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Department of Internal Medicine
's-Gravendijkwal 230
3015 CE Rotterdam
The Netherlands
Tel.: +31 (0)10-703 59 54
Fax: +31 (0)10-703 32 68
E-mail: p.l.a.vandaele@erasmusmc.nl
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EDITORIAL

What is the optimal treatment for benign multinodular goitre?

E.T. Massolt*, R.P. Peeters

Department of Internal Medicine, Rotterdam Thyroid Center, Erasmus Medical Center, Rotterdam, the Netherlands, *corresponding author: tel: +31(0)10-7044986, email: e.massolt@erasmusmc.nl

In this issue of the journal Attaallah *et al.* describe a retrospective study on the rate of progression and the reoperation rate after hemithyroidectomy for benign multinodular nodular goitre (BMNG).[1] After a relatively short follow-up time (mean of 31 months), progression of the nodular goitre was already observed in the remnant lobe in 32% of the patients. Due to this short period of follow-up, only 2% of the patients in this study underwent a contralateral hemithyroidectomy due to this progression. More than one fifth of the patients (22%) required levothyroxine-replacement therapy after hemithyroidectomy.

BMNG is one of the most common thyroid disorders. The appropriate treatment is often a matter of debate, with different preferences in different countries.[2,3] Surgery is the recommended treatment of choice when facing a large goitre or when malignancy cannot be ruled out. In other cases, ^{131}I therapy is a good alternative for the treatment of symptomatic non-toxic BMNG, since it results in a mean thyroid volume reduction of ~40% one year after treatment along with a very high degree of patient satisfaction and few side effects.[2,4] However, the goitre volume reduction is inversely correlated to the initial goitre size.[5] Another drawback of ^{131}I therapy when treating large goitres is the need for relatively high ^{131}I activities, requiring expensive and inconvenient inpatient treatment. For toxic BMNG, a cure rate (euthyroidism) of 52% within three months after one ^{131}I treatment can be expected with an overall cure rate of 92% with one or two treatments.[6] In addition, a reduction of the median thyroid volume by 43% is reported and only a minority of patients (14%) develop hypothyroidism within five years of treatment.[6] In the current study by Attaallah *et al.*, 23% of the patients were hyperthyroid.[1] It is not clear why ^{131}I treatment was not considered in these patients. When surgery is chosen as definitive management, current guidelines and evidence-based reviews recommend total thyroidectomy for bilateral BMNG and toxic BMNG.[7,8] Arguments for total thyroidectomy are high recurrence rates after subtotal thyroidectomy requiring re-intervention of > 10% during long-term follow-up as well as evidence that permanent complication rates of hypoparathyroidism and vocal palsy associated with subtotal and total thyroidectomy are not different while re-intervention increases the risk of these complications.[7-9] Furthermore, 3.5% of BMNG patients initially treated with subtotal thyroidectomy have to undergo re-operation for completion thyroidectomy because of incidental thyroid cancers.[7]

However, some authors state that unilateral thyroidectomy can be considered for unilateral BMNG, as evidenced by a 2% recurrence rate (requiring re-intervention) and maintenance of euthyroidism in 73% of patients.[10,11] The current study by Attaallah *et al.*, in which the majority of patients (75%) had no nodules in the contralateral lobe preoperatively, shows very similar results.[1] However, it is very well possible that the re-intervention rate in the patients of this study will increase with a longer follow-up time.

Once the diagnosis and indication for treatment of BMNG has been made, the treating physician and patient should discuss each of the treatment options, including the logistics, benefits, expected speed of recovery, drawbacks, side effects, costs and then decide on the best treatment modality for that particular patient, taking into account the patient's age and comorbidities.

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REVIEW

Late-onset inflammatory bowel disease in the very elderly

I.C. van Walree[1]*, S.A.C. van Tuyl[2], M.E. Hamaker[3]

Departments of [1]Internal Medicine, [2]Gastroenterology, [3]Geriatric Medicine, Diakonessenhuis Utrecht, Utrecht, the Netherlands, *corresponding author: tel.: +31(0)50-234421, fax: +31(0)88-2509118, email: inezvanwalree@gmail.com

ABSTRACT

Elderly-onset inflammatory bowel disease (IBD) will be seen more frequently with the ageing of the population and the increasing incidence of IBD. However, knowledge regarding the best approach to IBD in this population is scarce. Furthermore, differential diagnosis in elderly patients with diarrhoea, rectal blood loss or a changed defecation pattern is comprehensive and IBD is not always considered. In this case series, we present three elderly patients with late-onset IBD, demonstrating the difficulties in diagnosing and treating IBD in this patient population; in addition an overview of IBD in the elderly is provided.

KEYWORDS

Ulcerative colitis, Crohn's disease, elderly, inflammatory bowel disease

INTRODUCTION

The incidence of inflammatory bowel disease (IBD) is increasing and with the ageing of the population, elderly-onset IBD will be seen more frequently.[1] Approximately 15% of IBD cases manifest in individuals over 65 years of age,[1] with a similar distribution between Crohn's disease and ulcerative colitis. IBD in elderly patients accounts for roughly 25% of all IBD-related hospitalisations.[2] Recognition of elderly-onset IBD remains poor as the differential diagnosis in older patients with a changed defecation pattern or rectal blood loss is extensive and IBD is not the most obvious cause. Furthermore, most evidence regarding IBD's presentation, treatment and prognosis is obtained from studies excluding elderly patients or those with comorbidity. With the ageing of the population and the subsequent increasing burden of IBD in the elderly, more knowledge about this population is necessary to assure recognition, prevent treatment delays or inappropriate surgical procedures and optimise medical treatment. In this case series, three very elderly patients (> 80 years) are presented who demonstrate the difficulties in diagnosing and treating IBD in this patient population; in addition an overview of IBD in the elderly is provided.

Patient A, an 84-year-old female, was hospitalised due to weight loss and diarrhoea five times a day. The diarrhoea had been present for many years and had thus far been attributed to the use of levothyroxine. Although the diarrhoea restricted her social life, no further analysis had been performed by the general practitioner. In recent months, the frequency of the diarrhoea had increased, resulting in hospitalisation. On admission, physical examination revealed multiple perianal fistulae. Colonoscopy identified superficial inflammation of the sigmoid mucosa (*figure 1*) as well as several fistulae and superficial ulceration in the rectum. Tissue biopsies revealed an inflammatory infiltrate with granulocytes and impairment of the crypt epithelium, focal ulceration of the colon mucosa and non-specific chronic active inflammation. Spirochetes and Ziehl-Neelsen staining and Elispot were negative as was the tuberculin skin test. Magnetic resonance imaging (MRI) confirmed the ulceration of the rectum extending into the internal anal sphincter as well as a suprasphincteric fistula and an intersphincteric fistula. Both macroscopic and microscopic findings were compatible with Crohn's disease. Because she was not experiencing any pain, surgical treatment was not indicated. Treatment with metronidazole, ciprofloxacin and prednisolone was started as well as azathioprine therapy. At discharge, the prednisolone was tapered by 5 mg per week. However, due to persistent production of the fistulae and perianal pain, treatment with infliximab was started during follow-up. After three infusions, the

symptoms resolved and the prednisolone was stopped. Maintenance therapy with azathioprine and infliximab was continued and her diarrhoea resolved.

Patient B, an 87-year-old female, visited the geriatric clinical centre because of constipation. For over a year, she had had slow bowel movements without any further symptoms. Treatment with psyllium was successful, however when stopping the medication her symptoms returned. As physical examination and biochemical testing did not reveal any abnormalities, she was given further advice regarding the constipation and treatment with psyllium was restarted. One year later, she developed diarrhoea up to five times a day with faecal incontinence and infrequent rectal bleeding. She had lost 10 kg in the course of a few months. Infectious colitis was ruled out with negative stool culture. Laboratory testing revealed an elevated erythrocyte sedimentation rate (> 95 mm/hour) and a computed tomography of the abdomen displayed increased signal intensity of the sigmoid compatible with colitis. Sigmoidoscopy was performed and revealed profound erythema, oedema, longitudinal ulcerations and aphthous lesions in the sigmoid and rectum while the distal rectum did not show any abnormalities (*figure 2*). Histopathology revealed alternating active inflammation and normal mucosa and many granulocytes in the lamina propria. Microscopic findings were non-specific, but considering the clinical presentation and endoscopic findings, therapy for IBD was initiated. Infection with *Mycobacterium tuberculosis* was excluded. As treatment with budesonide achieved an insufficient effect, prednisone was started at 30 mg daily in a tapering schedule together with psyllium. Initially, remission was induced successfully; however, her symptoms returned at a dose of prednisone 5 mg daily. Therefore, budesonide and azathioprine were started which achieved a good response.

Patient C, an 84-year-old female, was admitted to the hospital with progressively painful abdominal cramps during the last years. Her medical history included diabetes mellitus type II and in 2011 ulcerative proctitis with complaints of rectal bleeding and difficulty with defecation. For two years she was successfully treated with 5-aminosalicylate (5-ASA) enemas. At current admission, this treatment was no longer sufficient. Her defecation pattern had changed again, alternating between constipation and diarrhoea with occasionally red blood loss per anum. She complained about uncontrollable flatulence and sometimes faecal incontinence. In six months, she had lost 5 kg in weight. Colonoscopy and biopsy findings were suggestive of severe Crohn's disease extending from the terminal ileum to the rectum. Treatment with dexamethasone intravenously was started, which was complicated by moderate hyperglycaemia. Her abdominal symptoms improved significantly and therapy was switched to oral prednisolone 30 mg tablets in a tapering schedule. Infection with *M. tuberculosis* was excluded. Subsequently, she was treated with azathioprine as maintenance therapy, which achieved a good clinical response.

BACKGROUND AND SYMPTOMS

The present case series describes three very elderly patients (> 80 years) with late-onset IBD. We were specifically interested in late-onset IBD in the very elderly, not to be confused with long-standing IBD in elderly patients. However, except for a few case reports, literature regarding this very old population is scarce. Therefore, we considered best available evidence, studies including IBD patients with onset of disease after the age of 60 years.

Figure 1 a+b. *Colonoscopy showing superficial inflammation of the sigmoid mucosa and superficial ulceration in the rectum*

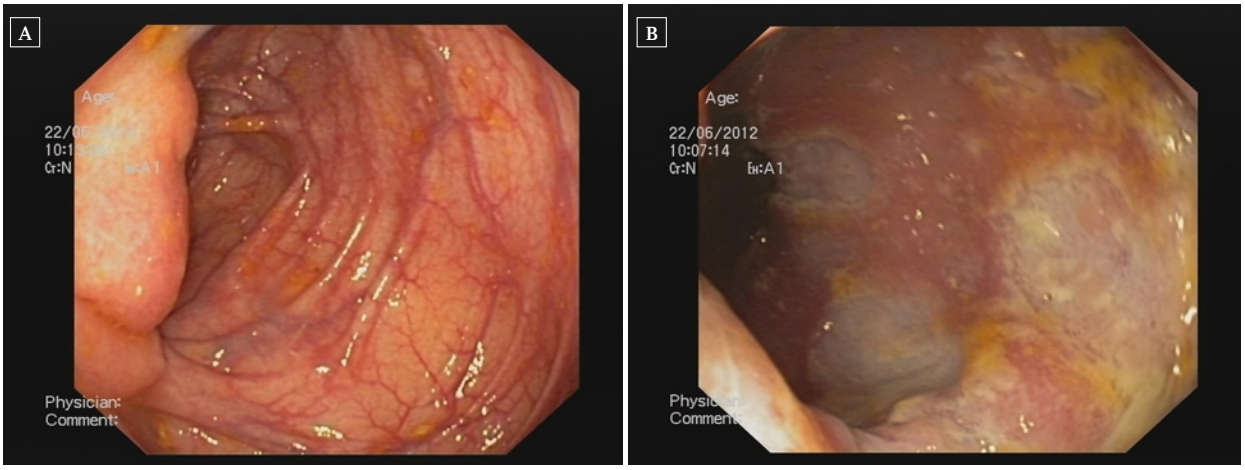
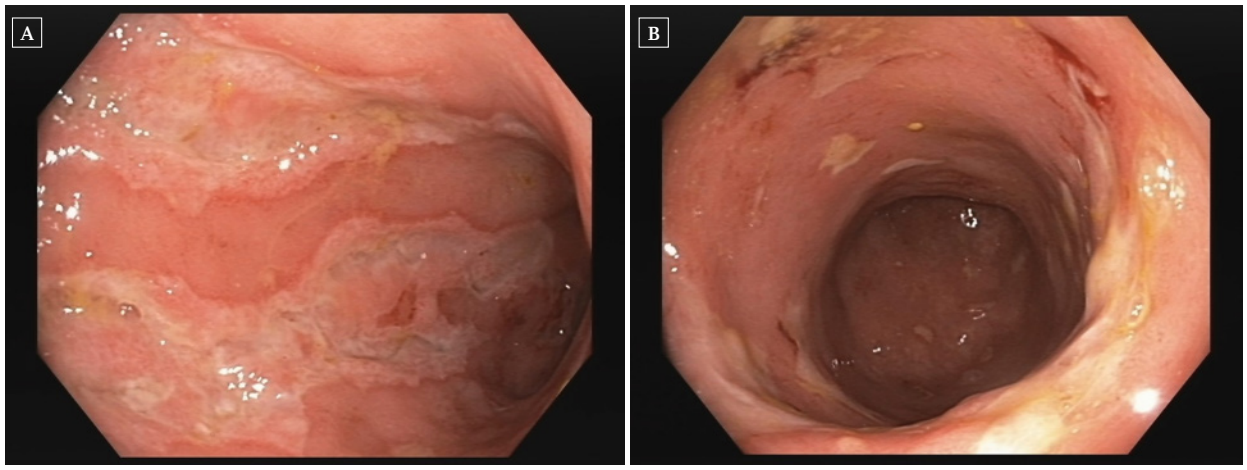


Figure 2 a+b. *Sigmoidoscopy revealed profound erythema, oedema, longitudinal ulcerations and aphthous lesions in the sigmoid and rectum*



Crohn's disease and ulcerative colitis are inflammatory bowel diseases, characterised by progressive, chronic inflammation of the gastrointestinal tract. Their aetiology remains to be unravelled. However, genetic, immunological and environmental factors all appear to influence the development of IBD.[3-6] IBD may occur at any age but a bimodal course has been reported. Although there is a preference for adolescents, approximately 10-30% of all new IBD patients are over 60 years of age. Of these 65% are in their 60s, 25% in their 70s and only 10% in their 80s.[7,8] The estimated incidence of IBD in patients over 60 years in Europe is 8-10/100,000.[9-11] Crohn's disease and ulcerative colitis are separate entities but distinction can be difficult. In ulcerative colitis, inflammation is limited to the colon and generally has a diffuse and superficial character. Crohn's disease, on the other hand, is characterised by a discontinuous transmural inflammation and may involve the entire digestive tract including the mouth and perianal area. In younger patients, the distal ileum and colon are frequently involved. However, in older patients, the primary location of Crohn's disease is the colon, making the distinction from ulcerative colitis less obvious.[12]

Clinical presentation in the elderly can be non-specific. Elderly patients may have had symptoms for many years – as demonstrated by patient A – before the diagnosis is established.[13] The average time to establish the diagnosis is six years in the elderly compared with two years in younger patients.[13] Hallmarks of Crohn's disease are prolonged diarrhoea with crampy abdominal pain without gross bleeding and systemic symptoms as weight loss, fatigue and fever. In ulcerative colitis, patients often present with bloody diarrhoea and frequent bowel movements. Elderly patients with IBD appear to have a less complicated and milder disease course compared with younger patients,[14] but will more often experience weight loss, anaemia and abdominal pain.[13,15] The disease course is different from young-onset IBD patients as disease extension rarely occurs in the elderly.[16] However, in patient C disease extension was seen. In elderly patients, constipation can also be the presenting symptom of IBD.[17] Although patient B had suffered from constipation for a year prior to IBD diagnosis, she did not experience any other symptoms at that time, making it less likely that the constipation was related to the Crohn's disease.

Differential diagnostic considerations

As the clinical presentation can be rather non-specific, particularly in the elderly, there is a long list of potential differential diagnoses. Other more prevalent disorders will often be considered initially, resulting in misdiagnosis and delays in initiating the appropriate treatment.[18]

In every elderly patient presenting with new abdominal symptoms, the differential diagnosis should include colorectal malignancy. Furthermore, colonic diverticulitis and segmental colitis associated with diverticular disease are causes of an altered defecation pattern or rectal blood loss in the elderly and may be easily confused with IBD. A relatively common cause of diarrhoea in the elderly is microscopic colitis, but it is rarely confused with IBD because of the lack of visible mucosal inflammation. Many drugs can also elicit abdominal symptoms or result in complications inducing those complaints, such as colonic ulcers induced by antibiotics and ulcers and strictures caused by non-steroidal anti-inflammatory drugs. In the initial phases of disease, IBD may also be confused with infectious diarrhoea. In patients with a history of radiation to the abdomen, one must be aware of the possibility of radiation enteropathy. Another differential diagnostic consideration not to be missed is ischaemic colitis. These patients often present

with acute abdominal pain and subsequently bloody stools. In patients with generalised peripheral arterial occlusive disease or mesenteric arterial thrombosis or embolism, inadequate blood flow causes segmental inflammation and injury of the colonic mucosa and in case of more profound ischaemia also transmural colonic damage. There is considerable overlap in the signs and symptoms of ischaemic colitis and Crohn's disease. Both often present with rectal preservation and a segmental distribution of disease, contrary to ulcerative colitis. Distinction is based on the combination of clinical, endoscopic and histological findings. Furthermore in ischaemic colitis repeat colonoscopy may show rapid resolution of lesions.

Unfortunately, we did not repeat the colonoscopy after starting therapy to confirm the clinical response, which ideally should have been performed. In patient B, histological findings were non-specific and it could be discussed whether the diagnosis IBD is definitive. However, clinically she showed a good response to therapy. As endoscopy can be a strenuous investigation in elderly patients, it cannot always be repeated.

Because of the extended differential diagnosis of abdominal symptoms in the elderly, imaging studies and colonoscopy should be readily performed. If endoscopy and histology reveal findings compatible with inflammation and ulceration, IBD must be considered, even in patients over 80 years of age, as our cases illustrate.

Therapy

The choice of treatment will depend on multiple factors, including the severity, location and extension of disease, disease behaviour, extra-intestinal manifestations, comorbidity, use of other medications and patient compliance. Irrespective of treatment choice, maintaining adequate nutritional status is important. Malnutrition is relatively common in the older population, which can also affect treatment tolerance and increases the risk of infections. Furthermore, elderly-onset IBD has a less aggressive disease course,[14] and this has to be taken into account when making therapeutic decisions. On the other hand, over half of patients aged 65 years or more have at least three comorbidities and a recent study illustrated that elderly patients with Crohn's disease take a mean of 6.6 types of concurrent medication,[19] increasing the risk of drug interactions and adverse events.

5-aminosalicylates

First choice for treatment of mild to moderate ulcerative colitis is topical or oral 5-ASA. The use of 5-ASA in Crohn's disease is controversial due to inconsistent results regarding its efficacy.[20] Efficacy seems to be comparable in both young and elderly patients.[21] There are conflicting results regarding the renal impact of 5-ASA. Cases of 5-ASA nephrotoxicity and interstitial nephritis have been rarely reported,[22] but most did not demonstrate a relationship with the 5-ASA dose or duration of usage.[23,24] Evidence regarding the use of 5-ASA in elderly patients with impaired renal function is lacking. It is recommended to exercise caution in patients with known renal dysfunction and to evaluate renal function prior to initiation of 5-ASA and periodically thereafter.

Corticosteroids

Patients with mild to moderate ileal or ileocaecal disease, severe ulcerative colitis or those not responding to 5-ASA can be treated with oral corticosteroids. Induction therapy with budesonide is usually recommended for mild to moderate ileal or ileocaecal disease, as this causes less systemic side effects than other glucocorticoids. In patients who do not respond to oral therapy, temporary intravenous administration of corticosteroids may be necessary. Corticosteroids should not to be used as maintenance therapy because of decreasing efficacy in long-term use and side effects such as osteoporosis, risk for serious infections,[25] hyperglycaemia, cataract and neuropsychiatric disorders.[26] When starting glucocorticoids, appropriate osteoporosis prophylaxis according to guidelines should be started.

Immunomodulators and biological therapy

In patients who do not respond to oral glucocorticoids, the addition of immunomodulatory drugs (azathioprine and 6-mercaptopurine, 6-MP) or monoclonal anti-TNF antibodies can be considered. No differences in efficacy, metabolism and toxicity of immunomodulators have been found between older and younger patients.[27,28] They are generally well tolerated with a relatively low incidence of adverse effects. Adverse events include idiosyncratic reactions (fever, rash, pancreatitis and hepatitis) and bone marrow suppression.[29] Hence it is important to check the complete blood count and liver chemistry regularly. Possible drug interactions should be checked before starting therapy.

Biologicals are infrequently used in elderly IBD patients because of a lack of data regarding their use in this population. However, some data are available on the use of biologicals in patients with rheumatoid arthritis. Results regarding the occurrence of adverse events in the elderly are conflicting, with some suggesting a higher risk of serious adverse events such as infections while others did not.[30-32] We believe biologicals should be considered in elderly patients when other therapeutic strategies fail and contraindications for their use – such as congestive heart failure, significant hepatic disease and concomitant infections – have been excluded. In patient A, glucocorticoids and azathioprine therapy achieved insufficient results and then infliximab was started successfully.

Almost all agents used for IBD (corticosteroids, immunomodulators and biologicals) will compromise the patient's immune response to infectious agents. The odds for opportunistic infections is increased threefold (OR 2.9; 95% CI 1.5-5.3) when corticosteroids, azathioprine, 6-mercaptopurine or infliximab are used as monotherapy.[31] However, the risk of infection increases considerably when two or more drugs are used concomitantly (OR 14.5; 95% CI 4.9-43).[31] As elderly patients have a higher incidence of latent tuberculosis infection and higher mortality rates due to reactivation of *M. tuberculosis* when immunosuppressive treatment is started,[33] it is of particular importance to exclude latent tuberculosis infection prior to starting treatment. Furthermore, intestinal tuberculosis may mimic IBD's findings at colonoscopy and therefore should be excluded.

Surgery

When medical options do not achieve the desired results or in case of toxic megacolon, obstruction, fistula formation or incessant bleeding, surgery may be necessary. Recent reports suggest that indications for surgery in the elderly with ulcerative colitis should not differ from indications for surgery in younger patients.[34] However, the need for urgent surgery in the elderly was also a predictor of poor survival.[35] Furthermore, despite a significant decrease in the frequency of surgery-associated adverse outcomes in the elderly with ulcerative colitis, adverse events still occur in 27% of patients.[36] In addition to increased rates of postoperative complications, an increased length of hospital stay and increased operating room time have also been reported in the elderly with IBD.[37] Factors associated with poor outcome included male gender, low albumin levels and advanced age.[36]

With regards to Crohn's disease, elderly patients – who more often have colonic disease – undergo fewer surgical procedures compared with younger patients.[38] Surgery for complications of Crohn's disease in the elderly are technically not different.

After colectomy, restorative coloproctectomy with ileal J-pouch anal anastomosis (IPAA) can be successful provided the patient retains good anal sphincter function, has no history of faecal incontinence preoperatively and is autonomous. In the very old, one should carefully assess all these items when considering IPAA because problems are supposed to be more likely to develop in this age group. Recent studies in patients with IPAA showed no differences concerning complication rate and quality of life and function in the elderly compared with the younger population.[39,40] Patient satisfaction is high after IPAA: over 89% of patients older than 65 years report that they would undergo the same surgery again and more than 93% would recommend it to others.[41] It is not known if these data also pertain to the oldest old or can be extrapolated to older patients with comorbidities.

If IPAA is not possible, a protocolectomy or subtotal colectomy and end ileostomy can be performed.[42,43] Ileorectal anastomosis, mostly abandoned in young ulcerative colitis patients, still has indications in the elderly with lower life expectancy when functional outcome is most important.[44] Although ostomies are not uncommon and generally well-tolerated in the elderly, it is important to note these patients are more likely to suffer from dehydration due to stoma output when compared with younger patients.[39]

In conclusion, diarrhoea, abdominal symptoms and an altered defecation pattern in the elderly may have many causes. Elderly-onset IBD does not occur frequently and clinical features are non-specific, thus establishing the correct diagnosis is a challenge. However, not considering this diagnosis leads to delays in initiating the appropriate treatment, as well as potential preventable complications and persisting morbidity. Colonoscopy should be readily performed in the elderly in order to differentiate within the broad list of potential disorders compatible with abdominal symptoms. If endoscopy and histology reveal findings compatible with inflammation and ulceration, IBD must be considered, even in the very old. Although the choice of medical therapy is not essentially different from younger patients with IBD, elderly patients should be carefully monitored when medical therapy is started in order to avoid serious complications.

DISCLOSURES

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REVIEW

Susac syndrome: a report of four cases and a review of the literature

S.M. van der Kooij[1]*, M.A. van Buchem[2], O.M. Overbeek[3], G. Dijkman[4], T.W.J. Huizinga[5]

[1]Department of Rheumatology, Haga Hospital, The Hague, the Netherlands, Departments of [2]Radiology, [3]Neurology, [4]Ophthalmology, [5]Rheumatology, Leiden University Medical Centre, Leiden, the Netherlands, *corresponding author: email: s.m.vanderkooij@hagaziekenhuis.nl

ABSTRACT

In Susac syndrome, occlusions of pre-capillary arterioles of the brain, retina, and cochlea lead to the classical clinical triad of subacute encephalopathy, visual disturbances due to branch retinal artery occlusions and sensorineural hearing impairment. Its pathogenesis is still obscure, but it is presumed to be mediated by an autoimmune response to an as yet unknown antigen. The syndrome is considered a rare but important differential diagnosis in various neurological, psychiatric, ophthalmological, and ear-nose-throat disorders. Brain magnetic resonance imaging, retinal fluorescein angiography, and audiometry findings enable diagnosis. Early therapy may reduce relapses and improve recovery.

The features of four cases of this syndrome are presented, illustrating that cooperation among different medical specialists is essential, and that treatment may be best guided by an immunologist or rheumatologist as a case manager.

KEYWORDS

Susac syndrome, early treatment, resolution of MRI lesions, multidisciplinary cooperation, branch retinal artery occlusion, subacute encephalopathy

INTRODUCTION

Susac syndrome is a rare disease, named after John Susac (1940-2012) who in 1979 described two female patients with the classical triad of subacute encephalopathy, branch retinal artery occlusion (BRAO), and sensorineural hearing impairment.[1] To date, around 300 cases have been reported in the medical literature worldwide.[2] The course of the disease can be variable, from an initial good response to treatment with full recovery, to refractory cases with persistent, severe encephalopathy, visual and/or hearing loss with major implications on quality of life.

Importantly, patients often do not present with the typical triad, but may exhibit isolated encephalopathy, unexplained visual disturbance or hearing loss, delaying the diagnosis or resulting in misdiagnosis.[3-5] Rapid diagnosis is, however, essential to ensure early immunosuppressive therapy. Cerebral magnetic resonance imaging (MRI) and retinal fluorescein angiography play an important role in confirming the diagnosis.

Recently, all reported cases were reviewed and it was reported that resolution of abnormalities as demonstrated by T2 MRI is rare.[2] We now report four consecutive cases; in three patients treatment was initiated relatively rapidly with a favourable clinical outcome, with clearance of T2 MRI lesions, suggesting that early treatment is associated with resolution of abnormalities.

In addition, in diseases such as Susac syndrome it is often unclear which doctor is responsible for disease monitoring and gathering all the information to take treatment decisions. We suggest that the different specialists involved cooperate, and that treatment decisions are guided by a rheumatologist or immunologist.

CASE REPORTS

Case 1

A 38-year-old woman presented in October 2009 with intermittent paresthesias and numbness of her left hand and left cheek, diminished memory and reduction of vigilance. Physical examination was normal except for mild memory deficits. Routine laboratory studies were normal. Cerebrospinal fluid analysis showed 13/3 cells/ul, protein 1.71 g/l, without oligoclonal bands. Cerebral MRI showed

multiple symmetrical white matter lesions in the centrum semiovale, corpus callosum, left thalamus, left pons and right cerebellar peduncle. The aspect and distribution of these lesions favoured the diagnosis of multiple sclerosis (MS). One week later, the patient was admitted because of progressive cognitive impairment. Initial ophthalmological evaluation was normal. Repeated brain MRI showed rapid progression of the white matter lesions. The differential diagnosis consisted of acute disseminated encephalomyelitis (ADEM) or primary cerebral vasculitis. She was treated with pulse methylprednisolone 1000 mg/day for five consecutive days, after which cognitive function improved.

Three weeks after presentation, the patient complained of blurred vision and a black spot in the left eye. Fundoscopy showed abnormalities suspect for vasculitis in both eyes. Under the working diagnosis of cerebral and ocular vasculitis, treatment with prednisolone 1 mg/kg/day and azathioprine 100 mg/day was initiated.

In the beginning of December, she presented with ataxia, vertigo, and vomiting. Fluorescein angiography revealed BRAOs in both eyes, confirming the diagnosis of Susac syndrome. In retrospect, BRAOs were also present one month earlier. Methylprednisolone 1000 mg/day was administered for three days. A few days later, tinnitus and perceptive hearing loss of the right ear occurred. Prednisolone was increased to 80 mg/day, a five-day course of intravenous immunoglobulins (IVIG) was prescribed, and aspirin was added. Consecutively, she started with monthly cyclophosphamide infusions.

In January 2010, she was retreated with methylprednisolone 1000 mg/day for five days because of progressive ataxia, headaches, paresthesias and memory loss. In March 2010 an additional IVIG course was given because of progressive visual loss caused by new BRAOs.

In June 2010, cognitive impairment prevented the patient from working, reading, writing, household activities and hobbies. Fluctuating perceptive hearing loss in both ears required hearing devices. Two infusions of rituximab 1000 mg 2 weeks apart were given. Cyclophosphamide was continued as maintenance therapy once every three months until March 2011, and the prednisolone was gradually tapered and finally discontinued in June, 2011. No new BRAOs had occurred.

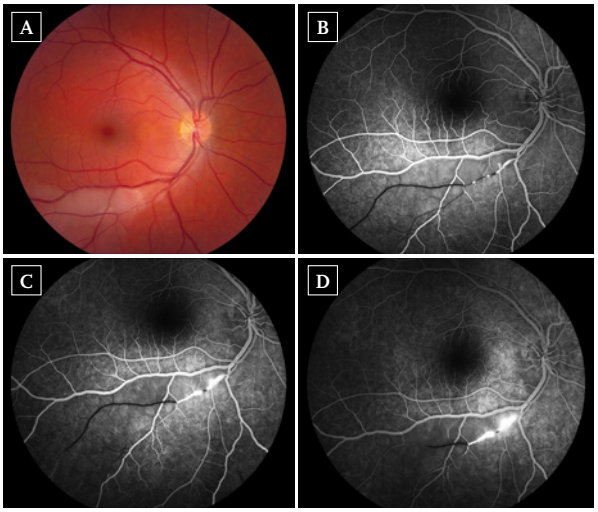
In September 2010 she complained of feeling increasingly depressed and was referred to a psychiatrist. A depressive disorder was diagnosed, most likely as a consequence of the severe disability, possibly secondary to central nervous system damage. Her depressive complaints improved with sertraline, and she was referred for further neurological and cognitive revalidation and rehabilitation. She retained severe neuropsychological sequelae (memory problems and disturbed executive capacities). Follow-up MRI studies in October 2010 and June 2011 showed a slight decrease in lesion load and volume with discrete parenchymal defects in previously active lesions, without active or new lesions.

Case 2

A 34-year old woman first presented in August 2010 with sudden occurrence of a black spot in the right eye. She had a one-year history of progressive migraine-type headaches with visual aura, and Raynaud's phenomenon of the hands. Physical examination and routine laboratory studies were normal. Fluorescein angiography revealed a BRAO of the right eye (*figure 1*). Cerebral MRI was performed, revealing multiple lesions in the corpus callosum, including a typical snowball lesion. In addition, a few white matter lesions and some lesions in the right frontal lobe were noted. Audiometry was normal. Based on the typical MRI findings combined with BRAO, the diagnosis of Susac syndrome was made.

The patient was treated with methylprednisolone 1000 mg/day for three consecutive days, followed by oral prednisolone 1 mg/kg/day, and aspirin. Mycophenolate mofetil 2dd 1000 mg was initiated because of fertility concerns related to cyclophosphamide use. She responded well to treatment and the prednisolone was gradually tapered to 10 mg/day after five months and eventually discontinued in June 2011 because of remission. She was functioning normally and had started working again. Follow-up cerebral MRI after one year revealed discrete resolution of white matter lesions, and a parenchymal

Figure 1A. *Photograph showing occlusion in inferior temporal artery with white discoloration in the occluded area*
B. *Angiography, early phase, showing no perfusion of the inferior temporal artery*
C and D. *Angiography, late phase, demonstrating segmental leakage of the vascular wall (C) and retrograde filling of the vessel (D)*



defect on the site of the initial snowball lesion in the corpus callosum.
In August 2011 mycophenolate mofetil was switched to azathioprine 150 mg/day because of anaemia and a wish to become pregnant. In June 2012, recurrence of BRAO in the left eye and subtle cognitive dysfunction required reinstitution of the mycophenolate mofetil and corticosteroids. In October 2012, azathioprine was started again because of a pregnancy wish and, while pregnant, azathioprine was discontinued in July 2013 because of anaemia. In August 2013, a healthy daughter was born by caesarean section. Six weeks after delivery, however, she presented with a relapse of disease activity including mild hearing loss of the right ear, visual auras, and a new BRAO with leakage of fluorescein. Prednisolone was increased to 60 mg/day and the azathioprine was restarted. She responded very well with full recovery of her symptoms.

Case 3

A 39-year-old woman presented to the emergency ward of another hospital in August 2012 with vertigo, gait ataxia, headaches with photopsia, nausea and vomiting. Medical history was unremarkable except for familial hypercholesterolaemia for which she had been using statin therapy since 1994. Three days after presentation, she developed a bilateral perceptive hearing loss of 30-35 dB. She also experienced transient visual symptoms, central facial paresis, and paresthesias in the right arm and cheek. Cerebrospinal fluid analysis showed 8 cells/ul, and protein of 2.34 g/l. Cerebral MRI showed T2 hyperintense lesions in the basal ganglia and posterior fossa, as well as leptomeningeal enhancement on post-gadolinium T1; no abnormalities were observed in the corpus callosum. The ophthalmologist diagnosed a trochlear nerve paresis of the right eye. Differential diagnoses included infectious causes as well as neurosarcoidosis. Reinvestigation by the ophthalmologist provided the clue to the diagnosis 2.5 weeks after presentation, when BRAOs with typical segmental fluorescein leakage proximal of the occluded areas were visualised in both eyes, confirming the diagnosis of Susac syndrome. The patient was transferred to our hospital. Her symptoms had improved in the meantime, with only a slight gait ataxia and a visual field defect in the right eye.
Three weeks after the initial presentation, treatment was started with methylprednisolone 500 mg/day for five days, followed by oral prednisolone 1 mg/kg/day. Azathioprine 150 mg/day was added. Further clinical improvement in the next weeks enabled the prednisolone to be gradually tapered to 10 mg/day in April 2013. Ophthalmological evaluation had improved without new BRAOs, audiometry confirmed mild stable perceptive hearing loss especially of the left ear. Repeated MRI of the cerebrum after seven months was completely normal, all the T2 hyperintense lesions in the posterior fossa as well as leptomeningeal enhancement had disappeared. After one year, the prednisolone was discontinued, and the patient continued on azathioprine 150 mg/day.

Case 4

A 22-year-old woman was admitted to the neurology ward of another hospital in the beginning of January 2013. In the past ten weeks, she had experienced several episodes starting with paresthesias in the left arm and leg, followed by a right-sided headache, initially diagnosed as migraine with aura. In the weeks before admission the headaches became more severe, together with occurrence of a progressive gait disorder, fatigue and memory loss. On neurological examination at admission, she was bradyphrenic and bradykinetic, and had a decreased sensation, hyperreflexia and a grade 4 paresis of the left arm and left leg. Short-term memory was impaired. Laboratory tests were normal. Cerebrospinal fluid analysis showed a lymphocytic pleocytosis with 4 cells/ul and a total protein of 2.29 g/l. Brain MRI revealed multiple hyperintense lesions on the FLAIR and T2-weighted images in the corpus callosum, pons, basal ganglia, thalamus and periventricular area, not typical for MS (*figure 2*). The next day, sudden severe perceptive hearing loss of the right ear occurred, followed by acute visual loss in the right eye the day thereafter. Ophthalmological evaluation revealed BRAOs in the right eye. A diagnosis of Susac syndrome was made.
The patient was treated with two three-day courses of methylprednisolone 1000 mg/day one week apart, followed by oral prednisolone 60 mg/day, and aspirin. In addition, mycophenolate mofetil 2dd 1000 mg was started. Soon after commencing treatment, the left-sided neurological symptoms resolved, although some small new BRAOs did occur in the first weeks after treatment initiation. The deafness of the right ear persisted. She was referred to a rehabilitation clinic.
In May 2013, further clinical improvement was noted: the right ear showed a small perceptive loss, no new BRAOs occurred, although a persistent visual field defect in the upper part of the right eye remained. Follow-up MRI of the brain showed a dramatic improvement with almost no hyperintense lesions left on FLAIR and T2-weighted images (*figure 2*). Prednisolone was tapered to 10 mg/day in August 2013, and mycophenolate mofetil was continued.

DISCUSSION

Epidemiology

Most cases of Susac syndrome occur in young women aged 16-40 years, with a mean age of 31.6 years (range 8-65 years). Of the 304 patients recently reviewed by Dorr, 78% were female, which is in line with the presumed

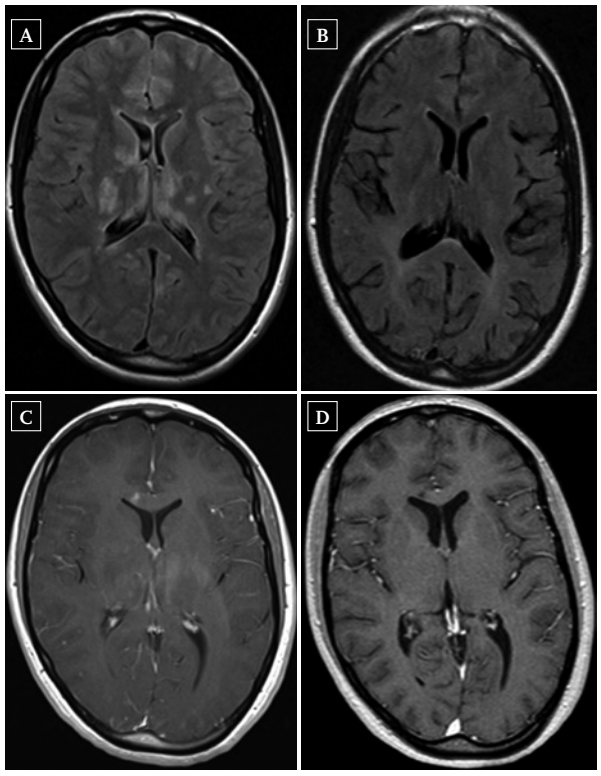
autoimmune aetiology of the disease. No racial trends have been detected.[2] True incidence and prevalence is unknown, as the disorder is possibly underdiagnosed.

Aetiology

The pathophysiology of Susac syndrome is still unclear; however, an immune-mediated injury involving the endothelium of retina, cochlea and cerebral vasculature is the leading hypothesis. This was suggested by biopsy studies in which endothelial cell necrosis, basement membrane thickening with deposition of collagen, mural and intra-luminal fibrin deposition, and C3d and C4d deposition in capillaries were found.[6] Narrowing or occlusion of microvasculature then results in ischaemic injury of the brain, retina, and cochlea. Similar findings have been reported in muscle and skin biopsy studies in patients with dermatomyositis, suggesting a possible associated disease mechanism.[7,8]

Case reports have found anti-endothelial antibodies of IgG1 subclass in patients with Susac syndrome.[9-11] However, these antibodies were also found in patients with Sjogren syndrome and dermatomyositis, and it is unclear if they are involved in the development of endothelial injury, or if they are an unspecific epiphenomenon of the disease.

Figure 2A. *Axial flair MRI, basal ganglia, before treatment. Diffuse hyperintense lesions in the corpus callosum, pons, basal ganglia, thalamus and periventricular area*
B. *Axial flair MRI, basal ganglia, after treatment. Marked improvement of diffuse hyperintense lesions, almost no lesions left*
C. *Axial T1 weighted, gadolinium-enhanced MRI, before treatment, showing a contrast-enhanced corpus callosum lesion*
D. *Axial T1 weighted gadolinium-enhanced MRI, after treatment, showing disappearance of the contrast enhancement in corpus callosum*



Disease course

The clinical course of Susac syndrome can be divided into a monocyclic, polycyclic and a chronic continuous course.[5] The monocyclic course is defined as a fluctuating disease that self-limits after a maximum period of two years and does not recur; the polycyclic course is characterised by relapses of disease activity following a period of remission, continuing beyond two years after presentation. A disease-free period of 18 years between two relapses has been described.[12] Dorr and colleagues could classify 54% of 114 patients as monocyclic, 42% as polycyclic, and only 4% (four patients) as having a chronic continuous course, questioning the clinical relevance of this third category.[2] In our four patients, two could not yet be classified due to a follow-up of less than one year, but were in remission; patient 1 had a monophasic course with severe residual symptoms, and patient 2 had a polycyclic course with recurrences after two and three years, with the second recurrence manifesting six weeks after delivery.

Clinical symptoms

The typical clinical triad consists of subacute encephalopathy, visual loss due to BRAO, and sensorineural hearing impairment. It is important to emphasise that only 13% of Susac patients presented with the characteristic triad at disease onset, impeding an early correct diagnosis. In virtually all patients, the full triad will develop during the disease course, after on average five months.[2] Indeed, none of our four patients presented with the classical triad.

The most common clinical manifestations at onset are central nervous system (CNS) symptoms, observed in two-thirds of patients, followed by visual symptoms and hearing disturbances in around 40% of patients at presentation. Migraine-like headaches are reported in 80% of patients at disease onset.[2]

Encephalopathic CNS symptoms include cognitive impairment (48% of patients), confusion and/or disorientation (39%), emotional disturbances (16%), behavioural changes (15%), personality changes (12%), apathy (12%), psychosis (10%) and reduction of vigilance (9%).[2] Other CNS manifestations include gait ataxia (25%), vertigo (25%), sensory disturbances (24%), upper motor neuron signs (21%), paresis (20%), nausea and vomiting (15%), dysarthria (13%), oculomotor dysfunction (10%), urinary dysfunction (9%) and diplopia (5%).[2]

Reported visual symptoms are black or grey scotomata in the visual field, photopsia, occasionally scintillating scotomata, and visual acuity loss when the central retina is involved. However, patients may also be asymptomatic if only the far periphery of the retina is affected. Visual field loss is permanent.

Hearing loss is irreversible in the majority of patients, and may occur rapidly or develop overnight. Severe hearing loss is often accompanied by vertigo and tinnitus, and may require cochlear implants. Some patients complain about myalgia and/or arthralgia, and might exhibit dermatological signs, such as livedo racemosa.[8,13]

It has been suggested that patients who present with encephalopathy are more likely to experience a monocyclic course, and that presentation with visual or hearing impairment without clinically evident encephalopathy is likely to have a prolonged polycyclic course,[2,13] as was the case in our patients 1 and 2, respectively.

Diagnostic procedures

Cerebral MRI, retinal fluorescein angiography and audiometry are considered crucial investigations to enable diagnosis, especially since pathology on these tests has been described more often than symptoms being clinically evident, emphasising an appropriate diagnostic workup.

Fluorescein angiography exhibits multifocal non-perfused arterioles (BRAOs) in 99% of patients,[2] highlighting the importance of this investigation. Additional abnormalities include typical segmental fluorescein leakage of the arteriolar wall, and/or yellow retinal arterial wall plaques (Gass plaques).[14]

Audiometry reveals perceptive hearing loss in almost every patient, typically involving the low or middle frequencies, because these microvessels are affected first. The evaluation of hearing loss in the encephalopathic patient may be very difficult.

MRI

Cerebral MRI typically reveals multifocal T2-hyperintense lesions of 3-7 mm in diameter most frequently involving the white matter, especially the corpus callosum, periventricular areas, centrum semiovale and subcortical regions. Involvement of the corpus callosum, especially the presence of 'snowball lesions' in the centre of the corpus callosum, is considered pathognomonic and was found in all 27 patients with Susac syndrome in a previous MRI study.[15] In two recent reports, however, 21-22% of patients did not have callosal involvement, suggesting that callosal involvement is not mandatory for the diagnosis of Susac syndrome.[2,16] Deep grey matter, basal ganglia and thalamus involvement was described in 70% of patients; cerebellar involvement in 52%; leptomeningeal enhancement in 33%; and brainstem involvement in 30%.[15,17] Over time, atrophy of the corpus callosum, cortex and cerebellum may develop. Sometimes residual holes in the central fibres of the corpus callosum emerge, representing micro-infarctions; these lesions may be pathognomonic.

Resolution of white matter lesions is rare, but has been reported in some studies.[18-20] Interestingly, we observed complete resolution of white matter abnormalities in patient 3, and almost complete resolution in patient 4.

MRI is also helpful in clarifying the differential diagnosis between Susac, MS, and ADEM patients: in MS, corpus callosum lesions are located in the periphery instead of the centre; leptomeningeal enhancement is absent in MS or ADEM, but present in 30% of Susac patients; and deep grey matter involvement seldom occurs in MS but is present in 70% of Susac patients. Kleffner and colleagues suggested that diffusion tensor imaging is superior to conventional MRI, as all patients had disruption of fibre integrity in the genu of the corpus callosum.[21]

Additional diagnostic procedures

Additional diagnostic tests are often performed, but are mainly useful for the exclusion of other diagnoses. Routine laboratory measures are usually normal; the erythrocyte sedimentation rate and C-reactive protein may be mildly elevated. The rate of ANA positivity is around 7% and therefore comparable with the healthy population.[2]

Anti-endothelial cell antibodies have been detected in the serum of patients with Susac syndrome,[9,10,22] but were reported in other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome and sarcoidosis as well.

Cerebrospinal fluid analysis is important in patients with CNS symptoms to rule out infectious encephalitis. It usually shows a moderately elevated protein of up to 2 g/l with a mild lymphocytic pleocytosis (5-30 cells/mm^3). Isolated oligoclonal bands are rare in Susac syndrome, but are found in up to 98% of MS patients.[23]

Cerebral angiography might be helpful in the differential diagnosis of cerebral vasculitis, but is normal in Susac syndrome, since the precapillary arteriole is below the resolution of angiography. Brain biopsy was mainly performed in the older literature, showing focal microangiopathic and gliotic changes in the majority of patients. No overt demyelinisation was reported in any of the cases.

Treatment

No evidence-based standardised treatment protocols exist, as a consequence treatment of Susac syndrome is based on case reports and small case series.[5,7,16] In concordance with the presumed autoimmune endotheliopathic aetiology, treatment has to be immunosuppressive. It seems important that the disease should be treated early, aggressively and long enough to prevent relapses, but the appropriate treatment duration is anecdotal.

In the acute phase, pulse methylprednisolone 1000 mg/day for three to five days should be initiated, followed by oral prednisolone 1 mg/kg/day for four weeks. Corticosteroids can then be slowly tapered to 10-15 mg/day after six months, and thereafter to zero in another six months.[24] Additional immunosuppressive medication should be started in the induction phase. Different treatment strategies include cyclophosphamide (monthly infusions of 750 mg/m^2), mycophenolate mofetil (2dd 1000 mg), or possibly rituximab (375 mg/m^2 once weekly for four weeks). To reduce the risk of thrombosis of the small arterioles, it is recommended to add aspirin in all patients.[7] In severe or refractory cases, IVIG (2 g/kg monthly for six months) or plasmapheresis may be useful.[7,16] Infliximab was reported to give striking improvement in headache and ataxia in a single patient who did not respond to, and experienced side effects from prednisolone.[25]

Following induction therapy, maintenance therapy may consist of cyclophosphamide infusions every three months, mycophenolate mofetil, or azathioprine for at least two years.[7]

Long-term treatment management is challenging and guided by serial ophthalmological, audiological, neuropsychiatric, and MRI evaluations. Patients with severe hearing loss benefit from cochlear implants.

In all four of our patients, treatment decisions were guided by an experienced rheumatologist as a case manager, reviewing diagnostic studies. All patients were treated with methylprednisolone followed by oral prednisolone. Patient 1 received cyclophosphamide in association with IVIG, and at a later stage rituximab, and cyclophosphamide maintenance treatment every three months; patient 2 received mycophenolate mofetil induction and azathioprine maintenance; patient 3 was treated with azathioprine alone; and patient 4 was treated with mycophenolate mofetil alone.

Prognosis

In the majority of patients, the disease course is monocyclic without relapses after two years. Up to 40% of patients, especially those patients presenting with visual or hearing impairment, experience a polycyclic disease course with remissions followed by exacerbations. While some patients recover without or with minimal sequelae, most patients have residual symptoms despite immunosuppressive treatment, ranging from mild symptoms to severe psychoneurological deficits, hearing loss, and/or visual impairment.[26] In contrast with earlier reports, in our population, three out of four patients had favourable outcomes, possibly reflecting early treatment, although follow-up time is limited in two patients.

CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, we present four new cases of Susac syndrome, illustrating different disease courses and favourable outcomes in three patients. Susac syndrome is an important differential diagnosis in numerous disorders and should be suspected also in case of isolated encephalopathy, visual field defects or hearing loss, as early treatment seems to improve outcomes. To accomplish this, fruitful cooperation between rheumatologist, ophthalmologist, neurologist and ENT specialist is necessary, and we suggest that an immunologist or rheumatologist coordinates treatment decisions. For the future, large prospective cohorts of patients with Susac syndrome are needed to systematically test different treatment regimens and assess outcomes in a standardised way, aiming at better care for patients with this rare but potentially incapacitating disorder.

DISCLOSURES

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ORIGINAL ARTICLE

Is hemithyroidectomy a rational management for benign nodular goitre?

A Multicentre Retrospective Single Group Study

W. Attaallah[1]*, S. Erel[2], N.Z. Canturk[3], Y. Erbil[4], S. Gorgulu[5], H. Kulacoglu[6], M.A. Kocdor[7], A. Kebudi[8], S. Ozbas[9], B.M. Gulluoglu[1], and Turkish Endocrine Surgery Study Group (TESSG) Investigators

[1]Department of General Surgery, Marmara University School of Medicine, Istanbul, Turkey, [2]Department of Surgery, Ankara Training and Research Hospital, Ankara, Turkey, [3]Department of General Surgery, Kocaeli University School of Medicine, Kocaeli, Turkey, [4]Istanbul Faculty of Medicine, Surgery Unit E, Istanbul University, Istanbul, Turkey, [5]Department of General Surgery, Gulhane Military Medical Academy, Ankara, Turkey, [6]Department of Surgery, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey, [7]Department of General Surgery, Dokuz Eylul University School of Medicine, Izmir, Turkey, [8]Department of General Surgery, Maltepe University School of Medicine, Istanbul, Turkey, [9]Department of General Surgery, Adnan Menderes University School of Medicine, Aydin, Turkey, *corresponding author: tel.: +90 2166570606, fax: +90 2166570695, email: drwafi2003@yahoo.com

ABSTRACT

Background: The incidence and potential risk factors for the recurrence of benign nodular goitre after unilateral thyroidectomy are not clearly defined. The aim of this study was to assess the rate of progression of nodular goitre in the contralateral thyroid lobe and of hypothyroidism requiring replacement therapy after unilateral thyroid lobectomy for benign nodular goitre.

Patients and Methods: Patients who underwent hemithyroidectomy for benign nodular goitre between 2000 and 2009 were included in the study. The primary outcome of this study was the reoperation rate for recurrent goitre, the rate of progression of nodular goitre and the rate of hypothyroidism requiring L-T4 replacement therapy. Clinical factors that have an effect on progression were further analysed.

Results: 259 patients were included for study. Progression of the nodular goitre in the remnant lobe was observed in 32% (n = 83) of the patients. However, over time, only 2% of these 83 patients underwent contralateral hemithyroidectomy due to this progression. Fifty-six (22%) patients required L-thyroxin replacement due to persistent hypothyroidism after hemithyroidectomy. The factors shown to affect progression of nodular goitre were advanced age, preoperative hyperthyroidism, preoperative diagnosis of toxic nodular goitre and the presence of surgical indication for a toxic goitre causing hyperthyroidism and a definitive pathological diagnosis of nodular hyperplasia.

Conclusion: There was a progression of the nodular goitre in the remnant lobe in about one-third of the patients who underwent hemithyroidectomy. However, only 2% of these patients underwent complementary contralateral hemithyroidectomy due to clinical progression in 31 months of follow-up.

KEYWORDS

Benign nodular goitre, hemithyroidectomy, hypothyroidism, recurrence

INTRODUCTION

Benign nodular goitre is the most common endocrine disorder, especially in countries where iodine deficiency is endemic.[1] Surgery is the common method for the treatment of benign nodular goitre, whereas radioactive iodine is considered a good treatment option as well.[2] The optimal operative strategy for treating benign nodular goitre remains controversial. Factors affecting the extent of resection are mostly the risk of postoperative hypothyroidism and rate of surgical complications.[3-9] Hemithyroidectomy is the basic surgical procedure for benign nodular goitre restricted to one lobe. In patients who have undergone hemithyroidectomy, there is a

potential for a progression of the disease in the remnant lobe.[3] The incidence and potential risk factors for the development of such progression after hemithyroidectomy are not clearly defined.[6-8]

Management of benign nodular goitre is surgical if it is symptomatic, or fine needle aspiration biopsy turns out to be suspicious for malignancy. Patients with nodules other than these can be followed up. Therefore, multiple nodules in both lobes should not lead to bilateral surgery if the nodules on one side are asymptomatic and benign. This prevents 70-80% of patients from having permanent hypothyroidism.[3]

The aim of this retrospective study was to assess the rate of reoperation of the remnant thyroid lobe in patients living in an iodine-deficient region who had undergone unilateral hemithyroidectomy for benign nodular goitre.

PATIENTS AND METHODS

Study design and setting

The study was planned as a multicentre, retrospective, single-arm cohort study (TESSG-TINOTA Study).

Patients

Patients who underwent surgery at a tertiary referral hospital with an endocrine surgery unit between 2000 and 2009 were included in the study. All patients who had undergone hemithyroidectomy for whom a preoperative fine needle aspiration biopsy had shown a benign goitre were included in the study. Hemithyroidectomy was defined as a thyroid lobectomy and isthmusectomy with preservation of the contralateral thyroid lobe.

Ethics

The Marmara University School of Medicine Research Ethics Committee approved the study protocol. Study variables were retrieved from prospectively collected data at each institution's archives. A retrospective chart review was done from consecutive series of patients operated during the study period. Patients who were included in the study were operated on by the same surgeon at each single institution. Only patients older than 18 years were included in the study. We excluded patients who turned out to have cancer after the final pathological results/observations, whose preoperative thyroid function tests and neck ultrasonography results were not available, who were known to be pregnant or lactating, who had previously undergone more than one thyroid operation or who were not available for follow-up after the initial thyroidectomy.

Outcomes

The primary outcome was the number of patients who underwent secondary surgery for thyroid disease (complementary contralateral lobectomy). Secondary outcomes were the progression rate (increase in size and number of nodules or appearance of new nodules in the remnant lobe), the number of patients with postoperative hypothyroidism who required thyroxin treatment, the indications for contralateral lobectomy and the factors that predicted progression rate.

Data

Factors which were assessed for disease progression included the following: patient's age at the time of surgery, gender, number of nodules and the diameter of the largest nodule in the removed lobe, the number of nodules in the remnant lobe and the diameter of the largest, the functional status of the thyroid gland, final histopathological findings, indications for surgery, previous exposure to ionising radiation, having a family history of thyroid cancer, serum anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) levels and length of follow-up.

Progression was defined as the need for complementary contralateral lobectomy or the appearance of new nodules, or an increase in size of the nodules in the remnant lobe of at least 3 mm.

A positive family history was defined as the occurrence of thyroid cancer (any type) for any first-degree relative. Previous radiation exposure was defined as any occupational exposure to radiation, accidental exposure to environmental radiation or receiving any radiation as a form of medical treatment.

Having high titres of any or both antibodies (against TPO and Tg) in the serum was regarded as thyroid autoimmunity regardless of pathology assessment.

Serum TSH, free T3, free T4, anti-TPO, anti-Tg calcium levels and neck ultrasonography results were retrieved from the database. Current permanent use of L-thyroxin was noted. Also, indications for the complementary contralateral lobectomy surgery, final histopathology and operative complications were recorded.

Statistical analysis

Statistical analyses were done by the SPSS software package (version 11.0). A two-tailed chi-square or a Fisher's exact test were used to compare categorical variables, whereas independent two-sample t-tests were used for continuous variables. Continuous variables were given as mean (± standard deviation; SD). A logistic regression test was used to analyse the independent factors for progression. Factors which were found to be significant in the univariate analysis were tested by multivariate analysis in order to find independent factors. All statistical tests were two-sided and a p value of less than 0.05 was considered significant.

RESULTS

A total of 259 patients from nine tertiary endocrine surgery units in Turkey, who had undergone hemithyroidectomy between November 2000 and December 2009, were included in the study. The mean age of the patients was 48 years and 75% were female. Of the patients, 60 (23%) had overt hyperthyroidism and 12 (5%) patients had elevated levels of at least one of two thyroid antibodies. Two patients had a family history of thyroid surgery. No patients had a history of previous radiation to the neck. Most patients (n = 195; 75%) had no nodules in the remnant lobe as a preoperative ultrasonography finding. The mean size of the largest nodule in the remnant lobe was 9.3 ± 5.3 mm for patients with at least one nodule left in situ after the hemithyroidectomy (*table 1*).

The most common indications for surgical treatment were hyperthyroidism (n = 66; 25%) and compression of a solitary normo-active nodule (n = 65, 25%; *table 2*). The most common findings were nodular hyperplasia and colloid nodules (n = 176; 68%). The mean follow-up time was 31 (25.5; *table 3*) months within the range of 6-126 months.

Fifty-six (22%) patients received L- thyroxin supplementation due to permanent hypothyroidism after the initial hemithyroidectomy. Anti-TPO and/or anti-Tg titres (autoimmunity) were not found to be predictive for hypothyroidism requiring supplementation after surgery (*table 4*).

Progression of nodular goitre was observed in 83 (32%) patients. New nodules developed in 77 (30%) patients. The median number of newly developed nodules was 3.5 (1-6). In patients with at least one nodule left in the remnant lobe, the nodules were enlarged in 54 (21%) patients. The median increase in size was 8 (3-18) mm. Only five (2%) patients underwent complementary contralateral hemithyroidectomy due to progression of nodular goitre. The mean follow-up period in patients with progression

Table 1. *Demographic features and preoperative ultrasonography findings of patients*

	Patients with progression (n = 83)	Patients without progression (n = 176)	Total (n = 259)	P
Sex				**0.54**
• Female	65 (78%)	130 (74%)	195 (75%)	
• Male	18 (22%)	46 (26%)	64 (25%)	
Age, mean (SD)	47.9 (10.7)	40.8 (12.2)	43.1 (12.2)	**0.0001**
Operated lobe				**0.94**
Number of nodules, n(%)				
• 0	0 (0%)	0 (0%)	0(0%)	
• 1	52 (63%)	124 (70%)	176(68%)	
• 2	16 (19%)	25 (14%)	41(16%)	
• More than 2	15 (18%)	26 (15%)	41(16%)	
Remnant lobe				**0.27**
Number of nodules, n(%)				
• 0	59 (71%)	136 (77%)	195(75%)	
• 1	13 (16%)	16 (9%)	29 (12%)	
• 2	6 (7%)	15 (9%)	21 (8%)	
• More than 2	5 (6%)	9 (5%)	14 (5%)	
Size of nodule, mean, mm(SD)	10.7 (6.9)	8.5(4)	9.3 (5.3)	**0.1**
Pre-op function of thyroid, n(%)				**0.0001**
• Euthyroid	45 (54%)	149 (85%)	194 (75%)	
• Hyperthyroid	36 (43%)	24 (13%)	60 (23%)	
• Hypothyroid	2 (3%)	3 (2%)	5 (2%)	
Autoimmunity, n(%)				**0.058**
• No	75 (90%)	170 (97%)	245 (95%)	
• Yes	7 (9%)	5 (3%)	12 (5%)	
• Unknown	1 (1%)	1 (1%)	2 (%)	
Family history, n(%)				**1.0**
• No	83 (100%)	173 (98%)	256 (99%)	
• Yes	0 (0%)	2 (2%)	2 (1%)	
• Unknown	0 (0%)	1 (1%)	1 (0.3%)	
History of RT to neck, n(%)				**1.0**
• No	83 (100%)	175 (100%)	258 (100%)	
• Yes	0 (0%)	0 (0%)	0 (0%)	
• Unknown	0 (0%)	1 (1%)	1 (0.3%)	

SD = standard deviation; RT = radiation treatment.

Table 2. *Preoperative diagnosis and surgical indications*

	Total progression n = 259	Patients without progression n = 176	Patients with progression n = 83	p
Preop diagnosis; *n (%)*				0.0001
• Solitary euthyroid nodule	115 (44)	88 (50)	27 (32)	
• Unilateral euthyroid MNG	33 (13)	16 (9)	17 (21)	
• Bilateral euthyroid MNG	33 (13)	29 (16)	4 (5)	
• Solitary toxic nodule	50 (18)	24 (14)	26 (31)	
• Unilateral toxic MNG	7 (3)	3 (2)	4 (5)	
• Bilateral toxic MNG	4 (2)	1	3 (4)	
• Follicular/Hurthle cell neoplasm	17 (7)	15 (9)	2 (2)	
Surgical indications; *n (%)*				0.0001
• Compression	65 (25)	52 (30)	13 (16)	
• Hyperthyroidism	66 (25)	29 (16)	37 (45)	
• Suspicious FNAB	52 (20)	45 (26)	7 (8)	
• Insufficient FNAB	35 (14)	23 (13)	12 (14)	
• Asymptomatic	33 (13)	23 (13)	10 (12)	
• Other	8 (3)	4 (2)	4 (5)	

MNG = multinodular goitre; FNAB = fine needle aspiration biopsy.

Table 3. *Definitive histopathology findings and follow-up period of patients*

	Total n = 259	Patients without progression n = 176	Patients with progression n = 83	p
Histopathology results; *n (%)*				0.0001
• Nodular hyperplasia	110 (43)	57 (32)	53 (64)	
• Colloidal nodule	66 (25)	55 (31)	11 (13)	
• Follicular adenoma	65 (25)	49 (28)	16 (19)	
• Hurthle cell adenoma	17 (7)	14 (8)	3 (4)	
• Other	1	1 (1)	0	
Follow-up time; *month (SD)*	**31 (25.5)**	**24.8 (20.7)**	**43.6 (29.4)**	0.0001

Table 4. *The features of patients according to their L-T4 requirement*

	Patients requiring no L-T4 replacement n = 203	Patients requiring L-T4 replacement n = 56	p
Autoimmunity; *n (%)*			0.14
• No	194 (96)	51 (91)	
• Yes	7 (3)	5 (9)	
• Unknown	2	0	
Preoperative thyroid function; *n (%)*			0.003
• Euthyroid	151 (74)	43 (77)	
• Hyperthyroidism	51 (25	9 (16)	
• Hypothyroidism	1 (1)	4 (7)	
Interval time; *month (SD)*	**27.6 (23.5)**	**43.6 (28.9)**	0.0001

of nodular goitre (43.6 months) was significantly longer than for those with no such progression (24.8 months, p = 0.0001; *table 3*).

Multivariate analysis showed that advanced age, preoperative hyperthyroidism, preoperative diagnosis of toxic nodular goitre and a definitive pathological diagnosis of nodular hyperplasia are factors which had an independent effect on the progression of nodular goitre.

DISCUSSION

The reported recurrence rate following surgical resection for benign nodular thyroid disease varies from 0.3-80% depending on the extent of the initial surgery, the regional iodine-deficiency status and the length of follow-up.[1-10] However, surgery is the common method for the treatment of benign nodular goitre, whereas radioactive iodine is

also considered to be a reliable treatment option. The choice of surgical procedure for symptomatic benign nodular goitre is still controversial. Some surgeons prefer a hemithyroidectomy or subtotal thyroidectomy because of their lower complication rates. However, after these procedures the need to reoperate may arise due to the recurrence of symptomatic benign nodular goitre. Recently, with the advancement made in surgical techniques and increased experience, total thyroidectomy was preferred by some surgeons because of its low incidence of recurrence.[12-14] However, total thyroidectomy is associated with a potentially higher morbidity and a need for life-long thyroid hormone replacement therapy after the procedure. The advantage of hemithyroidectomy is that half of the thyroid gland remains. Therefore, most of the patients do not need to take thyroid supplements. Moreover, because the one lobe of the thyroid is untouched, there is no risk of damaging the contralateral recurrent laryngeal nerve and parathyroid glands. In this current study, most of the patients underwent surgery for unilateral disease.

Recurrent benign nodular goitre was defined as the return of the benign nodular goitre causing symptoms necessitating thyroid resection. In a study, with up to 134 months of follow-up, a higher recurrence rate (11%) in the unilateral resection group was reported when compared with the bilateral group (3%).[14] Other studies showed that the recurrence rate for benign nodular goitre in patients undergoing hemithyroidectomy is 1.2-26%, with a mean time to recurrence being 10-16 years and the recurrence rate for patients undergoing total thyroidectomy was found to be 3%. However, not all patients (especially the elderly) with recurrent symptoms required reoperation, thus the rate of reoperation was about 0.4%.[7,15] In our study, we found that out of 83 (32%) patients who had a progression of the nodular goitre only two (2%) were reoperated for recurrent benign nodular goitre. The fact that only 2% of patients underwent a reoperation is likely to be due to the short follow-up time in our study. The number of patients who would need further operation may very well increase when follow-up is extended.

We defined progression as the need to operate on the remnant lobe, the emergence of a new nodule or an increase in the diameter of an old nodule by more than 3 mm. In this study, progression of the nodular goitre was observed in 83 (32%) patients. In all the cohort, the medial follow-up time was 31 months, the longest being 126 months.

All factors that had an independent effect on progression, except advanced age, were in accordance with previous studies, which reported that undergoing an operation at a younger age increased the incidence of recurrent benign nodular goitre. This result is consistent with the natural course of benign nodular goitre, which is typically slow-growing so that the rate of recurrence increases as time elapses after the initial operation.[3] It has also been reported that there is a linear relationship between the patient's age, thyroid volume, and nodularity, respectively, with an average increase in thyroid volume of 4.5% per year based on serial ultrasound measurements.[16]

Other authors have found that even patients who had initially undergone hemithyroidectomy for a solitary nodule were subsequently found to have multinodular disease in the resected lobe on the final pathological examination. However, in these patients reoperation was rarely necessary (3%) after a mean follow-up of 14 years.[15] In our study the reoperation rate was 2% in accordance with previously reported series.

According to our results a definitive pathological diagnosis of nodular hyperplasia was associated with a greater risk of progression. Previous studies showed that follicular adenoma has a low recurrence rate, because adenoma is considered to be a solitary disease in a normal thyroid gland, rather than a lesion that develops in a diseased thyroid gland, as usually seen in nodular hyperplasia. However, it is remarkable that many patients with a solitary hyperplastic nodule, according to the ultrasonographic findings, developed a nodular relapse or a parenchymal irregularity.

In this study, only 56 (22%) patients needed to receive L-thyroxin supplementation due to postsurgical permanent hypothyroidism. By reserving total thyroidectomy only for patients with bilaterally symptomatic benign nodular goitre, nearly 80% of patients who had undergone hemithyroidectomy avoided thyroid hormone supplementation. It is well known that most patients after thyroid lobectomy are euthyroid (60-90%) and do not require thyroid hormone replacement therapy.[17-21] However, the incidence and contributing factors for hypothyroidism after hemithyroidectomy remain uncertain. The likelihood of thyroid hormone replacement demonstrated a trend with a contralateral nodule and a significant association with thyroiditis on the basis of the pathological findings.[22] Stoll *et al.*[23] concluded that patients with preoperative TSH levels greater than 1.5 μIU/ml or low free T4 levels or Hashimoto's thyroiditis are at increased risk for permanent hypothyroidism. They recommended that these patients should be counselled and followed appropriately. Piper *et al.*[24] also showed that 18% of patients become hypothyroid after hemithyroidectomy. However, they noted that some patients who became hypothyroid became euthyroid over time, even without any supplementation.

In our study, cancer was not reported for any of the patients who had progression after hemithyroidectomy for benign nodular goitre.

From our results, it is expected that the overall recurrence rate would increase with a longer follow-up time. Having a relatively short follow-up period was the major limitation of our study, and thus we emphasise the importance of

performing a regular annual follow-up for patients after hemithyroidectomy for benign nodular goitre. Nodular hyperplasia, preoperative hyperthyroidism, preoperative diagnosis of toxic nodular goitre, surgical indication for toxic goitre causing hyperthyroidism and a definitive pathological diagnosis of nodular hyperplasia were found to be associated with progression of remnant nodules after hemithyroidectomy.

There are some limitations of our current study which might have caused selection bias. We could not provide data regarding the total number of hemithyroidectomies done in all centres for any reason. This was one of the downsides of our retrospective design. Another drawback of the present study is the missing data regarding time to progression. Also, nearly 15% of the cohort were found to have undergone surgery, although they were asymptomatic. We could not determine exactly the reason for operation in detail for these patients since we admit that asymptomatic patients do not require surgical treatment.

In conclusion, according to the results of our study the progression rate after hemithyroidectomy is as high as 31%. However, the need for secondary surgical intervention is very low. Our results suggest that patients with unilateral or bilateral benign nodular goitre with asymptomatic nodules on one side can safely undergo hemithyroidectomy.

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DISCLOSURES

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ORIGINAL ARTICLE

Thromboprophylaxis for lower leg cast immobilisation and knee arthroscopy: a survey study

R.A. van Adrichem[1,2], J.P. van Oosten[1], S.C. Cannegieter[1,3], I.B. Schipper[4], R.G.H.H. Nelissen[2]*

Departments of [1]Clinical Epidemiology, [2]Orthopaedic Surgery, [3]Thrombosis and Haemostasis, [4]Trauma Surgery, Leiden University Medical Center, Leiden, the Netherlands, *corresponding author: tel.: +31(0)71-5263606, email: R.G.H.H.Nelissen@lumc.nl

ABSTRACT

Background: The effect of prophylaxis on the prevention of symptomatic venous thrombosis in patients with lower leg cast immobilisation or after knee arthroscopy is not clear. Our aim was to assess the current practice of thrombosis prophylaxis in Dutch hospitals and to determine considerations for prescribing prophylaxis.

Methods: Electronic questionnaires regarding thrombosis prophylaxis in patients with lower leg cast immobilisation or after knee arthroscopy were sent to all orthopaedic (90) and trauma surgery departments (89) and orthopaedic clinics (16) in the Netherlands.

Results: Response rate was 88% for orthopaedic surgery departments/clinics and 81% for trauma surgery departments. Analysis of the questionnaires reveals that prophylaxis was not provided for patients with lower leg cast immobilisation at only 3 (4%) orthopaedic and 3 (4%) trauma surgery departments, while 10 (11%) orthopaedic surgery departments did not provide prophylaxis for patients undergoing knee arthroscopies. Substantial differences in prophylactic strategies were observed as these strategies were dependent on both the indication for treatment and on the presence of concomitant risk factors for venous thrombosis. The most reported rationales for prescribing prophylaxis were: the perceived risk reduction of prophylaxis outweighs the bleeding risk; the experience that prophylaxis is effective; to act in accordance with hospital guidelines.

Conclusion: Despite the lack of a solid evidence base, it seems that the large majority of patients with lower leg cast immobilisations, along with those undergoing knee arthroscopy, do receive thrombosis prophylaxis. However, depending on the indications, large variations within prophylaxis strategies seem to exist, which demonstrate the need for an evidence-based uniform prophylaxis scheme.

KEYWORDS

Thrombosis prophylaxis, lower leg cast immobilisation, knee arthroscopy, survey study

INTRODUCTION

The effect of thrombosis prophylaxis on prevention of symptomatic venous thrombosis for two of the most commonly performed orthopaedic treatments world-wide (lower leg cast immobilisation and arthroscopy of the knee) is not well established.[1-14] With this survey study we aim to provide insight into the thrombosis prophylaxis policies of orthopaedic and trauma surgeons, the relevant indications, and the considerations for providing such therapy.

Venous thrombosis (i.e. deep vein thrombosis and pulmonary embolism) occurs in about 1-2 per 1000 persons per year in the general population and is a serious condition leading to chronic morbidity (e.g. post-thrombotic syndrome and pulmonary hypertension) and an increased mortality.[15-19] The risk of venous thrombosis is increased after surgery, and is particularly high after orthopaedic surgery (estimated 4% in 35 days after major orthopaedic surgery).[3,20,21] Because of this high risk, thrombosis prophylaxis is recommended for these patients.[3,4,8] However, most trials investigating patients with lower leg cast immobilisation and knee arthroscopy were underpowered, included patients at additionally high risk for venous thrombosis (i.e. complete leg cast immobilisation, ligament reconstructions), or used asymptomatic venous thrombosis as the primary endpoint.[1-14] For these reasons, most national and international guidelines advise against thrombosis prophylaxis for these patients while others recommend instead the use of prophylaxis only in patients with an increased risk for venous thrombosis (e.g. longer duration/

more extensive surgery or in patients with additional risk factors) or leave it to the clinician to decide whether to provide prophylactic treatment.[3,4,8]

Despite the lack of an evidence base and ambiguous guidelines, 70% of orthopaedic and trauma surgeons provided thrombosis prophylaxis to patients with lower leg cast immobilisation and 71% of orthopaedic surgeons did so for patients who underwent knee arthroscopy in the Netherlands in 2007.[22] The reasons behind this large-scale use of thrombosis prophylaxis are unknown.[22-24] Clinical experience suggests that the proportion of surgeons providing prophylaxis to these patients has increased since 2007. Therefore, the aim of this survey study was to obtain insight into the thrombosis prophylaxis policies and rationales of orthopaedic and trauma surgeons for patients with lower leg cast immobilisation and those undergoing arthroscopy of the knee.

MATERIALS AND METHODS

In July 2013, a digital survey (NetQuestionnaires, version 6.0, NetQuestionnaires Netherlands B.V, Utrecht, the Netherlands) was sent to all departments of orthopaedic surgery (90 hospital departments and 16 private orthopaedic clinics) and all departments of surgery (89 hospital departments*) in the Netherlands. The survey concerned thrombosis prophylaxis policy in patients with lower leg cast immobilisation and patients undergoing arthroscopy of the knee. Careful attention was put into designing unambiguous and non-leading questions and response choices.[25,26] A copy of the survey (in Dutch) is available as supplement material. A link to the survey was included in a personalised email sent on behalf of the heads of the (sub)departments of orthopaedic surgery and trauma surgery (RGHHN and IBS) of the Leiden University Medical Center. The survey was sent to one orthopaedic surgeon and one trauma surgeon for every hospital department or private clinic. Trauma surgeons were selected based on their registration as trauma surgeons and orthopaedic surgeons based on their registration as orthopaedic surgeons and/or lower extremity or knee surgeons. Surgeons who did not respond promptly were sent two reminders before another orthopaedic or trauma surgeon from the same department was contacted.[27]

For orthopaedic surgeons working in hospitals, the survey regarded the thrombosis prophylaxis policy in patients with lower leg cast immobilisation and those undergoing arthroscopies of the knee. For orthopaedic surgeons working in a private clinic, only questions regarding arthroscopy of the knee were included. Trauma surgeons were asked about the thrombosis prophylaxis policy in patients with lower leg cast immobilisation.

All data were analysed anonymously using SPSS version 20.0.0 (IBM, Armonk, New York, US). For knee arthroscopy, the results of the hospital departments and orthopaedic private clinics were combined as these results were similar. For lower leg cast immobilisation, the data were separately analysed for orthopaedic and trauma surgeons. Answers to open questions were categorised. Categorical data were expressed as proportions using percentages.

RESULTS

The survey was completed in 93 of the 106 contacted departments of orthopaedic surgery (79 hospital departments (88%) and 14 orthopaedic private clinics (88%)). Trauma surgery departments had a response rate of 81% with 72 of 89 departments completing the questionnaire. Of these departments, 69 (96%) trauma surgery and 70 (89%) orthopaedic surgery departments

Table 1. *Guidelines used as basis for department or hospital protocols*

	Lower leg cast		Knee arthroscopy
Guideline used	**Trauma surgery (n = 72), n (%)**	**Orthopaedic surgery (n = 79), n (%)**	**Orthopaedic surgery (n = 93), n (%)**
No protocol	3 (4)	9 (11)	9 (7)
Not based on a guideline*	15 (21)	12 (15)	13 (14)
CBO†/NOV‡	29 (40)	34 (43)	45 (48)
CBO†/NOV‡+ AAOS§	3 (4)	4 (5)	3 (3)
CBO†/NOV‡+ ACCP¶	3 (4)	0 (0)	2 (2)
CBO†/NOV‡+ AAOS§+ACCP¶	1 (1)	2 (3)	0 (0)
CBO†/NOV‡+ AAOS§+ACCP¶+ CDER**	0 (0)	0 (0)	1 (1)
AAOS§	1 (1)	1 (1)	2 (2)
ACCP¶	2 (3)	0 (0)	0 (0)
AAOS§+ACCP¶	0 (0)	0 (0)	1 (1)
Not known by respondent	15 (21)	17 (22)	17 (18)

***Predominantly Cochrane review regarding this subject or own review of the literature; †CBO = Centraal Begeleidings Orgaan (Dutch Institute for Healthcare Improvement); ‡NOV = Dutch Orthopaedic Society (The NOV refers to the CBO guideline for thrombosis prophylaxis in orthopaedic surgery patients); §AAOS = American Academy of Orthopaedic Surgeons; ¶ACCP = American College of Chest Physicians; **CDER = Cardiovascular Disease Education and Research Trust.**

had protocols concerning thrombosis prophylaxis in patients with lower leg cast immobilisation while 84 (90%) orthopaedic surgery departments had thrombosis prophylaxis protocols for knee arthroscopy patients. The majority of these protocols were based on the guidelines of the Dutch Institute for Healthcare Improvement (CBO) (*table 1*).

Thrombosis prophylaxis

Thrombosis prophylaxis for patients with lower leg cast immobilisation is certainly the norm with only 3 of the 72 (4%) trauma surgery departments and 3 of the 79 (4%) orthopaedic surgery departments opting against the practice. The remaining departments base the decision on whether or not to give thrombotic prophylaxis upon patients' ability to bear weight, the presence of risk factors, and type of surgical intervention (*table 2*).

Knee arthroscopy patients never receive prophylactic treatment at 10 (11%) of the 93 orthopaedic surgery departments. In departments that do provide prophylactic therapy, the decision to prescribe prophylaxis is highly dependent on the indication for knee arthroscopy (*table 3*). Further, for both indications, the decision to give prophylactic treatment is dependent on the presence of additional risk factors for venous thrombosis, the presence of risk factors for bleeding and the use of co-medications that influence the coagulation system, such as non-steroidal anti-inflammatory drugs and platelet aggregation inhibitors. Surgeons that provide prophylaxis only to patients with additional risk factors do so predominantly for the following risk factors: previous episode of venous thrombosis (22 (96%) of trauma surgeons and 61 (90%) of orthopaedic surgeons); family history of venous thrombosis or hereditary thrombophilia (18 (96%) of trauma surgeons and 45 (66%) of orthopaedic surgeons); obesity (BMI ≥30) (17 (74%) of trauma surgeons and 28 (41%) of orthopaedic surgeons); hormonal contraception use (14 (61%) of trauma surgeons and 31 (46%) of orthopaedic surgeons).

Table 3. *Thrombosis prophylaxis policies for knee arthroscopy*

	Orthopaedic surgery (n=93)		
Type of knee arthroscopy	**Always, n (%)**	**Risk factors*, n (%)**	**Never, n (%)**
Diagnostic	30 (32%)	39 (42%)	24 (26%)
Loose body removal	30 (32%)	40 (43%)	23 (25%)
(Partial) meniscectomy	30 (32%)	39 (42%)	24 (26%)
Microfracture surgery	39 (42%)	34 (37%)	20 (22%)
Meniscal suture	48 (52%)	26 (28%)	19 (20%)
ACL reconstruction	72 (77%)	11 (12%)	10 (11%)

***Thrombosis prophylaxis is only provided to patients with additional risk factors for venous thrombosis. ACL = anterior cruciate ligament.**

Type of thrombosis prophylaxis

The prophylactic treatment of choice for patients with lower leg cast immobilisation is low-molecular-weight heparin (LMWH) at 67 trauma surgery departments (97%) and 74 orthopaedic surgery departments (97%). The most commonly used LMWH is nadroparin. LMWH is used in all (83 (100%)) of the orthopaedic surgery departments providing prophylaxis with the most common choice again being nadroparin.

Duration of prophylaxis

In patients with lower leg cast immobilisations, prophylactic treatment is almost always provided for the duration of immobilisation (trauma surgery departments 66 (96%) and orthopaedic surgery departments 68 (89%)). At the other departments, prophylaxis is provided during hospital stay, for a fixed period of time, or for the period of cast immobilisation plus one week thereafter.

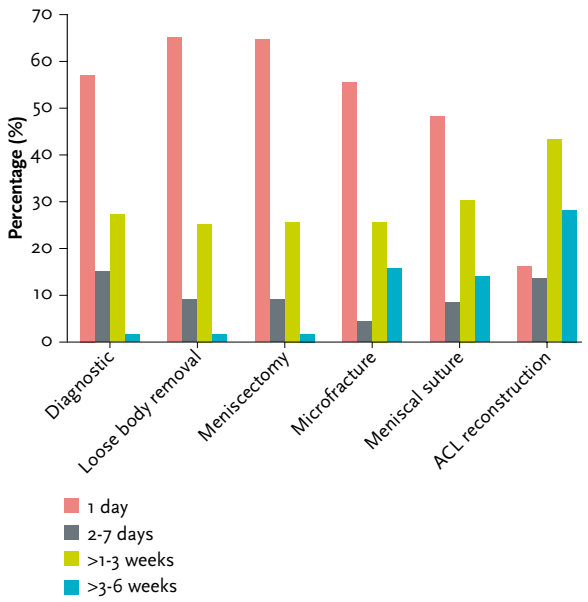
For knee arthroscopy patients the duration of prophylaxis ranges from one day to six weeks and strongly depends on the indication for the knee arthroscopy. Further, the duration of prophylactic treatment per indication varies widely between hospitals (*figure 1*).

Table 2. *Thrombosis prophylaxis policies for patients with lower leg cast immobilisation*

Type of treatment	**Always**		**Risk factors***		**Never†**	
	Trauma surgery (n = 72), n (%)	**Orthopaedic surgery (n = 79), n (%)**	**Trauma surgery (n = 72), n (%)**	**Orthopaedic surgery (n = 79), n (%)**	**Trauma surgery (n = 72), n (%)**	**Orthopaedic surgery (n = 79), n (%)**
Conservative						
• Non-weight bearing	57 (79%)	50 (63%)	11 (15%)	26 (33%)	4 (6%)	3 (4%)
• Weight bearing	52 (72%)	46 (58%)	14 (19%)	27 (34%)	6 (8%)	6 (8%)
Surgical						
• Non-weight bearing	51 (71%)	63 (80%)	17 (24%)	13 (16%)	4 (6%)	3 (4%)
• Weight bearing	54 (75%)	56 (71%)	13 18%)	18 (23%)	5 (7%)	5 (6%)

***Thrombosis prophylaxis is only provided to patients with additional risk factors for venous thrombosis; †On 3 (4%) trauma surgery and 3 (4%) orthopaedic surgery departments thrombosis prophylaxis is never provided to patients, irrespective of the indication of cast immobilisation.**

Figure 1. *Duration of thrombosis prophylaxis for different types of knee arthroscopies*



The graph shows the percentages of orthopaedic surgeons that provide thrombosis prophylaxis for 1 day, 2-7 days, >1- 3 weeks or >3-6 weeks for different types of knee arthroscopies. ACL = anterior cruciate ligament.

Reasons for thrombosis prophylaxis

Rationales for the prescribing of prophylactic therapy include the assumption that the reduction in risk of thrombosis outweighs the associated increased bleeding risk, that some individual clinical experience suggests prophylaxis is effective, and that clinicians are acting in accordance with their department or hospital protocol (*table 4*).

Choice for type of thrombosis prophylaxis

The most prevalent reason for LMWH as prophylactic treatment of choice in patients with lower leg cast immobilisation is that this action is in accordance with hospital or department protocol in 54 trauma surgery (81%) and 57 orthopaedic surgery departments (77%). In addition, in 28 trauma surgery (42%) and 29 orthopaedic surgery departments LMWH is considered the safest prophylactic treatment, in 19 (28%) trauma surgery and 29 (39%) orthopaedic surgery departments it is preferred because of extensive clinical experience and in 15 trauma surgery (22%) and 14 orthopaedic surgery departments (19%) it is considered to be the most effective prophylactic treatment. The rationales for the preference for LMWH as prophylactic treatment prior to knee arthroscopies are varied. The use of LMWHs is in accordance with the department or hospital protocol at 49 (59%) departments; LMWHs are considered the safest option at 47 (57%) departments; LMWHs are considered to be the most effective option at 28 (34%) departments and at 25 departments (30%) LMWHs are preferred because of extensive clinical experience with this type of anticoagulants.

DISCUSSION

In this survey study, we were able to give a detailed overview of current thrombosis prophylaxis policies in the Netherlands for patients with lower leg cast immobilisation and for patients who had a knee arthroscopy. Despite insufficient evidence on the effect of prophylaxis on the prevention of symptomatic events and on its cost-effectiveness, prophylaxis seems to be prescribed in the large majority of clinical practices. Further, substantial differences exist in prophylactic strategies between departments depending on the indication for below-knee cast immobilisation or knee arthroscopy and on the presence of additional risk factors for venous thrombosis. The most important reasons for providing prophylactic treatment as indicated by respondents were the assumption that the risk reduction for thrombosis outweighs the bleeding risk; that clinicians have the experience that prophylaxis is effective; and that clinicians

Table 4. *Reasons for providing thrombosis prophylaxis*

	Lower leg cast	Knee arthroscopy	
Reason	**Trauma surgery (n = 72), n (%)**	**Orthopaedic surgery (n = 79), n (%)**	**Orthopaedic surgery (n = 93), n (%)**
Prophylaxis	**69 (96%)**	**76 (96%)**	**83 (89%)**
• Reduced thrombosis risk outweighs bleeding risk	45 (65%)	49 (64%)	30 (36%)
• Clinical experience shows prophylaxis is effective	17 (25%)	19 (25%)	9 (11%)
• Negative experience without prophylaxis	0 (0%)	1 (1%)	3 (4%)
• Risk of complications of prophylaxis considered very small	0 (0%)	0 (0%)	2 (2%)
• Act in accordance with hospital or department protocol	52 (75%)	54 (71%)	48 (58%)
No prophylaxis	**3 (4%)**	**3 (4%)**	**10 (11%)**
• No clear scientific evidence for efficacy	2 (67%)	3 (100%)	7 (70%)
• Clinical experience shows prophylaxis is not effective	0 (0%)	0 (0%)	2 (20%)
• Act in accordance with hospital or department protocol	2 (67%)	2 (67%)	6 (60%)

act in accordance with department or hospital protocol by providing prophylaxis.

In trials regarding thrombosis prophylaxis in patients with below knee cast immobilisation or undergoing knee arthroscopy, asymptomatic venous thrombosis has generally been used as a primary endpoint. The incidences of these events in the trials' control groups varied between 0-15.6% for knee arthroscopy (follow-up 1 week to 3 months) and between 4.3-36% during 4-6 weeks of cast immobilisation.[1,2,5-7,9-14] However, these trials were underpowered to draw conclusions on the prevention of symptomatic venous thrombosis as the risks of these events were much lower (between 0-2.5% for knee arthroscopy and 0-5.5% for cast immobilisation).[3,4,8] The risks of these symptomatic events are further not representative for below knee cast immobilisations and regular knee arthroscopies because of the inclusion of patients with more extensive trauma or surgery (complete leg cast and ligament reconstructions) for whom the expected risk of venous thrombosis is higher.[28-32] Because of this, a balance between the benefit (prevention of symptomatic events) and risk of complications, such as bleeding events, cannot be established here.

This lack of evidence is reflected in the variation among guideline recommendations. The guideline of the American College of Chest Physicians recommends no prophylaxis while the guideline of the National Institute for Clinical Excellence (United Kingdom) recommends considering prophylaxis in the presence of additional risk factors.[3,4] Further, the guideline of the CBO gives no definite recommendation for patients with lower leg cast immobilisation. For knee arthroscopy in general it recommends no prophylaxis; however, for reconstructive surgery or in patients with additional risk factors prophylaxis can be considered.[8] Considering that the majority of department protocols are based on the CBO guideline, the variation in treatment strategies in the Netherlands may be explained by the fact that these guidelines can be interpreted in several ways, which is again due to the lack of evidence in the literature.

In comparison with previous survey studies, there seems to be a further increase in the use of thrombosis prophylaxis. For lower leg cast immobilisation, the proportion of departments where prophylaxis is never prescribed further decreased from 50% in 2002 and 30% in 2007 to only 4% in 2013.[22-24] For knee arthroscopy the proportion of departments that never use prophylaxis decreased from 40% in 2002 and 48% in 2007 to 11% in 2013.[22,23] In addition, there are international differences. For example, in the United Kingdom in 2010, only 16% of the orthopaedic surgery departments routinely provided prophylaxis to patients with lower leg plaster casts.[33] In Italy, as early as 2004, 94% of orthopaedic surgery departments were providing thrombosis prophylaxis for knee arthroscopy.[34]

When interpreting our results, some limitations need to be taken into account. In this study, we assessed the prophylaxis policies at department but not at the individual physician level. The response of the single individual surgeon does not necessarily represent that of the department. However, the vast majority of orthopaedic surgery departments (89% for lower leg cast immobilisation and 90% for knee arthroscopy) and trauma surgery department (96%) have a protocol regarding thrombosis prophylaxis in these patients. We expect that any variation within departments will therefore be small. Furthermore, the response rate of our study is not 100%. However, our response rates of 81% and 88% are still high and well above the 70% needed to limit non-response bias.[35,36] In addition, a non-validated survey was used. Furthermore, as in most survey studies, there is a risk of the respondent answering what he or she feels is appropriate rather than true. Because of this, particular attention was put into the design of non-leading and unambiguous questions and answer options.[25,26]

While we can only speculate about possible explanations for the recent further increase in the use of thrombosis prophylaxis, it could be that defensive medicine has become more predominant over evidence-based medicine. However, the large-scale use of thrombosis prophylaxis without a proper scientific basis for a beneficial effect may have medico-legal implications for involved clinicians, especially when (bleeding) complications occur. Although the bleeding risk with LMWH is perceived to be low, the absolute number of bleeding events can be high since both knee arthroscopy and lower leg cast immobilisations are frequently performed procedures.

Our results indicate that there is a clear need for high-quality research on this topic. Uniform evidence-based prophylactic treatment across hospitals is needed in order to improve the quality of care of patients. Instead of focusing on asymptomatic venous thrombosis, the primary endpoint of new studies should be symptomatic venous thrombosis.[3,30] In addition, complications of prophylactic therapy, such as bleeds, need to be taken into account in order to establish a benefit-risk ratio. As for cast immobilisations, only patients with lower leg cast immobilisations should be included while for knee arthroscopy there is a need for trials with better stratification in terms of arthroscopy type.[30] Further, identification of high-risk groups is needed, which can lead to individualised prophylactic therapy in order to optimise the benefits and risks from anticoagulant therapy.[3]

CONCLUSION

Based on this questionnaire study it seems that thrombosis prophylaxis is given to patients with lower leg cast immobilisation and around knee arthroscopies

at the large majority of orthopaedic and trauma surgery departments in the Netherlands, despite insufficient evidence for a beneficial effect. In addition, large variations in prophylaxis strategies appear to exist between departments for different types of indications for lower leg cast immobilisation and arthroscopy of the knee. Uniform prophylactic treatment across hospitals, based on good quality evidence, is needed to improve the quality of care of these patients.

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ORIGINAL ARTICLE

Dysphagia, malnutrition and gastrointestinal problems in patients with mitochondrial disease caused by the m3243A>G mutation

P. de Laat[1#], H.E.E. Zweers[2*#], S. Knuijt[3], J.A.M. Smeitink[1], G.J.A. Wanten[2], M.C.H. Janssen[1,4]

[1]Department of Pediatrics, Nijmegen Centre for Mitochondrial Disorders, Departments of [2]Gastroenterology and Hepatology, [3]Rehabilitation/Speech Pathology, [4]Internal Medicine, Radboudumc, Nijmegen, the Netherlands, *corresponding author: tel.: +31(0)24-3619190, email: Heidi.Zweers-vanEssen@radboudumc.nl, [#]Both authors contributed equally

ABSTRACT

Background: Previous research has shown that dysphagia and gastrointestinal problems occur frequently in carriers of the m.3243A>G mutation; however, the exact frequency and severity have not been determined. We hypothesise that adult carriers have an increased risk for malnutrition.
Methods: In this observational study we evaluated the presence of gastrointestinal problems and dysphagia in 92 carriers of the m.3243A>G mutation. The severity of the general disease involvement was classified using the Newcastle Mitochondrial Disease Adult Scale (NMDAS). Gastrointestinal involvement, dysphagia and the risk for malnutrition were scored using the Gastrointestinal Symptoms Questionnaire and the Malnutrition Universal Screening Tool. Gastrointestinal symptoms and anthropometrics were compared with healthy controls.
Results: Our results show that the height, weight and body mass index (BMI) of these carriers were lower than the national average ($p < 0.05$). Seventy-nine carriers (86%) suffered from at least one gastrointestinal symptom, mainly flatulence or hard stools. Both frequency and severity of symptoms were significantly increased compared with reference data of healthy Dutch adults. Of the carriers, 45% reported (mostly mild) dysphagia. Solid foods cause more problems than liquids. A negative correlation between BMI and heteroplasmy levels in urinary epithelial cells (UEC) was present (Spearman correlation coefficient = - 0.319, $p = 0.003$).
Conclusion: Dysphagia and gastrointestinal problems, especially constipation, are common symptoms in the total m.3243A>G carriers cohort and are not related to heteroplasmy levels in UEC or disease severity. The severity of gastrointestinal problems as well as overall disease severity is associated with an increased risk for malnutrition.

KEYWORDS

Dysphagia, gastrointestinal problems, malnutrition, maternally inherited diabetes and deafness (MIDD), MELAS, m.3243A>G mutation, mitochondrial medicine

INTRODUCTION

Mitochondria and the m.3243A>G mutation

Mitochondrial diseases are the most prevalent inherited metabolic diseases, with an incidence of approximately 1:5000 live births.[1] Mitochondria are the cellular organelles responsible for oxidative phosphorylation, which produces energy in the form of adenosine triphosphate. This process is accomplished by the four complexes (complex I-IV) of the respiratory chain and F_1-F_o ATP synthase. Mitochondrial dysfunction can result from mutations in either nuclear DNA (nDNA) or mitochondrial DNA (mtDNA).
The acronym MELAS was first used by Pavlakis and Phillips[2] to describe a group of patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. In 1990 the m.3243A>G mutation was found as the molecular basis of this disease.[3,4] The mutation is located in the *MT-TL1* gene and is the most common pathogenic mitochondrial mutation,[5-7] commonly described as the MELAS mutation. The phenotype maternally inherited diabetes deafness (MIDD) is also caused by this same mutation and is much more frequent.[8] Other phenotypic expressions of the m.3243A>G mutation include hypertrophic cardiomyopathy,[9] retinal dystrophy,[10] focal segmental glomerulosclerosis,[11] myoclonic epilepsy with ragged-red fibres[12] and oligo-symptomatic variants of the acronym MELAS.[13,14] The percentage of affected mitochondria per cell in a specific tissue is referred

to as heteroplasmy, and the level of heteroplasmy may vary widely between tissues of a single individual. This marked intra-individual and inter-individual variation in mitochondrial heteroplasmy partially explains why there is a wide spectrum of diseases and disease severity observed between family members that carry the same mitochondrial mutation. Previous studies have shown that urinary epithelial cells (UEC) are the best non-invasively available tissue to test the level of heteroplasmy of the m.3243A>G mutation.[15,16]

Gastrointestinal involvement in m.3243A>G carriers

Dysphagia and gastrointestinal problems occur frequently in mitochondrial patients, including patients carrying the m.3243A>G mutation.[17-19] However, the exact frequency and severity of these symptoms have not been determined. In a population study of carriers of the m.3243A>G mutation, 61% of the subjects had gastrointestinal problems. These were, after hearing loss, the most frequently reported symptoms of the m.3243A>G mutation using the Newcastle Mitochondrial Disease Adult Scale (NMDAS).[20] The NMDAS is, however, not a specific instrument to study gastrointestinal problems.

Previously, in a small cohort of MIDD patients, a high prevalence of constipation and/or diarrhoea (88%) was found.[21] Severe gastrointestinal problems such as the pseudo-obstruction syndrome, surgery-requiring constipation and pancreatitis have been described in patients carrying the m.3243A>G mutation, although the incidence in these patients remains unclear.[18,21] Gastrointestinal problems are frequently reported in healthy controls as well,[22] and so far studies comparing the frequency and severity of gastrointestinal problems in patients with a mitochondrial disease and healthy controls are lacking.

Dysphagia in mitochondrial disease has been described in several studies which are hard to compare because of variations in definitions and study methods. In patients with the m.3243A>G mutation, incidences vary from 18% in a study using the NMDAS to score dysphagia to 38% in a study performed using a more specific approach.[23,24] Also, short stature and lower bodyweight are frequently described in mitochondrial disease. Patients with an MIDD phenotype have a lower body mass index (BMI, weight(kg)^2/height(m)) compared with other diabetic patients.[25,27]

For both dysphagia and gastrointestinal problems a relation with lower body weight and risk for malnutrition in patients with a mitochondrial disease has been suggested but never proven.[18,21] The present study therefore focused on dysphagia and gastrointestinal problems in a cohort of carriers of the m.3243A>G mutation and identification of symptoms that lead to decreased BMI and increased risk for malnutrition.

MATERIALS AND METHODS

Patients

At the Nijmegen Center for Mitochondrial Disorders (www.ncmd.nl) at Radboud university medical center, 114 adult carriers of the m.3243A>G mutation participated in our cohort study.[24] All participants received the questionnaire. This study was approved by the ethics committee of the Nijmegen-Arnhem region. Written informed consent according to the Helsinki agreement was obtained from all carriers.

General symptoms

All carriers were scored using the NMDAS.[28] The NMDAS constitutes a validated method to monitor the clinical expression of mitochondrial disease and to follow up the course of disease over time. The NMDAS consists of the following four sections: 1) Current function, which gives insight into the general functioning of patients in the past four weeks, including swallowing; 2) System-specific involvement, which uses a clinical history supplemented by specific information to gain insight into the functioning of individual organ systems including gastrointestinal symptoms; 3) Current clinical assessment, i.e. a general and neurological clinical examination, which gives insight into the current functional status of the patient; 4) For quality of life, we used a Dutch translation of the SF-12v2 quality of life test.

Gastrointestinal symptoms evaluation

All participants received the Gastrointestinal Symptoms Questionnaire.[29,30] This self-report questionnaire contains 16 items regarding gastrointestinal involvement of disease for the past four weeks. Severity of the symptoms is scored on a 7-point Likert scale, where 0 indicates no symptoms and 6 indicates extreme symptoms. The final question of the questionnaire is a 50-point scale asking about the overall burden of the gastrointestinal symptoms. We added specific questions on dysphagia and frequency of stools. The validated Malnutrition Universal Screening Tool (MUST)[31] was used to collect the self-reported anthropometric data and to screen for the risk for malnutrition. We compared the data to age-matched anthropometric data from the Dutch Central Bureau of Statistics (CBS) 2011 (n = 2034) and to a Dutch reference database from the Gastrointestinal Symptoms Questionnaire (n = 1616). Data collection for this reference database was done in 2006, participants who matched the general Dutch population were selected with CBS statistics.[22]

Mutation analysis

Heteroplasmy levels of the m3243A>G mutation were determined in UEC in all participants using

Pyrosequencing™ technology (Pyrosequencing, Uppsala, Sweden) as described earlier.[11] The pyrosequence reaction of the m.3234A>G mutation had a precision of 1.5%, and the mutation was detected from a heteroplasmy level of 5%. The detection limit for the mutation was determined by serial dilution of a sample containing this mutation with wild type mtDNA.

Statistics

We used descriptive statistics to present the heteroplasmy levels in our patients. Means (±SD) are presented with their standard deviation. The independent samples T-test was used to calculate the significance of the different variables in relation to BMI and gastrointestinal symptoms. We corrected for multiple testing using the Bonferroni test. The Pearson correlation coefficient was used to evaluate the relationship between severity of gastrointestinal problems, and BMI. The Spearman correlation coefficient was used to evaluate the relationship between heteroplasmy in UEC, gastrointestinal problems, and BMI. We used the Pearson chi-square to compare BMI category for males and females and carriers with healthy controls.

RESULTS

General patient characteristics and anthropometrics

Data were collected from September to November 2011. From the 114 questionnaires that were sent out, 92 were returned (81% response rate). Of these 92 patients 68% (n = 63) were female. Mean age was 45 years (±14.3). In the Gastrointestinal Symptoms Questionnaire database mean age was 52.3 ± 17.2, 66% (n = 1067) were female.

Mean NMDAS score was 15.7 (±10.9), range 0-56, and average heteroplasmy level in UEC was 50% (range 5-98%). Thirty-eight patients (41%) were diagnosed with diabetes, of whom 22 (24%) used insulin. Hearing loss was reported by 59 patients (64%), 27 patients (29%) had a hearing aid. Six patients (6.5%) had severe neurological symptoms, of which five (5.4%) suffered from epilepsy and two (2.2%) had had stroke-like episodes in the past year.

Female carriers were 2.7 cm shorter (average 164.8 cm vs. 167.5 in healthy, p = 0.004) than healthy controls; in male carriers there was no significant difference between carriers and healthy controls (average 178.4 m vs. 180.9 in healthy controls, p = 0.099) (*table 1*). Male subjects weighed 8.2 kg less than controls (75.8 vs. 84 kg, p = 0.002) and females weighed 4.8 kg less (65.2 vs. 70 kg, p = 0.005).

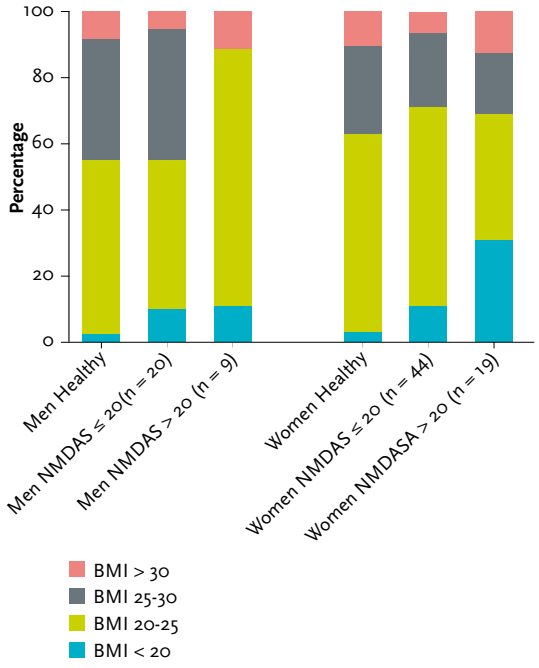
Carriers had a significantly lower frequency of overweight (BMI > 25 kg/m²) or obesity (BMI> 30 kg/m²) (32%) compared with the average Dutch population (48%) (*figure 1*). They were significantly more frequently underweight (BMI < 20 kg/m²) than the average Dutch

Table 1. *Anthropometrics in male and female m.3243 A>G carriers and healthy 40 to 50-year-old Dutch controls*

	m.3243A>G	Healthy	P value
Height men (cm)	178.4 (± 6.9)	180.9 (± 7.9)	0.1
Height women (cm)	164.8 (± 8.3)	167.5 (± 7.1)	0.004*
Weight men (kg)	75.8 (± 12.8)	84 (± 12.8)	0.002*
Weight women (kg)	65.2 (± 17.7)	70 (± 12.8)	0.005*
BMI men (kg/m²)	23.8 (± 3.6)	25.6 (± 5.4)	0.08
BMI women (kg/m²)	23.9 (± 6)	24.6 (± 8.4)	0.5
BMI category			0.00*
Overweight or obesity: BMI >25 n (%) men	11 (37)	588 (59.9)	
Overweight or obesity: BMI >25 n (%) women	19 (30)	444 (42.2)	
Healthy weight: BMI 20-25 n (%) men	16 (53)	391 (39.9)	
Healthy weight: BMI 20-25 n (%) women	34 (54)	595 (56.5)	
Low BMI < 20 n (%) men	3 (10)	2 (0.2)	
Low BMI < 20 n (%) women	10 (16)	14 (1.3)	

***p = <0.05. BMI = body mass index.**

Figure 1. *Body mass index in male and female m.3243A>G carriers and healthy Dutch controls*



population: 14 vs. 2%. Of the women with a NMDAS score above 20, 31% were underweight. Carriers with BMI < 20 kg/m² had a significantly higher NMDAS (p = 0.01). A negative correlation between BMI and heteroplasmy levels in UEC was present in carriers of the m.3243A>G mutation (Spearman correlation coefficient = - 0.319, p = 0.003). Of the carriers, 19% (n = 17) had a MUST score of 1 or 2: average (12%) to high (7%) risk for malnutrition. In 14 carriers this score was based on their low BMI. Of the other three carriers with a risk for malnutrition, two had a healthy weight and one was overweight; their MUST scores were based on more than 5% loss of bodyweight in the last six months.

The majority of carriers (81%) had a MUST score of zero: no risk of malnutrition. Five percent of the m.3243A>G carriers used medical feeding supplements; no patients were dependent on tube feeding.

Gastrointestinal symptoms

In the four weeks prior to answering the questionnaire, 79 carriers (86%) suffered from at least one gastrointestinal symptom. Nearly all gastrointestinal symptoms had a higher frequency and increased severity in carriers of the m.3243A>G mutation compared with the average Dutch population (*figure 3*). The most frequent problems were bloating, hard stools and flatulence. Nausea and diarrhoea and alternately solid or loose stools were also common but there was no significant difference to the controls for these symptoms.

Hard stools or constipation were reported by 48% and 38% of the carriers, respectively, whereas controls only reported these symptoms in 22% and 14%, respectively (p < 0.001). Fourteen percent of the patients used laxatives and 44% had a stool frequency of less than once a day.

Overall, 69% of the carriers of the m.3243A>G mutation reported one or more constipation-related symptom (use of laxatives, stool frequency of < 1 time a day, hard stools and/or self-reported constipation).

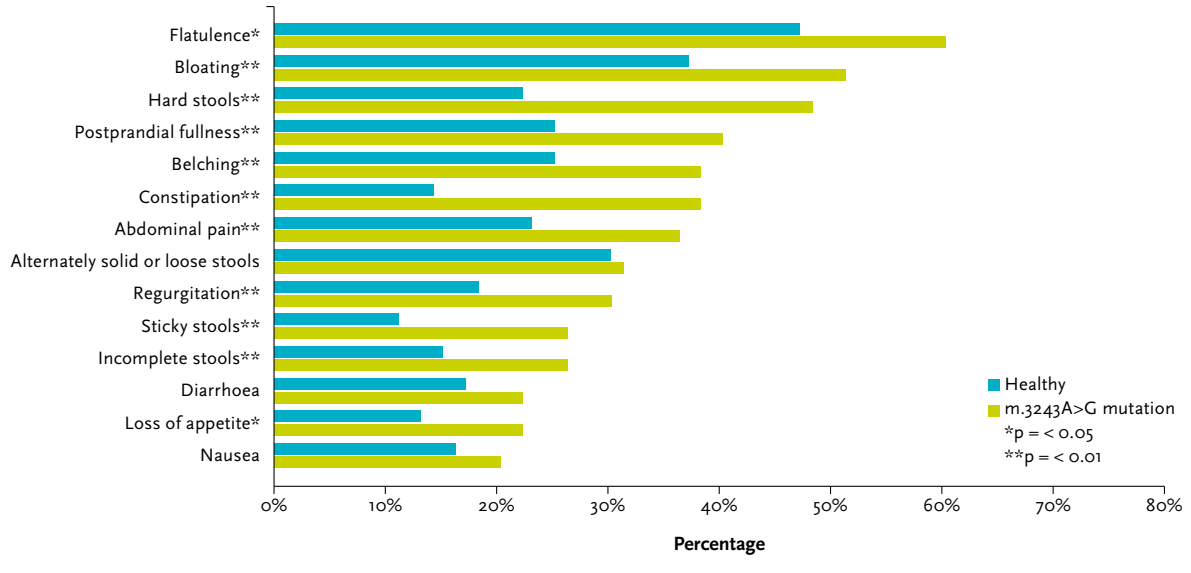
Mean severity score of gastrointestinal problems was 10.7 (± 11.9), range 0-50. Carriers with a BMI <20 (n = 13) (p = 0.028) and female carriers (p = 0.009) had a significantly higher severity score of gastrointestinal symptoms. Patients with postprandial fullness (p = 0.045) or vomiting (p = 0.048), had a significantly lower BMI compared with carriers without this specific symptom. Severity of gastrointestinal problems was not clinically relevantly related to BMI (correlation coefficient -0.152, p = 0.013)

The gastrointestinal symptoms that were most frequently reported as severe (5, 6 or 7 on the 7-point Likert scale) were: hard stools (14%), constipation (11%), flatulence (11%) and bloating (10%). All of these symptoms were significantly more frequently scored as severe by carriers compared with controls. Also significantly more frequently scored as severe were regurgitation (8%), postprandial fullness (9%), belching (10%), dysphagia for solids (2%), incomplete stools (8%) and sticky stools (7%).

One patient in this cohort had a pancreatitis in the past, two patients needed surgery for severe constipation.

There was no correlation between heteroplasmy levels in UEC and gastrointestinal symptoms. Frequently reported symptoms in patients carrying the m.3243A>G mutation are myopathy and diabetes. The presence and severity of these symptoms had no significant relation to the gastrointestinal problems.

Figure 2. *Gastrointestinal symptoms in m.3243 A>G carriers and healthy Dutch controls*

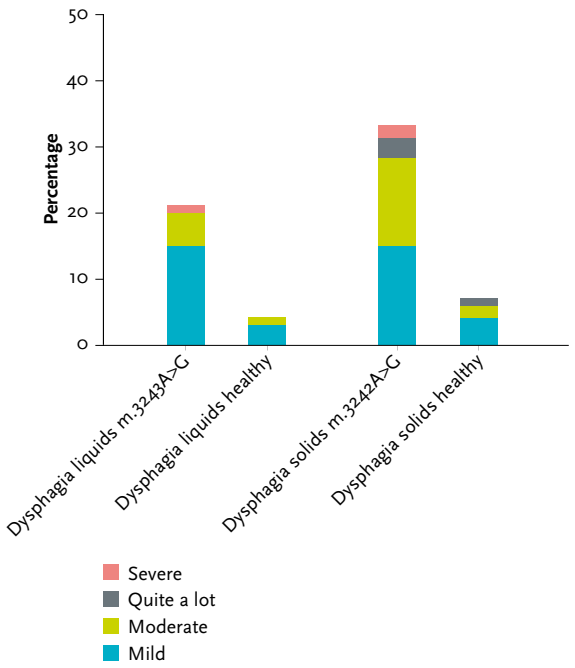


Dysphagia

In this study 21% of m.3243A>G carriers had trouble swallowing, as scored by the physician who performed the NMDAS. When we specifically asked for all sub-items of the NMDAS swallowing score in the questionnaire, this frequency was much higher: 45%. Using the Gastrointestinal Symptoms Questionnaire, dysphagia seems to be a frequent problem (33%), but the severity was not very high (*figure 3*). Liquids are less of a problem compared with solids; the difference with controls was significant both in the carriers who have trouble with liquids ($p = 0.008$) as with solids ($p < 0.001$).

No significant differences in BMI were present in carriers reporting dysphagia compared with carriers without dysphagia. In six carriers with more severe complaints of trouble with swallowing liquids there was a significant difference in BMI: whereas carriers without trouble swallowing liquids had an average BMI of 24.1 (±5.5), carriers with such problems had an average BMI of 20.7 (±3.1) ($p = 0.046$).

Figure 3. *Dysphagia in solids and liquids in m.3243 A>G carriers and healthy Dutch controls*



DISCUSSION

As there currently is no cure for mitochondrial disease,[32] optimising nutrition and treating major symptoms such as constipation may be one of the few methods to improve quality of life. Because gastrointestinal symptoms are very common in these carriers as well as in the general population, and these often have a non-specific character, there may be a considerable risk for under-diagnosis of these possibly treatable problems.

The present study shows for the first time in a robust cohort that dysphagia and gastrointestinal problems, and more specifically constipation, are very common in carriers of the m.3243A>G mutation. These symptoms are common in the total patient cohort and are not related to heteroplasmy levels in UEC, disease severity or the presence of diabetes.

The severity of gastrointestinal problems as well as the overall disease severity and heteroplasmy levels in UEC are associated with a decreased BMI and an increased risk for the development of malnutrition. Strong points of this investigation include the high number of enrolled carriers with a homogeneous genetic background, despite the low incidence of this disease. Also, the high response rate renders these data highly relevant for the guidance and treatment of these carriers.

The high frequency of gastrointestinal problems has been previously described.[17,18,21] We compared our cohort of 92 carriers of the m.3243A>G mutation with a cohort of 1627 healthy Dutch controls to identify those gastrointestinal problems that are specifically more frequent in carriers of the m.3243A>G mutation. Our study shows that motility problems of the bowel are probably the most frequent symptom: for instance, constipation was found in 69% of carriers of the m.3243A>G, i.e. much higher than in healthy controls.

Patients presented with a range of underlying gastrointestinal problems. Some were diagnosed with irritable bowel syndrome (IBS) prior to the mitochondrial diagnosis which does not seen surprising given the diversity of symptoms. Although nausea, diarrhoea and alternately solid or loose stools are common in this cohort, similar symptoms occur just as frequently in the control population, and do not seem to be specific for the m.3243A>G mutation, yet remain potentially treatable.

We show in this study that severe gastrointestinal symptoms increase the risk for malnutrition in carriers of the m.3243A>G mutation. Fourteen percent of carriers had a BMI of <20 kg/m² and in more severely affected patients (NDMAS >20) even up to 31% had a BMI of <20 kg/m². There was no relevant correlation between gastrointestinal problems and BMI, indicating that probably several other confounders such as depression or fatigue may contribute to the risk of malnutrition. Screening for malnutrition or gastrointestinal symptoms can lead to early detection, and hence early treatment of these problems. Since malnutrition has been related to secondary mitochondrial dysfunction and may worsen outcomes,[33-35] as in other disease,[36,37] this remains a major concern in these patients.

Dysphagia may well be more common than both doctors and patients realise. In a non-specific questionnaire for swallowing problems (as included in the NMDAS), a low prevalence of dysphagia was reported. For instance, in our previous study we reported an 18% incidence of dysphagia in a cohort of m.3243A>G carriers.[24] In a partly overlapping cohort we now found that 45% of patients suffered from dysphagia using a more specific questionnaire based on the NMDAS.

A patient-reported incidence of dysphagia of 33% was found using the Gastrointestinal Symptoms Questionnaire. These differences in reported incidences of dysphagia show that the method to diagnose dysphagia is instrumental when assessing its incidence and suggests that the NMDAS underestimates this problem.

Dysphagia usually develops slowly and is not severe in most patients, and patients may therefore adapt their eating pattern sufficiently. This notion might also explain why no differences in BMI between patients with mild dysphagia and without dysphagia were found. As with other neuromuscular disorders, solid foods seem to cause more problems than liquids.[38] Muscle weakness is the most likely cause for dysphagia in this patient group and demands a different treatment strategy than dysphagia from other causes.[19,38] For example, in dysphagia due to cerebral damage, it is very common to prescribe thickened drinks which will aggravate dysphagia in mitochondrial patients and will take more energy to consume.

In this study we used low BMI as a marker for malnutrition, because it is an easily available variable suitable for comparison with healthy controls and for statistical analyses. BMI, however, is not a validated variable for malnutrition in neuromuscular disorders and it is known that patients with normal BMI could suffer from low fat-free mass which is also an important marker for malnutrition. In future studies we would like to recommend to use body composition as an additional marker.

In conclusion, gastrointestinal problems and dysphagia are common in carriers of the m.3243A>G mutation. The severity of the gastrointestinal problems as well as the overall disease severity is associated with an increased risk for the development of malnutrition. The common disease scores used to identify severity of disease in mitochondrial patients are insufficient to recognise these gastrointestinal symptoms. Healthcare professionals treating patients with the m.3243A>G mutation should be aware of this high prevalence and should therefore actively ask about gastrointestinal symptoms to ensure a timely treatment of these problems.

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DISCLOSURES

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CASE REPORT

Cutaneous hyperpigmentation induced by doxycycline: a case series

S.P. Keijmel[1,2,*], M.E.E. van Kasteren[5], W.A.M. Blokx[4], J.W.M. van der Meer[1,2], M. van Rossum[3], C.P. Bleeker-Rovers[1,2]

[1]Radboud Expert Centre for Q fever, Departments of [2]Internal Medicine, Division of Infectious Diseases, [3]Dermatology, [4]Pathology, Radboudumc, Nijmegen, the Netherlands, [5]Department of Internal Medicine, St. Elisabeth Hospital, Tilburg, the Netherlands, *corresponding author: tel.: +31(0)24-3618819, fax: +31(0)24-3541734, email: Stephan.Keijmel@radboudumc.nl

ABSTRACT

Cutaneous hyperpigmentation is a well-known side effect of tetracyclines, but doxycycline-induced cutaneous hyperpigmentation has only been described in one patient with a therapeutic dosage of doxycycline, and in one patient using suprapharmacological doses. We describe four patients with cutaneous hyperpigmentation in previously unaffected skin, and speculate that this was due to treatment with doxycycline in therapeutic doses. After cessation of therapy, the hyperpigmentation diminished in all four patients, illustrating the need for recognition and timely cessation of therapy.

What was known on this topic?
Cutaneous hyperpigmentation induced by doxycycline is a very uncommon side effect.

What does this add?
Cutaneous hyperpigmentation is a potential side effect of doxycycline. Awareness and recognition of this reversible or partially reversible side effect of this widespread prescribed antibiotic is necessary in order to discontinue therapy in time.

KEYWORDS

Cutaneous, doxycycline, hyperpigmentation, side effect, skin

INTRODUCTION

Well-known side effects of doxycycline are photosensitivity, teeth discolouration, nausea, vomiting, and diarrhoea. Cutaneous hyperpigmentation is a common side effect of minocycline and, to a lesser extent, of other tetracyclines, with only one report of a patient with progressive, symmetric blue-grey periocular discolouration due to three years of treatment with therapeutic doses of doxycycline.[1] Furthermore, hyperpigmentation has been described in one patient with self-induced intoxication by doxycycline (1 gm/day) for 12 years.[2] Both brown discolouration of the fingernails and discolouration of acne scars have been described after a short course of doxycycline.[3,4] We report four patients who received long-term treatment with doxycycline and hydroxychloroquine because of either chronic Q-fever or Whipple's disease. They showed extensive cutaneous hyperpigmentation in previously unaffected skin, probably induced by doxycycline.

CASE DESCRIPTIONS

Case 1

A 75-year-old man with an abdominal aneurysm, immunosuppressive therapy because of rheumatoid arthritis and a known valvulopathy was diagnosed with chronic Q-fever. Doxycycline 200 mg/day was initiated, in addition to hydroxychloroquine 400 mg/day, which he had already been taking for more than five years because of rheumatoid arthritis. After four months, doxycycline 300 mg/day was introduced because of persistently low doxycycline levels. Eight months after the start of therapy, progressive bluish-purple to black cutaneous hyperpigmentation of his lower arms, back of his hands, and interdigital areas

(*figure 1A*) developed since increasing the doxycycline dose (serum concentrations of 5.8 µg/ml). The doxycycline was stopped and hydroxychloroquine was continued. The hyperpigmentation slowly diminished, but 12 months later dark bluish-grey macules were still visible on the back of his hands and his lower arms (*figure 1B*).

Case 2

A 72-year-old man, diagnosed with relapse of Whipple's disease, was treated with ceftriaxone for four weeks, followed by doxycycline 200 mg/day and hydroxychloroquine 600 mg/day. Eight months later, increasing black discolouration on the back of both hands was seen (doxycycline serum concentrations of 5.7 µg/ml) (*figure 2A*). Therapy was stopped, and co-trimoxazole was reintroduced. Ten months later his cutaneous hyperpigmentation was slowly fading (*figure 2B*).

Figure 1. *A 75-year-old man with chronic Q-fever, with a progressive bluish-purple to black cutaneous hyperpigmentation of his lower arms, back of his hands, and interdigital area, during therapy with doxycycline (A). Twelve months after stopping doxycycline, the cutaneous hyperpigmentation had diminished. However, dark bluish-grey macules were still visible (B). No fluorescent signal of the hyperpigmentation was obtained using Wood's light, 12 months after cessation of therapy (C).*

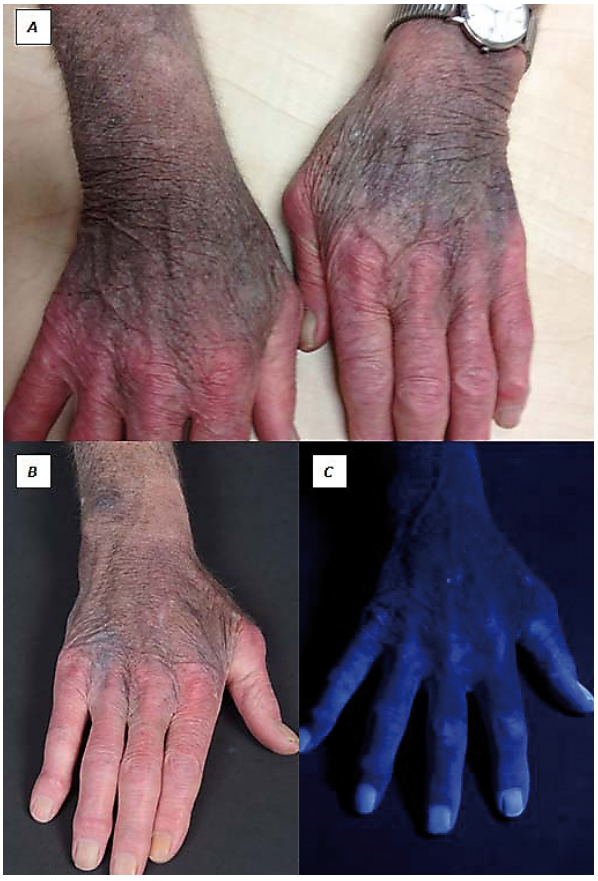
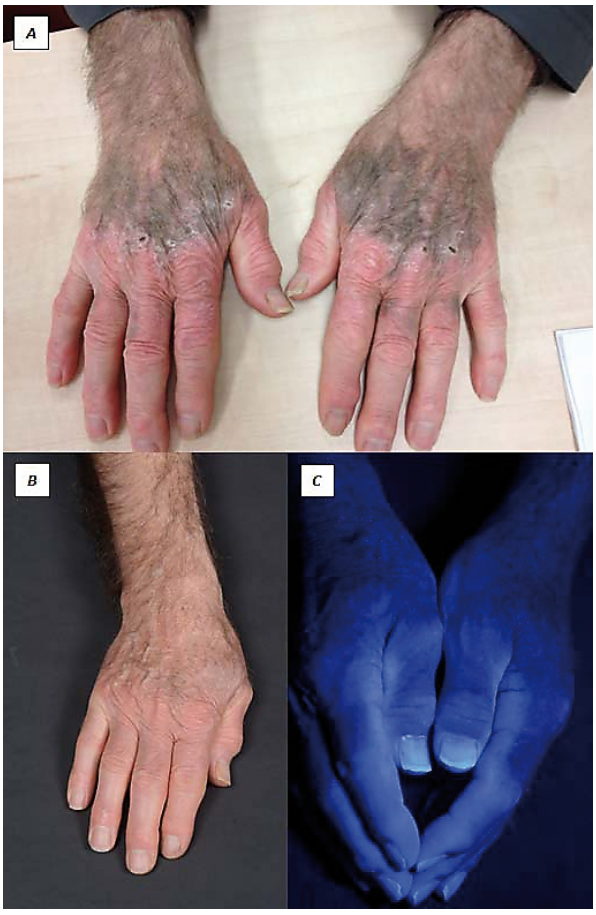


Figure 2. *A 72-year old man, with Whipple's disease, presented with black discolouration on the back of his hands during therapy with doxycycline and hydroxychloroquine (A). Ten months after discontinuation of therapy, the cutaneous hyperpigmentation was significantly reduced, but confluating grey-brown-bluish macules were still visible (B). Wood's light investigation showed no fluorescent signal, ten months after cessation of therapy (C).*



Case 3

A 71-year-old man with an endovascular aneurysm repair (EVAR) and a femoral-popliteal bypass was referred because of aortitis due to chronic Q-fever, and started on doxycycline 200 mg/day and hydroxychloroquine 600 mg/day. After 48 months of therapy, he reported increasing pretibial bluish-brown-black discolouration on both legs, and the dorsal side of his feet (*figure 3*). In retrospect, the discolouration started 11 months before, but he had never reported it. Doxycycline and hydroxychloroquine were substituted by moxifloxacin and rifampicin. Six months later, the discolouration diminished.

Case 4

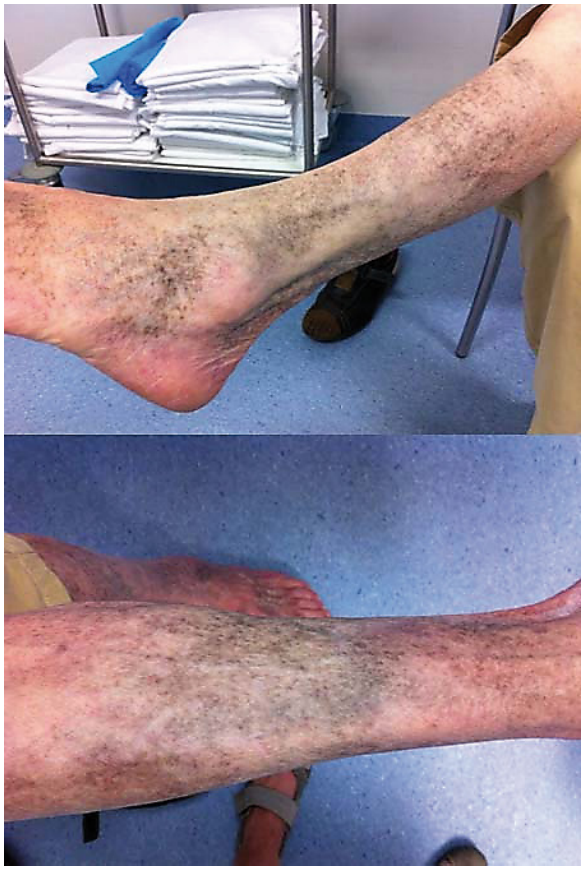
A 72-year-old man with an infected EVAR with retroperitoneal abscesses due to chronic Q-fever was

referred for surgery. He had already received six months of doxycycline 300 mg/day and hydroxychloroquine 600 mg/day (doxycycline serum concentration: 6.2 µg/ml), which was continued post-surgery. For six months, he received doxycycline 200 mg/day because of side effects. However, because of a low doxycycline serum concentration (2.8 µg/ml), doxycycline 300 mg/day was reintroduced, leading to a near-therapeutic concentration (4.7 µg/ml). Eight months post-surgery, he presented with increasing black discolouration around the surgical scars on both legs. Doxycycline and hydroxychloroquine were substituted by moxifloxacin. Two months later, the black discolouration diminished.

DISCUSSION

We describe four patients with hyperpigmentation of previously healthy skin after prolonged use of doxycycline. This has been described before in only one patient with therapeutic doses of doxycycline,[1] and in a patient with self-induced doxycycline intoxication (1 g/day during 12 years leading to doxycycline serum concentrations of 34 µg/ml, normal therapeutic range: 1-5 µg/ml, for chronic Q-fever: 5-10 µg/ml).[2,5] In our cases, patients received relatively high doses with serum concentrations in the therapeutic range, and developed marked cutaneous hyperpigmentation. However, compared with other indications for which doxycycline is given, chronic Q-fever and Whipple's disease require prolonged treatment with a higher therapeutic range. Because tetracyclines produce autofluorescence, with positive *in-vivo* conjunctival autofluorescence of palpebral conjunctival minocycline deposits,[6] the hyperpigmentation of the first two cases was investigated with Wood's light (extinction 365 nm). However, no fluorescent signal was obtained (*figures 1C and 2C*). This may have been due to the long time that elapsed between the cessation of doxycycline and this investigation (12 and 10 months, respectively). As the dorsal side of the hands of the first patient still showed clear pigmentations (*figure 1B*), the pigment might not represent the doxycycline itself. Previously, biopsies of doxycycline-induced hyperpigmentation revealed increased melanisation in the basal layers of the epidermal keratinocytes,[4,5] suggesting activation of melanocytes either by the tetracycline derivative itself or by another co-stimulus. Also, indications were found for the presence of melanin or melanin-like pigment in the histiocytes of the upper dermis. In contrast, in histiocytes of the lower dermis and subcutaneous fat, pigment was stored with increased amounts of iron and calcium, and no melanosomes were detected, suggesting a different nature of the pigment. Furthermore, data suggested that doxycycline, possibly chelated with iron and/or calcium, was directly deposited in the lesional skin.[5] The role of hydroxychloroquine and its interaction with doxycycline in these cases cannot be completely ruled out, as cutaneous hyperpigmentation induced by hydroxychloroquine has been described in 13% of treated patients, mainly as a bluish-grey pigmentation,[7] mostly localised at the hard palate, gums, face, and pretibial area.[8] To our knowledge, no literature exists describing an increased risk of hyperpigmentation using doxycycline and hydroxychloroquine concomitantly. As both medications can cause cutaneous hyperpigmentation a synergistic effect on the development of hyperpigmentation might exist. However, based on the localisation of hyperpigmentation, without mucosal involvement,[9,11] doxycycline is still thought to be the main aetiological agent in our cases. Furthermore, in the first patient, hyperpigmentation developed after introduction of doxycycline 300 mg/day, and significantly diminished after stopping doxycycline, while hydroxychloroquine was continued. And, as seen in our fourth patient, discolouration restricted to scars has been reported with doxycycline.[4] Most described

Figure 3. *A 71-year-old man with chronic Q-fever developed an increasing bluish-brown-black pretibial discolouration on both legs, and the dorsal side of his feet, during therapy with doxycycline and hydroxychloroquine. Six months after stopping therapy, the cutaneous discolouration had clearly diminished.*



cases of cutaneous hyperpigmentation during tetracycline treatment are induced by minocycline,[12] which is frequently prescribed for long periods. However, indications for prolonged therapy with doxycycline also exist, with an increasing number of chronic Q-fever patients.[13] It should be advised to discontinue therapy. As in our patients, partial to complete resolution of cutaneous hyperpigmentation has been described eight months after cessation of prolonged doxycycline therapy.[1] Furthermore, in the case with doxycycline intoxication, the pretibial hyperpigmentation had faded significantly one year after doxycycline cessation.[2] Finally, almost complete disappearance of methacycline-induced hyperpigmentation was reported five years after onset, except for two patients who were substituted with doxycycline.[14] Complete disappearance of hyperpigmentation after cessation of therapy is possible; however, recovery may take up to several years.[14]

In conclusion, cutaneous hyperpigmentation is a potential side effect of doxycycline therapy within the therapeutic dose range, and the chance to evoke this adverse effect might be increased with the concomitant use of hydroxychloroquine. Given the widespread use of doxycycline, in both short and prolonged regimens, it is important to recognise this reversible or partially reversible side effect in order to discontinue therapy. Especially its use in chronic Q-fever, when prolonged relatively high doses are given nowadays in combination with hydroxychloroquine, prescribers and patients should be aware of this side effect.

DISCLOSURES

The authors declare that they have no competing interests. The authors declare that the final manuscript has not been submitted or accepted for publication elsewhere.

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CASE REPORT

Generalised peliosis hepatis mimicking metastases after long-term use of oral contraceptives

A.M.M. Kootte[1]*, A.M. Siegel[1], M. Koorenhof[2]

Departments of [1]Internal Medicine, [2]Hospital Pharmacy, Rijnland Hospital, Leiderdorp, the Netherlands, *corresponding author: email: a.kootte@rijnland.nl

ABSTRACT

Peliosis hepatis (PH) is a rare vascular condition of the liver characterised by the presence of cystic blood-filled cavities distributed randomly throughout the liver parenchyma. PH should be considered in the differential diagnosis of women with a long history of use of oral contraceptives with suspected hypervascular lesions diagnosed by imaging, but with an unknown primary tumour. Because of the extensive use of oral contraceptives in the general female population worldwide, PH should be added to the differential diagnosis of suspected hypervascular liver lesions.

KEYWORDS

Peliosis hepatis, oral contraceptives, mimicking metastases

What was known on this topic?
Peliosis hepatis (PH) is a rare vascular condition of the liver characterised by the presence of cystic blood-filled cavities distributed randomly throughout the liver parenchyma. It has been associated with multiple drugs, chemicals, infections, haematological disorders, malignancies, renal transplantation, HIV infection and a variety of other conditions.

What does this case add?
PH should be considered in the differential diagnosis of women with a long history of use of oral contraceptives with suspected hypervascular lesions diagnosed by imaging but with an unknown primary tumour.

INTRODUCTION

Peliosis hepatis is a rare vascular condition of the liver characterised by the presence of cystic blood-filled cavities distributed randomly throughout the liver parenchyma. The term originates from the Greek 'pelios' which means 'lead-coloured' (extravasated blood). Peliosis is most commonly found in the liver, but can also involve other organs. An aetiology remains unclear in up to 50% of the patients. Peliosis hepatis has been described primarily in patients on androgenic steroid medication and patients with tuberculosis.[1,2] Nowadays, it has been associated with multiple drugs (such as oral contraceptives as in our patient), chemicals, bacterial and HIV infections, haematological disorders, malignancies and renal transplantation.[3,4] Some studies have described the prevalence of peliosis hepatis in patients with associated conditions, such as 0.2% in patients with tuberculosis[1,2] and 0-22% after renal transplantation.[4] No numbers are known on the prevalence of peliosis hepatis in association with oral contraceptives. In the described patient, the diagnosis of peliosis hepatis was not made by the imaging modalities, which suggested metastases, but by liver biopsy. Peliosis hepatis should nowadays be considered in the differential diagnosis of suspected hypervascular liver lesions diagnosed by imaging, in women with a history of long-term use of oral contraceptives.

CASE REPORT

An otherwise healthy 47-year-old woman presented for evaluation of an elevated erythrocyte sedimentation rate and abnormal liver function tests in the outpatient

department. She reported vague epigastric pains and nausea. She had no history of dark urine or hepatitis. She had a more than 30-year history of use of oral contraceptives as treatment of acne vulgaris. In 1980, when she was 16 years old, she used Androcur (cyproterone acetate 50 mg) for nine months in combination with Lynoral (ethinyl oestradiol 0.05 mg). She was treated with 100 mg cyproterone acetate for 10 days and 0.05 mg ethinyl oestradiol for 21 days; the treatment was started on day 5 of the cycle. Afterwards she used several other oral contraceptives such as Diane 35 (cyproterone acetate 2 mg / ethinyl oestradiol 0.035 mg) from 1982 until 1995. Then she used Marvelon (ethinyl oestradiol 0.03 mg/ desogestrel 0.15 mg) for at least one year. At the time of presentation she had been taking Microgynon 30 (ethinyl oestradiol 0.03 mg / levonorgestrel 0.150 mg) since 2001; no other concomitant medication, drugs or alcohol were used. On physical examination no abnormalities were found. The liver was not enlarged. Laboratory studies showed a slightly elevated sedimentation rate and anaemia in the presence of excessive menstrual bleeding. The alkaline phosphatase was 299 U/l (normal 40-120 U/l) and gamma-glutamyltransferase was 120 U/l (normal up to 40 U/l). An ultrasonography of the liver and a computed tomography (CT) scan (64 slice MDCT Philips) (*figure 1*) showed multiple hypoechoic and hyperechoic lesions. On CT these lesions were from heterogenous densities and were hypodense in the venous phase, suggesting the evidence of multiple hypervascular, possibly metastatic, lesions. PET-CT yielded no evidence of a primary tumour. A liver biopsy was taken at that time and showed occasional dilated sinusoids suggesting peliosis hepatis (*figure 2*). The biopsy was complicated by a subcapsular liver haematoma and the patient was admitted to hospital. After three days of observation she was discharged. The alkaline phosphatase was raised up to 378 U/l after biopsy, presumably caused by the bleeding. Because of the association of peliosis hepatis with long-term use of oral contraceptives, the Microgynon was stopped. No other cause of peliosis hepatis was likely, because of the 30-year history of use of combined oral contraceptives and no other use of concomitant medication, drugs or alcohol. After two years of follow-up the serum alkaline phosphatase is 173 U/l and gamma-glutamyltransferase is 100 U/l. Regression of the multiple hypervascular lesions has been shown on serial repeated ultrasonography of the liver.

Figure 1. *CT scan with multiple hypervascular 'metastatic' lesions in the liver*

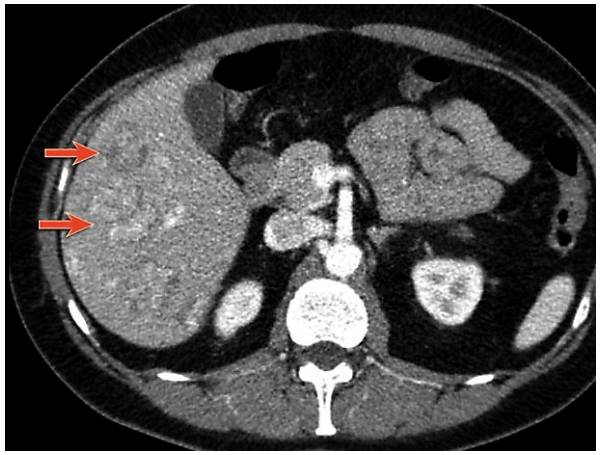
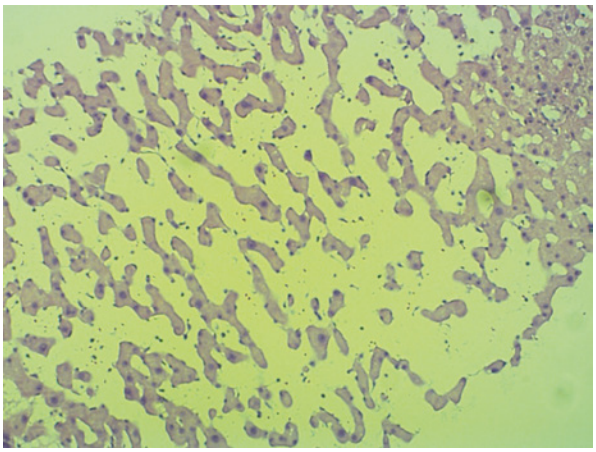


Figure 2. *Liver biopsy with H&E stain shows occasional sinusoidal dilatation of the liver parenchyma*



DISCUSSION

Both the epidemiology and natural history of peliosis hepatis are not completely understood. Most patients are asymptomatic and remain undiagnosed or have slowly progressive disease. Peliosis hepatis is often an incidental finding on abdominal imaging, as in our patient. On imaging studies, the differential diagnosis of peliosis hepatis includes other focal liver lesions including adenoma, haemangioma, focal nodular hyperplasia, abscess, hypervascular metastatic lesions, and hepatocellular carcinoma. On CT the lesions usually appear as heterogeneous densities that become hypodense in the late arterial and venous phase. On magnetic resonance imaging (MRI), peliosis hepatis lesions are typically of low signal intensity on T1-weighted images and of high signal on T2-weighted images, with late and slow but intense enhancement on contrast-enhanced T1-weighted images. The first report of generalised peliosis hepatis as a complication of long-term use of oral contraceptives was made by Van Erpecum *et al.* in 1988.[5] The pathogenesis of peliosis hepatis is unclear but probably involves hepatocellular necrosis and injury to the sinusoidal endothelium. However, oral contraceptives do

not cause sinusoidal endothelial cell injury, in contrast to other agents such as azathioprine, 6-thioguanine and oxaliplatin. Thus, the mechanism by which oral contraceptives lead to peliosis hepatis remains unclear. Any contributing effect of the earlier use of cyproterone acetate on peliosis hepatis in our patient has not previously been described. Regression of a mild form of peliosis hepatis after discontinuation of an oral contraceptive with resolution of the clinical, laboratory, and radiographic abnormalities is likely. In our patient, generalised peliosis hepatis was discovered during evaluation of abnormal liver enzymes. The diagnosis was not suggested by the various imaging modalities (ultrasonography, PET-CT), but by liver biopsy as earlier reported.[6] Biopsy of a suspected lesion established the diagnosis peliosis hepatis in our patient, but gave the complication of major bleeding due to the vascular nature of peliosis hepatis.

CONCLUSION

In the described patient, the diagnosis of peliosis hepatis was not considered before liver biopsy. Peliosis hepatis should be considered in the differential diagnosis of women with a long history of oral contraceptive use with suspected hypervascular lesions diagnosed by imaging but with an unknown primary tumour. Because of the extensive use of oral contraceptives in the general female population worldwide, peliosis hepatis should be added to the differential diagnosis of suspected hypervascular liver lesions in women with a long history of use of oral contraceptives.

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PHOTO QUIZ

Cutaneous ulcer after a stay in the tropics

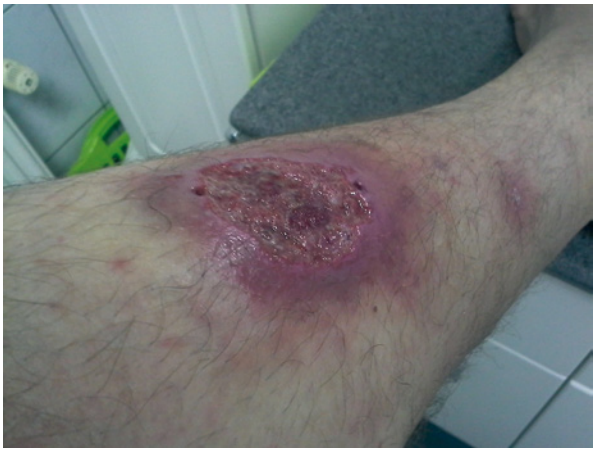
P. Vanbrabant[1,2]*, S. Van Den Broucke[3], P. Soentjens[1,3]

[1]Polyclinic Department, Military Hospital Queen Astrid, Brussels, Belgium, [2]General Internal Medicine, University Hospitals Leuven, Leuven, Belgium, [3]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium, *corresponding author: tel.: +32(0)2-2644577, fax: +32(0)2-2644566, email: peter.vanbrabant@mil.be

CASE REPORT

A 25-year-old patient was seen at the outpatient clinic of internal medicine three months after a two-month stay in South America because of a progressive (over two weeks) skin lesion (papule with evolution to an ulcer) on the left lower leg. He had participated to a survival training in the jungle of French Guiana. This training often impeded personal protective measures (use of long-sleeved clothing, insect repellents and impregnated bed netting). Prophylactic treatment with mefloquine was taken correctly. The clinical examination revealed an ulcer with a diameter of 3 cm on the left lower leg (*figure 1*). The patient was afebrile and the rest of the physical examination was unremarkable. A biopsy of the edge of the lesion was performed.

Figure 1. *Ulcer on the left lower leg*



WHAT IS YOUR DIAGNOSIS?

See page 49 for the answer to this photo quiz.

LETTER TO THE EDITOR

Are the current guidelines on contrast-induced nephropathy prevention superfluous?

M.A.G.J. ten Dam[1]*, J.F.M. Wetzels[2]

[1]Department of Internal Medicine, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands,
[2]Department of Nephrology, Radboud University Medical Centre, Nijmegen, the Netherlands,
*corresponding author: tel.: +31(0)24-3658739, email: m.t.dam@cwz.nl

To the editor,

Moos *et al.* prospectively evaluated the risk of contrast-induced nephropathy (CIN) in 998 patients undergoing intravenous contrast-enhanced computed tomography (CECT).[1] They conclude that 'extensive CIN prevention guidelines seem superfluous'.

Unfortunately, this conclusion is not supported by the data. The authors calculated that only 5.8% of the patients who were referred for CECT were at high risk for CIN using the Dutch guideline criteria. It is questionable if the data, obtained in an Academic Hospital, can be extrapolated to the population in a general hospital. Still, even the 5.8% percentage would implicate that in the Netherlands yearly 5000 patients at risk for CIN are evaluated by CECT. The introduction of a lower value of estimated glomerular filtration rate (eGFR) as threshold for defining risk would decrease the number of patients at risk, but not obviate the need for screening to detect the high-risk patient. As stated in the current clinical practice guidelines, ordering eGFR in all patients undergoing CECT is most efficient and considered cost-effective when compared with selection of patients based on history, drug use etc.

The authors conclude that the incidence of CIN in the studied population is low. This is a remarkable and incorrect conclusion. In our view, a diagnosis of CIN (or exclusion thereof) requires a valid serum creatinine value after contrast administration. In fact, the authors measured a follow-up serum creatinine in only 18 of 58 high-risk patients. CIN was found in two patients, with a calculated incidence of CIN of 11%, higher than reported in studies that followed the guidelines. The incidence of CIN was 9% (1/11) in hydrated patients versus 14% in non-hydrated patients. The low power of the study explains the lack of significance. Moreover, the study was uncontrolled, and thus biased by confounding by indication, with patients at highest risk more likely to receive therapy.

The study is also underpowered to reliably evaluate the need for dialysis. Moreover, long-term effects were not addressed, which are relevant in view of studies showing that episodes of acute kidney injury contribute to a persistent loss of kidney function and a faster subsequent rate of decline in kidney function.[2]

We agree that the current guidelines for prevention of CIN should be reconsidered. However, the study by Moos et al. provides no guidance. When rewriting the guidelines the Hippocratic injunction 'primum non nocere; above all, do no harm' should be kept in mind. Indeed, prophylactic hydration with intravenous saline solution may cause pulmonary oedema; hydration with sodium bicarbonate, in the amount that was introduced by Merten *et al.*,[3] has been shown to be at least as effective as the hydration with saline solution and has a substantially lower risk of pulmonary oedema.[4]

We agree with the authors that a randomised control trial, comparing at-risk patients receiving preventive hydration with at-risk patients not receiving preventive hydration, is necessary. This study should take into account both short-term and long-term effects in order to determine which patients benefit from such preventive measures.

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LETTER TO THE EDITOR

Unintentional nutmeg autointoxication

J.E. Roeters van Lennep*, S.C.E. Schuit, R.L. van Bruchem-Visser, B. Özcan

Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands, *corresponding author: tel.: +31(0)10-7040704, fax: +31(0)10-7033268, email: j.roetersvanlennep@erasmusmc.nl

ABSTRACT

Nutmeg ingestion in large amounts can cause toxic symptoms such as hallucinations, tachycardia and anticholinergic effects. We describe a case of a 37-year-old woman who experienced an unintentional autointoxication of nutmeg. It is likely that nutmeg intoxication is underreported. We suggest to specifically think of nutmeg ingestion in case of symptoms as mentioned above.

KEYWORDS

Intoxication, toxicity, nutmeg

What was known on this topic?
In large quantities, nutmeg has toxic effects including hallucinations, tachycardia, nausea, vomiting, agitation, and hallucinations. Because of these effects it is occasionally used as a recreational drug.

What does this add?
This case report shows how accidental autointoxication with nutmeg can occur. These cases are very rarely reported in the literature. However, we believe that because both patients and physicians are unaware of the possible toxic effects of nutmeg, many cases will not be recognised. In case of an unknown intoxication, consider to specifically ask about ingestion of nutmeg

INTRODUCTION

Nutmeg is a commonly used spice derived from the seed of the *Myristica fragrans* tree. The spice is normally used in small amounts to flavour food. When large amounts are taken, several toxic effects, including tachycardia, nausea, vomiting, agitation, and hallucinations, have been described.[1-4] Because of the hallucinatory effects, nutmeg is occasionally used as a recreational drug. Therefore, most intoxications are described in the context of intentional exposure.[1-5] Unintentional autointoxication in adults is rare because the toxic effects only occur when large quantities are eaten. However, it is expected that the actual number of accidental nutmeg intoxications is underreported because many patients and physicians are unaware of the toxic effects of nutmeg. We present a case of an unintentional autointoxication which would have been unrecorded if the patient had not made the diagnosis herself.

A 37-year-old woman presented at the emergency department with confusion, incoherent speech and drowsiness. She had attended the yearly conference of the Dutch Society of Internists and had no symptoms until she woke up at 4 am and felt dizzy and confused, had a very dry mouth and a sense of incomplete voiding. Initially she blamed her condition on the fact that she had joined the annual party, although she had only consumed three units of alcohol throughout the whole evening. In the morning she could not find the dining hall of the hotel and did not recognise her colleagues. Because of this unusual behaviour, her colleagues took her to the emergency department of a nearby hospital. She did not have a relevant medical history, used no medication, did not smoke, used alcohol sparingly and did not use illicit drugs. At the emergency department she had a blood pressure of 120/65 mmHg and a sinus tachycardia of 120 beats/min. Further physical and neurological examination did not reveal any abnormalities. Standard blood and urine tests were normal. Screening of the urine for drugs of abuse was not performed. She was discharged without a diagnosis. Although she was more coherent by the time she left the hospital, she still felt 'groggy'. One hour later, when her colleagues drove her home, she suddenly realised what her diagnosis was.

During the dinner prior to the party she had added about two teaspoons of nutmeg to her asparagus, which was more than she intended. She had heard previously about a case of nutmeg intoxication and with some help from Google, she realised that the effects she had experienced were highly suggestive for a nutmeg overdose. The effect of mental confusion subsided within ten hours; however, the symptoms of a dry mouth and urine retention persisted for 36 hours. She recovered completely but has not eaten nutmeg since.

DISCUSSION

Nutmeg was used for its hallucinogenic and euphoric effects as early as during the Crusades. The first case of nutmeg intoxication described in literature was by Lobelius in 1576.[6] In the hippy culture of the 1960s and 1970s, nutmeg was temporarily fashionable as a cheap alternative as an hallucinogenic. However, because of the frequently encountered severe headache afterwards, described as the 'nutmeg hangover' it has never become a very popular drug and it has never been encountered as a problem for addiction on a large scale.

Four case series and several case reports of nutmeg intoxication have been published.[1-10] The majority of these reports describe intentional nutmeg ingestions, mostly adolescents with accidental overdoses leading to severe intoxication.[1,3-5,7] Accidental autointoxication accounts for <20% of the published case series and an occasional case report.[1-4,10] On the internet, however, several reports can be found of accidental nutmeg autointoxication.[11,12] The current case is highly suggestive for a nutmeg intoxication, although intoxication by other substances is still a possibility, despite the fact that the patient does not mention it.

The main symptoms of nutmeg overdose are cardiovascular, central nervous system, anticholinergic and local effects in the stomach. Cardiovascular symptoms consist of hypertension, tachycardia and can also include, in severe cases, hypotension and shock. Central nervous system symptoms described are agitations, lethargy/drowsiness, feelings of impending doom, anxiety, hallucinations, blurred vision, symmetric pupil dilation and hypothermia.[13] Anticholinergic effects such as urinary retention, dry mouth, tremor and seizures following nutmeg intoxication have been reported. Finally, local effects in the stomach can result in nausea, vomiting and abdominal pain. Toxic symptoms have been observed with a nutmeg dose of as little as 5 g, which is equivalent to two teaspoons or two-thirds of a tablespoon of grated nutmeg.[7] The toxic effects are attributed to the volatile oil myristicin, which is the active substance of nutmeg and in a lesser extent in spices such as parsley, dill and celery.

The exact mechanism of how myristicin can be attributed to the symptoms related to nutmeg overdose is not yet clear. It is known is that myristicin can be metabolised to 3-methoxy-4,5 methylenedioxyamphetamine also known MMDA. A more well-known analogue of MMDA is 3,4-methylenedioxy-N-methylamphetamine (MDMA), also known as ecstasy, which may explain the euphoric effect of nutmeg.[14] The triglyceride trimyristin, the oil of the nutmeg, has been associated with anxiogenic effects via serotonin and GABA receptors.[15]

Myristicin has been shown to be a (weak) monoamine oxidase (MAO) inhibitor in a rat model, which could also provide an explanation for nutmeg's sympathomimetic effects.[16] Other components of myristicin (linalool, safrol, isoeugenol, and eugenol) which are structurally similar to serotonin agonists may explain the cardiovascular response such as tachycardia.[17]

Symptoms usually occur three to eight hours after ingestion and can last for up to 48 hours. The clinical course is usually benign and self-limiting, although two deadly cases attributed to nutmeg overdose have been published.[2,8] Management is mainly supportive. In severe cases, administration of intravenous fluids and oral anti-emetics may be necessary.[1,4,10] Benzodiazepines are the mainstay of treatment in patients who present with agitation and anxiety.[1] A dose of activated charcoal may be helpful in alert patients with an intact airway.

CONCLUSION

This case demonstrates that unintentional nutmeg autointoxication can happen, and probably occurs more often than is recognised. Patients presenting with suspected intoxication of unknown origin is a regular occurrence at the emergency department. After ruling out easily traceable causes such as alcohol, benzodiazepines and cocaine, many cases remain unsolved. This would have been another of those cases if the patient herself had not made the diagnosis. We suggest that in case of unexplained symptoms of tachycardia, vomiting, agitation and hallucination, to think of nutmeg ingestion.

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ANSWER TO PHOTO QUIZ (PAGE 44)

CUTANEOUS ULCER AFTER A STAY IN THE TROPICS

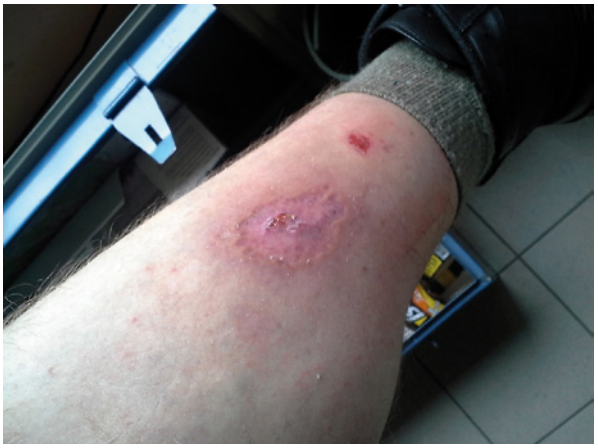
DIAGNOSIS

By means of direct microscopy, which determined *Leishmania* parasites, the diagnosis of cutaneous leishmaniasis was established. Species-specific diagnosis (*L. guyanensis*) was made by polymerase chain reaction (PCR). Treatment with intravenous pentamidine was administered with favourable evolution after three infusions: residual depressed and retracted scar (*figure 2*).
The spectrum of dermatological diagnoses in travellers is broad.[1] Because of his stay in South America, cutaneous leishmaniasis needed to be included in the differential diagnosis (*table 1*). However, a delay in diagnosis often occurs: the diagnosis was missed by the general practitioner in 38% of cases in a French study.[2]
Leishmaniasis is caused by various *Leishmania* parasite species and is transmitted through sandfly bites (*Phlebotomus* (Old World) and *Lutzomyia* (New World)). Depending on the causative *Leishmania* species and the host immune response, the clinical presentation is cutaneous, mucosal or visceral disease. Although all types of skin lesions (papules, nodules) might be seen in cutaneous leishmaniasis, ulcers are the most frequent. Incubation time varies (weeks to months). Occasionally, according to the species (and sometimes months after the appearance of the cutaneous leishmaniasis lesions) mucosal disease (nose and pharynx) can develop.[3] Central and South America (New World cutaneous leishmaniasis) and Africa and the Middle East (Old World cutaneous leishmaniasis) are leishmaniasis-endemic regions. Diagnosis can be made by microscopy (sensitivity 19-77%) and culture (sensitivity 58-62%). PCR, however, is the method of choice because it allows species determination and it has high sensitivity (89-100%).[3] Treatment modality (local vs. systemic) depends on the causative *Leishmania* species (PCR genotyping) and number, size and location of the lesion(s).[4]

Table 1. *Differential diagnosis of cutaneous ulcer after a stay in South America*

Parasite	Leishmaniasis
Bacterial	*S. aureus*, group A streptococci, anthrax, *Nocardia, Actinomyces, Fusobacterium*
Myobacterial	*M. tuberculosis*
Atypical mycobacterial	*M. marinum, M. fortiutum, (M. ulcerans)*
Fungal	Sporotrichosis, blastomycosis
Malignancy	Squamous and basal cell carcinoma
Other	Sarcoidosis, pyoderma gangrenosum

Figure 2. *Residual depressed and retracted scar*



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INFORMATION FOR AUTHORS

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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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