting at the home of the second editor in the history of the Journal, Van Leeuwen – with coffee and cakes – and three successive managing editors, now well into the age of retirement, were able to look back on a substantial part of the Journal's history and had the occasion to recall some almost forgotten events which contributed to its present success (*figure 2*).

Figure 2. *Three former managing editors together in 2006 (from left to right: Tontin van Leeuwen, Leo Offerhaus and Jan Geerling)*



NOTE

Invitational article on request by the editors of the *Netherlands Journal of Medicine*.

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Netherlands
The Journal of Medicine

PHOTO QUIZ

A patient with a neck mass

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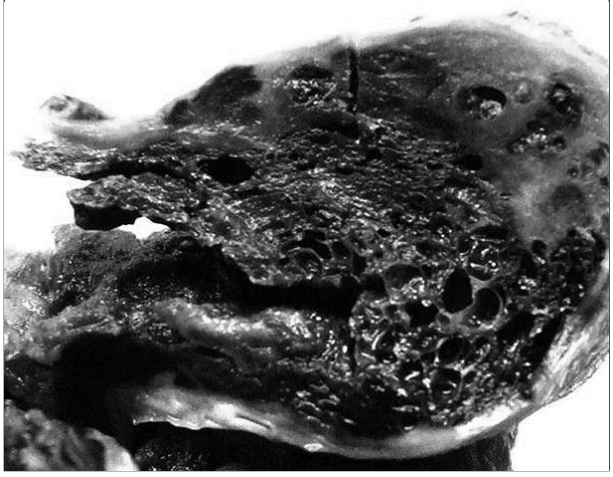
Departments of [1]Pathology and [2]General Surgery, Sutcu Imam University, Kahramanmaras, Turkey

CASE REPORT

A 64-year-old man presented with a two-year history of a swelling on the anterior side of the neck region. Physical examination revealed a palpable nodule measuring 70 mm in diameter, well-delimited, and located in the right lobe of the thyroid. The blood analysis and thyroid hormones were within normal limits. Thyroid ultrasonography revealed a multinodular goitre. Tc-99 scintigraphy was reported as a multinodular hyperplasia (*figure 1*). He had no history of previous fine needle aspiration. A right lobectomy was performed. Macroscopic observation showed a well-circumscribed nodular lesion surrounded by fibrous connective tissue. The nodular lesion measured 70 x 60 x 60 mm and contained many cystic spaces (*figure 2*). Microscopic examination revealed numerous proliferated vessels that enlarged into an irregular shape showing congestion (*figure 3*).

Figure 2. *Gross specimen of the thyroid*



WHAT IS YOUR DIAGNOSIS?

See page 39 for the answer to this photo quiz.

Figure 1. *The thyroid scintigraphy*

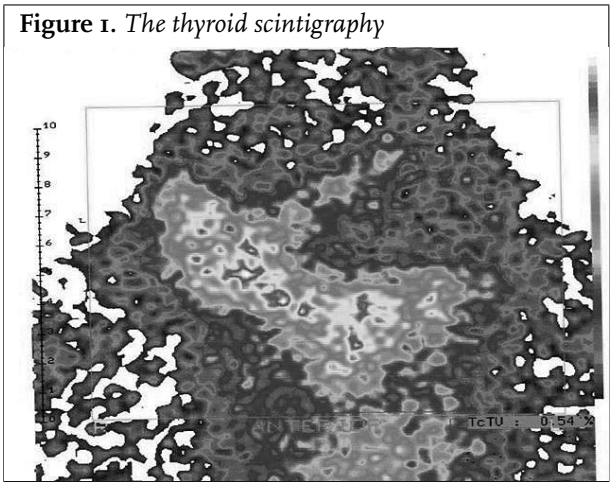
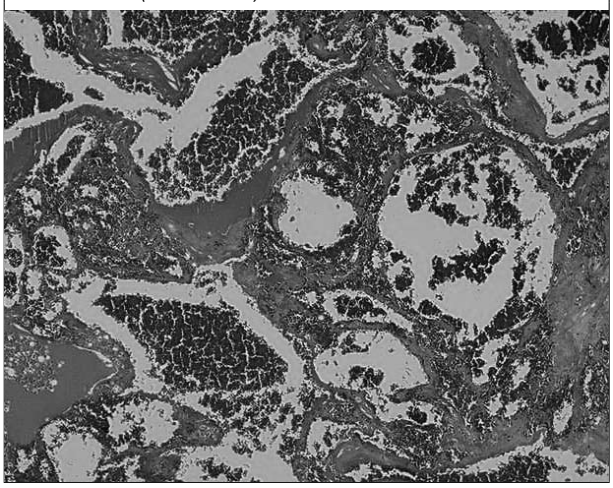


Figure 3. *Section of the thyroid showing irregular, dilated, congested, and anastomosed vascular structures. (H&E x 20)*



ANSWER TO PHOTO QUIZ (ON PAGE 38)

A PATIENT WITH A NECK MASS

DIAGNOSIS

Haemangiomas are benign vascular neoplasms that have a characteristic clinical course marked by early proliferation followed by spontaneous involution. Microscopically, they are classified into various types, including capillary haemangioma, cavernous haemangioma, venous haemangioma, and epitheloid haemangioma.[1] They occur in a number of organs, including the skin, lips, tongue, liver, colon, and brain.[1,2] Haemangiomas are extremely rare in the thyroid, with only 25 cases ever having been reported.[3]

The literature reports a large number of vascular alterations, benign and malignant, in the thyroid gland. Most of these thyroid lesions are related to previous fine needle aspirations and are the result of the organisation of the thyroid haematoma after the test.[2] Organisation of the haematoma generally results in complete resolution, but it can give rise to vascular and fibroblastic proliferative changes that resemble a cavernous haemangioma.[4] This is defined as secondary haemangioma.

Clinical onset is usually as an asymptomatic cervical tumour, occasionally fast-growing, especially if intratumoral bleeding is present. It is usually revealed in the right lobe of the thyroid. These tumours have a diameter between 20 and 40 mm. A slightly higher proportion of males are affected.

In the diagnosis of thyroid haemangioma, ultrasound usually detects a thyroid nodule. Computed tomography is good for defining the form, size and location of the tumour, and magnetic resonance imaging is very effective in showing the extent of cavernous haemangiomas.[1] 99mTc-labelled red blood cell scanning or 99mTc-labelled scanning by single-photon emission computed tomography are other good methods. Little or no increased activity is seen soon after injecting the label, and this appearance of poor perfusion and slow filling of the tumour is characteristic of cavernous haemangioma.[1] Haemangioma should be considered in the diagnosis of any pulsatile mass involving the thyroid gland. Diagnosis before surgery is difficult. Histology provides the final diagnosis of cavernous haemangioma.

Surgical treatment is indicated when there is a suspicion of malignancy or in the presence of compressive symptoms. Hemithyroidectomy or total thyroidectomy is best performed if the thyroid presents contralateral pathology.[2]

The diagnosis is cavernous haemangioma of the thyroid.

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LETTER TO THE EDITOR

Transmission of hepatitis C genotypes in the Netherlands amongst recently genotyped patients

In 2006 we reported the genotype distribution amongst unselected chronic hepatitis C infected (HCV) patients who were seen by physicians treating HCV in the Netherlands and who were genotyped between February 2002 and June 2005.[1] However, data on transmission of HCV genotype is lacking, hence we performed a survey to increase our knowledge of the transmission of hepatitis C genotypes in the Dutch population. The approach was similar to that used before, although this survey includes data on patients co-infected with HIV.[1]

A total of 27 physicians from 20 hospitals reported data for five novel genotyped HCV patients. We received data on 121 patients, coming from nine provinces of the Netherlands. The median date of the HCV diagnosis was September 2005 (range: January 1985 to November 2006); the majority of the patients were male (69.4%). Patients were genotyped between June 2006 and April 2007, a median of 49.0 days (range 0 days to 21.1 years) after diagnosis. The mean age at diagnosis was 44.3 ± 11.4 (SD) years and mean age at genotyping was 46.1 ± 10.7 years. Most physicians gave a wide time range in which HCV infection apparently took place, and taking the upper limit of the range resulted in a mean age at infection of 28.7 ± 10.5 years. This survey confirms the genotype shift observed previously in the Netherlands.[1,2] As follows from *table 1*, most patients were infected with

Table 1. *Transmission of hepatitis C genotypes in the Netherlands amongst recently genotyped patients*

		Genotype					
	All	**1**	**2**	**3**	**4**	**6**	**2 + 4**
Total patients, n (%)	121 (100)	63 (52.1)	11 (9.1)	34 (28.1)	10 (8.3)	2 (1.7)	1 (0.8)
Man/women, n/n (% men)	84/37 (69.4)	42/21 (66.7)	7/4 (63.6)	27/7 (79.4)	8/2 (80)	0/2 (-)	-/1 (-)
Country of origin, n (%):							
• The Netherlands	71 (58.7)	43 (68.3)	4 (36.4)	21 (61.8)	3 (30.0)	- (-)	- (-)
• Other	50 (41.3)	20 (31.7)	7 (63.6)	13 (38.2)	7 (70.0)	2 (100)	1 (100)
Country of infection, n (%):							
• The Netherlands	68 (56.2)	41 (65.1)	3 (27.3)	21 (61.8)	3 (30.0)	- (-)	- (-)
• Other	33 (27.3)	15 (23.8)	3 (27.3)	7 (20.6)	5 (50.0)	2 (100)	1 (100)
• Unknown	20 (16.5)	7 11.1)	5 (45.5)	6 (17.6)	2 (30.0)	- (-)	- (-)
Route of transmission, n (%):							
• Transfusion of blood/blood products	18 (14.9)	11 (17.5)	1 (9.1)	3 (8.8)	2 (20.0)	- (-)	1 (100)
• Medical treatment	6 (5.0)	3 (4.8)	- (-)	1 (2.9)	2 (20.0)	- (-)	- (-)
• Injection drug use	55 (45.5)	30 (47.6)	2 (18.2)	20 (58.8)	3 (30.0)	- (-)	- (-)
• Parenteral exposure (e.g. tattoo)	1 (0.8)	- (-)	- (-)	1 (2.9)	- (-)	- (-)	1 (100)
• Occupational exposure	3 (2.5)	1 (1.6)	2 (18.2)	- (-)	- (-)	- (-)	- (-)
• Born in an endemic country	7 (5.8)	2 (3.2)	1 (9.1)	1 (2.9)	2 (20.0)	1 (50.0)	- (-)
• Other	8 (6.6)	3 (4.8)	1 (9.1)	4 (11.8)	- (-)	- (-)	- (-)
• Multiple possible routes	2 (1.6)	1 (1.6)	- (-)	- (-)	1 (10.0)	- (-)	- (-)
• Unknown	21 (17.4)	12 (19.0)	4 (36.4)	4 (11.8)	- (-)	1 (50.0)	- (-)
Viral load, n (%):*							
• Low viral load	52 (45.2)	27 (44.3)	4 (44.4)	16 (48.5)	4 (44.4)	- (-)	1 (100)
• High viral load	63 (54.8)	34 (55.7)	5 (55.6)	17 (51.5)	5 (55.6)	2 (100)	- (-)
HIV co-infection, n (%):							
• No/unknown	113 (93.4)	58 (92.1)	11 (100)	31(91.2)	10 (100)	2 (100)	1 (100)
• Yes	8 (6.6)	5 (7.9)	- (-)	3 (8.8)	- (-)	- (-)	- (-)

*Low viral load defined as ≤800,000 IU/ml or ≤2,000,000 c/ml and high viral load as >800,000 IU/ml or >2,000,000 c/ml, no viral load known for six patients.

genotype 1, followed by genotype 3, and 2 and 4. Genotype 6 was rare. Most patients (n=71, 58.7%) originated from the Netherlands, and 64 of them had also been infected in the Netherlands. A large minority of patients came from abroad (n=50, 41.3%) and originated from 27 different countries. Twenty-eight of 50 patients were infected in the country of origin while for 17 patients the country of infection could not be assessed. Injection drug use was the main route of transmission (45.5%), while 14.9% of the patients were infected via transfusion of blood/blood products, and 5% were infected during medical treatment.

Data on 1867 hepatitis C infected patients reported to the Health Inspectorate in 1999-2002 have been published.[3] Sex and age at diagnosis of these patients are very comparable to the patients in our survey, most of whom were diagnosed some years later (median September 2005). However, of the patients reported to the Health Inspectorate whose country of origin was known, a higher percentage originated from the Netherlands: 71.0% compared with 58.7% in our survey.[3] This suggests that more of the recently diagnosed/genotyped patients originate from outside the Netherlands. Infection by injection drug use was the main route of transmission both in patients reported to the Health Inspectorate (54.0%) and in our survey (45.5%). Surprisingly, however, only a low percentage (4.0%) of the patients reported to the Health Inspectorate were infected via transfusion of blood/blood products. We found a higher frequency (14.9%) which, however, is not due to the fact that more patients in our survey acquired HCV in countries with less stringent HCV screening policies for blood transfusion, as 14 out of 18 patients who had been infected by transfusion originated from the Netherlands, where they had been infected prior to 1992.

So far, data relating the genotype to transmission routes are scarce. We found that transfusion of blood/blood products was responsible for infection in 17.5% (n=11) of genotype 1 patients. Among patients with genotype 1b, transfusion of blood/blood products was the main route of transmission (n=7, 35%), although a comparable percentage of patients were infected by injection drug use (n=6, 30%). Overall, injection drug use was the mode of infection in 47.6% of genotype-1-infected patients. Likewise, a total of eight out of ten genotype 1a patients were infected via this route. As described before, genotype 2 was prevalent in patients originating from Suriname; two out of three patients originating from Suriname were infected with genotype 2 and one with the combination genotype 2+4. Injection drug use was the mode of infection for 58.8% of genotype 3 and 59.1% of genotype 3a infected patients. Some six out of ten genotype 4 patients originated from Egypt. The routes of transmission were transfusion of blood/blood products (20%) or medical treatment (*Schistosomias* vaccination, 20%). As reported for other European countries, we found that genotype 4 has entered the intravenous drug scene in the Netherlands, as three genotype 4 patients were infected by injection drug use in the Netherlands.[4] The two patients infected with genotype 6 originated from and were infected in Asia (China and Korea). A minority of eight patients were known to be co-infected with HIV; they had genotype 1 or 3 in all cases and injection drug use was the major mode of transmission. We retrieved data on viral load for 115 patients. Some 55% had a high viral load, similar for genotypes 1 to 4.

This survey confirms the shift in genotype distribution amongst unselected HCV patients seen by Dutch physicians.[1,2] Moreover, it confirms and extends our knowledge of the demographic and epidemiological characteristics of HCV patients in the Netherlands, in particular in relation to their genotype.

NOTE

This survey was funded by Roche Nederland BV, Woerden, the Netherlands.

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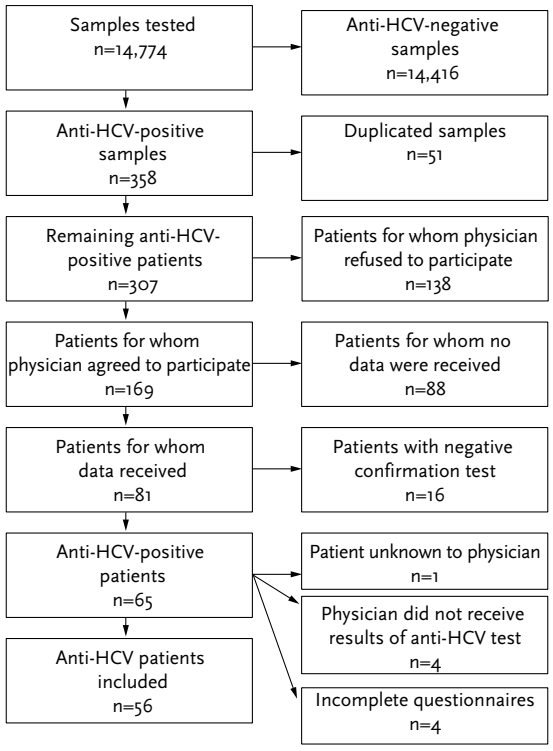
LETTER TO THE EDITOR

Referral of hepatitis C virus seropositive patients in primary care in the Netherlands

Worldwide there are approximately 170 million people with a chronic hepatitis C virus (HCV) infection. In the Netherlands the assessed prevalence in the population is between 0.1 and 0.4%.[1] HCV-seropositive patients should be referred via primary care to a specialist with experience in chronic HCV infection for medical assessment. Referral has become even more important since the introduction of more effective treatment with pegylated interferon and ribavirin.[2] The May 2000 Practice Guideline 'Viral hepatitis and other liver diseases' of the Dutch College of General Practitioners, which is regarded as the national guideline for general practitioners, advises that seropositive patients are referred to a specialist.[3] Because of a lack of current data for the Dutch situation we conducted a study on the referral of patients testing positive for HCV in primary care. This study was performed for patients testing anti-HCV positive in the years 2003-2006 by a servicing laboratory, the SHL, a Regional Centre for Diagnostic Support for Primary Care (Etten-Leur, the Netherlands). The SHL serves general practitioners and several institutions including centres for the care and treatment of drug addicts in the province of North Brabant. For each patient who tested positive a questionnaire was sent to the physician who requested the test and had agreed to participate. A positive HCV serology was found in 358 of a total of 14,774 samples tested (2.4%). A total of 81 (26.4% of the total anti-HCV positive patients) questionnaires were returned. Fifty-six questionnaires could be evaluated (*figure 1*). The majority of patients were male (69.9%) and the mean age was 46.4 ± 9.5 (SD) years. The majority of patients originated from the Netherlands (n=47), while nine originated from six other countries. The main reason for requesting the test was intravenous drug use in the past or present (51.8%). Possible HCV symptoms (general malaise, fatigue, reduced appetite and fever) in 10.7% and elevated liver enzymes (5.4%) were also reasons for requesting an anti-HCV test. Sexual history was the reason for testing in five cases (8.9%) and a prior blood product transfusion was the reason for performing serology in only one case. For 11 of the patients (19.6%) there were multiple reasons to test, often the combination of sexual history and drug use. The most probable source of transmission of HCV was intravenous drug use in most of the cases (62.5%). Although only risky sexual behaviour in men who have sex with men and are HIV infected may form a possible risk for transmission of HCV, the patient's sexual history was reported as the probable route of transmission for six patients (10.7%), three of whom were men having sex with men.[4] Two patients originated from an area where HCV is endemic. One patient was probably infected by a blood transfusion and another one by treatment for haemophilia, both prior to 1992. For several other patients the route of infection was unknown (n=6) or multiple transmission routes were possible (n=5). Only half of the patients (28/56) were referred to secondary care. Most patients were referred to a gastroenterologist (61.0%), a minority to an internist (32.0%) and a few patients to a

Figure 1. *Flowchart of anti-hepatitis C virus (HCV) tests and patients in the study*



A total of 307 HCV seropositive patients remained from the 358 anti-HCV positive samples, as several patients were tested more than once (51 duplicated samples).

specialist in infectious diseases. For almost half of the patients who were not referred (48.1%), the reason for not referring is unclear (*table 1*). A considerable number of patients were not referred to a specialist because treatment was not necessary according to the primary care physician (6/27), mainly because the liver enzymes in these patients were not or only slightly elevated (4/6). However, these patients may nevertheless have had significant chronic liver damage and should therefore have been referred.[5]

Table 1. *Reason why patients (27) were not referred to a medical specialist (data for one of the 28 patients are missing)*

Reason for patients not being referred	Patients (n)
Physician considered referral unnecessary	6 (22.2%)
Patient refusal	3 (11.1%)
Lost to follow-up before referral possible	3 (11.1%)
HCV-PCR negative	1 (3.7%)
Physician unaware of diagnosis	1 (3.7%)
Other, no specific reason supplied	13 (48.1%)

Three patients did not want to be referred. An HCV-PCR was performed for one patient, which indicated a resolved hepatitis. Half of the patients referred to a specialist were treated (14/28). In the Netherlands a retrospective study was performed before the introduction of effective treatment and largely before the publication of the Practice Guideline. This study was conducted to investigate the referral of patients who tested positive for HCV by a servicing laboratory for primary care in 1998-2000.[6] Of the 73 positive patients tested for primary care, 28 (38%) were tested for general practitioners, the others for the Community Health Service, care and treatment centres for drug addicts or prisons. Of the 59 patients for whom it was known whether they had been referred or not, only 23 (39%) had been referred to a specialist for medical assessment. Of the 49 patients for whom the complete follow-up was known, only 6% (n=3) had been treated. For 21 of the 46 untreated patients, the general practitioner was of the belief that treatment was not necessary, while for 11 patients the specialist was of the same opinion. Five patients were not treated because of their physical condition and nine patients refused treatment. One might expect the referral rate to have increased after the publication of the Practice Guideline for general practitioners and the introduction of more effective treatment. In our study with patients who were diagnosed as HCV positive after the Practice Guideline had been issued, the referral rate was still only 50%. Although this may indicate an increase in the referral rate, nevertheless, not all HCV-positive patients in primary care are referred to a specialist as advised in the Practice Guideline. If we assume that participating physicians were not more or less inclined to refer their patients, this study gives a clear indication of current referral practice with respect to seropositive HCV patients in Dutch primary care. However, if we suppose that physicians who refused to participate in this study are less likely to refer their patients, the percentage of patients who were referred will be even smaller than the results presented in this study. The possibility and necessity to treat should be evaluated by a specialist with experience in the management of HCV. Even if treatment is not initiated, the follow-up of patients with chronic HCV infection should be carried out by an expert in this field. This means that every patient with positive HCV serology should be referred to a specialist. The finding that 50% (14/28) of the patients who had been referred were treated illustrates the importance of referral. This study indicates that the advice in the Practice Guideline is still not being completely followed and more attention has to be given to making it more widely known to improve the referral practice of anti-HCV positive patients by primary care physicians, such as general practitioners.

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NOTE

This study was funded by Roche Nederland BV, Woerden, the Netherlands.

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LETTER TO THE EDITOR

Rationale and design of the virological response and ribavirin dosage (VIRID) study in hepatitis C

The introduction of peginterferon and ribavirin (an oral nucleoside analogue) for chronic hepatitis C has led to the concept that hepatitis C virus (HCV) infection is a curable disease. Not all HCV patients respond to therapy, and especially genotype 1 and 4 patients with a high baseline viral load fare poorly. Given the low sustained virological response (SVR) rates in genotype 1 patients (currently approximately 50%), improvement of treatment efficacy is a major challenge.

The exact mechanism of ribavirin in HCV is not well understood. There appears to be no direct inhibition of HCV replication, but there is rapid and lethal mutation of virions. In addition, there is depletion of intracellular guanosine triphosphate, necessary for viral RNA synthesis.[1] Several studies indicated that optimal ribavirin dosage is essential in achieving SVR.[2] A recent trial showed significantly higher SVR in patients receiving 15.2 mg/kg/day ribavirin compared with 13.3 mg/kg/day ribavirin, both in combination with peginterferon alpha-2b.[3] A small pilot study, in which 10 genotype 1 patients were treated with ribavirin dosages up to 3600 mg/day plus peginterferon alpha-2a, led to 90% SVR.[4] These data provide the rationale of a Dutch nation-wide investigator-initiated study in HCV: the VIRID study.

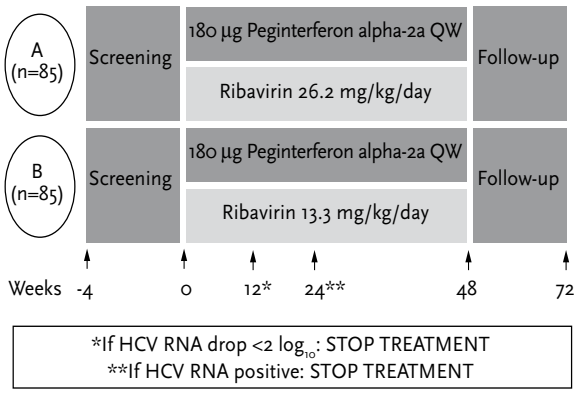
We propose a randomised controlled clinical trial that aims to compare the current standard therapy with a regimen that includes double dosage of ribavirin (*figure 1*).

Patients will be randomised to receive either 25-29 (mean 26.2) mg/kg/day ribavirin (Copegus, Roche) or 12-15 (mean 13.3) mg/kg/day. Both groups will receive once weekly 180 µg peginterferon alpha-2a (Pegasys, Roche). Treatment duration is 48 weeks, with a follow-up of 24 weeks. Ribavirin is associated with a dose-dependent anaemia and management of this side effect is important.[5] We will treat all patients, regardless of ribavirin dosage, with epoetin beta (NeoRecormon, 30,000 IU/ml/week, Roche) once Hb drops below 6.8 mmol/l. Patients with <2 $\log_{10}$ drop of HCV RNA at week 12 or HCV RNA positivity at week 24 will discontinue treatment. We made the following assumptions: high-dose ribavirin yields 67.5% SVR, based on cautious estimation of 20-25% improvement compared to standard treatment. With a two-sided 5% significance test, a power of 80% and an estimated dropout rate of 10%, this study requires 85 patients in each arm.

We ask Dutch physicians who see and treat HCV patients to participate in this trial. Patients will be treated by their own physician in their own centre. This nation-wide HCV project will include 20-30 academic and non-academic participating centres. Recruitment will start in March 2008 and will continue until March 2009. The main inclusion criteria include: serological evidence of chronic hepatitis C genotype 1 or 4, treatment naive, high viral load (≥400,000 IU/ml) and a liver biopsy within three years of screening. The main exclusion criteria include: signs of decompensated liver disease, HBV or HIV co-infection, evidence of hepatocellular carcinoma, significant cardiovascular, pulmonary or renal dysfunction, severe psychiatric disorder, pregnancy or breastfeeding.

Since there is a clear need for optimising the current anti-HCV therapy, different strategies have been proposed: induction dosing of peginterferon, prolonging therapy duration, increased weight-based ribavirin dosing and novel antiviral agents. Induction dosing of peginterferon did not lead to a major improvement of treatment outcome and data on prolongation of treatment duration are conflicting.

Figure 1. *Study design*



The new agents (e.g.: protease inhibitors and polymerase inhibitors) seem promising but will not be available for the coming years, development of antiviral resistance may temper initial expectations, and the tandem peginterferon/ribavirin will remain the template for therapy.

These considerations have led to development of the VIRID study. This study is unique in that it is investigator-initiated, and enjoys support of the Dutch Society of Hepatology. The VIRID study will be the first large study to definitely determine the role of high-dose weight-based ribavirin for treatment naive genotype 1 and 4 patients. Additional information can be found at: www.virid.nl.

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MONTHLY NJM ONLINE HITLIST

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Article	Hits
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REVIEWS	
Familial Mediterranean fever: clinical, molecular and management advancements	154
Water in health and disease: new aspects of disturbances in water metabolism	156
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Experience with alemtuzumab in treatment of chronic lymphocytic leukaemia in the Netherlands	99
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For all articles published in June 2007	103
Total	**1753**

INFORMATION FOR AUTHORS

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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.

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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.

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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.

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Keywords: Include three to five keywords.

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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.

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

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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.

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For all articles published in June 2007	103
Total	**1753**

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PHOTO QUIZ

A patient with abdominal pain and a rash

H.W.M. van Laarhoven[1*], W.A. Blokx[2], M.M.B Seyger[3], P.P. Koopmans[1]

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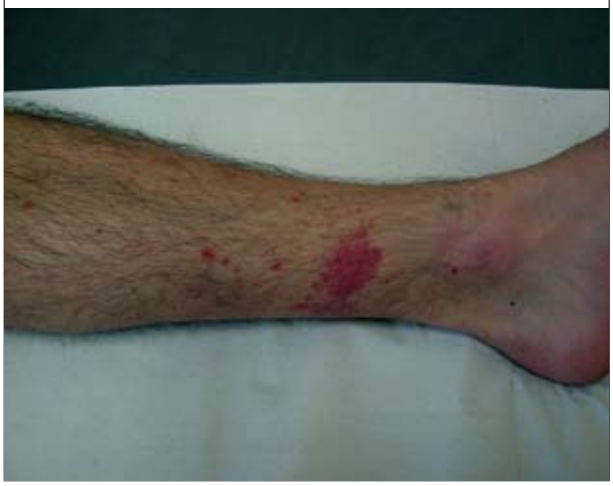
CASE REPORT

A 24-year-old male presented to the emergency room because of fever, abdominal pain nausea and vomiting. He complained of having had painful wrists, elbows, knees and shoulders for the past two days. His left ankle was swollen and red. Eight days before presentation he had noticed red, non-painful spots on both legs which increased in size during the course of the week. Six weeks before presentation he had suffered from a sore throat with fever. He was not taking any medication and had no relevant medical history.

On examination he was afebrile (temperature 37.8°C) and not in distress, blood pressure 156/94 mm Hg, pulse rate 64 beats/min. His left tonsil was enlarged. Purpuric macules were observed on both legs. (*figure 1*). Further general physical examination revealed no abnormalities. C-reactive protein was 67 mg/l, liver and kidney function were normal. Urine analysis showed 1 to 5 erythrocytes and protein 0.26 g/l. The chest X-ray was normal.

Figure 1. *Rash on the left leg, consisting of purpuric macules*



WHAT IS YOUR DIAGNOSIS?

See page 48 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (ON PAGE 47)

A PATIENT WITH ABDOMINAL PAIN AND A RASH

DIAGNOSIS

The patient presented with the clinical picture of Henoch-Schönlein purpura (HSP), namely purpura, joint pain, abdominal symptoms and kidney disease. A skin biopsy of the purpura showed a histological picture consistent with leucocytoclastic vasculitis and vascular IgA deposits on direct immunofluorescence study, supporting the diagnosis of HSP.[1,2]

HSP is much more common in children than in adults (estimated incidence 22.1 *vs* 1.3 per 100,000 population, respectively).[3] However, it is crucial to recognise that HSP does occur in adults, as shown in our case, because complications may be severe. After the acute phase, when gastrointestinal haemorrhage can occur due to gastrointestinal vasculitis, end-stage renal failure develops in 0 to 49% of the adult patients.[3] In children the risk of developing end-stage renal failure ranges from 5 to 15%. Risk factors for adults with HSP for developing end-stage renal failure include proteinuria ≥1 g/24h during follow-up, hypertension at presentation and during follow-up, renal impairment at presentation, age <30 years and male sex.[3]

In contrast with the Chapel Hill Consensus Conference criteria for HSP,[1] the American College of Rheumatology (ACR) does not require a biopsy of the skin or kidney with the presence of IgA immune deposits for the diagnosis of HSP.[2] However, when based on clinical signs only, the diagnosis of HSP may be missed and patients may be inappropriately discharged from follow-up.[4] Conversely, in IgG or IgM associated leucocytoclastic vasculitis complications are less frequent[5] and without biopsy patients may be overdiagnosed as HSP and submitted to unnecessary follow-up.

In conclusion, although HSP is usually a paediatric disease, it can occur in adults. It is essential to make the correct diagnosis based on the clinical signs and symptoms as well as immune fluorescent staining of a skin or kidney biopsy to ensure adequate follow-up.

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