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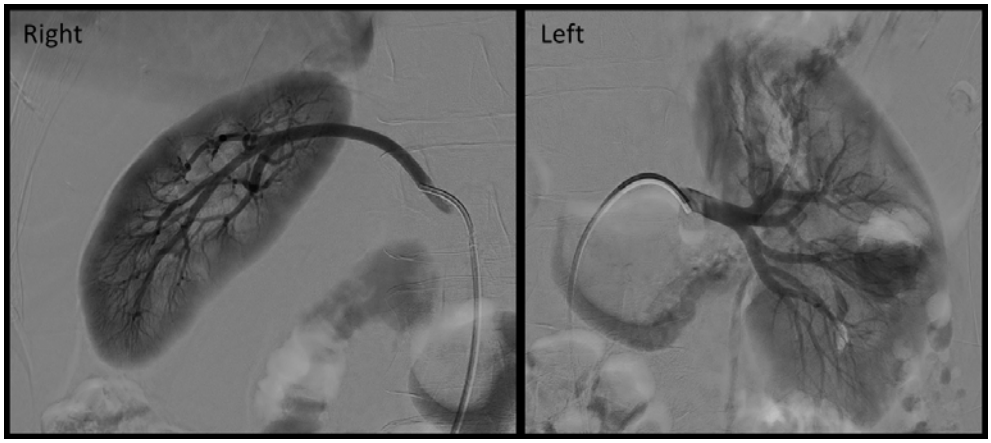

A young man with hypertension; what is your diagnosis?

Treatment of acromegaly

•

Oral anticoagulant or vitamin K antagonist?

•

Prophylactic nadroparin in renal insufficiency

•

Cyclic vomiting syndrome

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EDITORIAL

Direct oral anticoagulants: to switch or not to switch?

A clinician and patient decision

S. Lugthart, F.W. Leebeek

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Fifty years after the introduction of vitamin K antagonists (VKAs) a novel group of oral anticoagulants has been introduced. The currently named direct oral anticoagulants (DOACs) represent a landmark in anticoagulant care. The direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and direct factor IIa inhibitors (dabigatran) are being prescribed more frequently, as both clinicians and patients are getting more familiar with these agents and indications broaden. DOACs are approved in non-valvular atrial fibrillation to prevent ischaemic stroke and as thromboprophylaxis following elective hip and knee replacement surgery (dabigatran, rivaroxaban and apixaban). All DOACs have been approved for treatment and secondary prevention of deep venous thrombosis and pulmonary embolism. The arrival of this new class of anticoagulant drugs poses the question to both doctors and patients whether they should be treated with these newer agents instead of VKAs, or even to be switched from their current treatment with VKA to a DOAC. In the article by Boom et al.,[1] in this issue of the Journal, the authors asked patients about their preferences for anticoagulant drugs. It is clear that patients may have a different view and preference for using a specific drug than their doctors. Therefore, both prescribing physicians and patients should consider the advantages and the disadvantages of DOACs compared with VKAs before deciding what is best for the individual patient.

Why should we stop prescribing VKAs, known to be very effective in preventing thrombotic events and start with DOACs instead?

DOACs have several advantages including rapid onset of action, large therapeutic window, short half-life and fewer drug-drug and food-drug interactions. The short half-life of DOACs will lead to simplification of bridging of anticoagulant therapy, for instance in case of planned surgery. In addition, advantages for the patients using DOACs include no need for laboratory monitoring, a fixed once or twice daily dose, lower risk of major bleeding and fatal bleeding. Recent meta-analysis in patients with non-valvular atrial fibrillation has shown that DOACs are as effective as VKAs in preventing stroke or systolic emboli (RR 0.81).[2] Even a lower overall mortality was seen in the DOAC (dabigatran, rivaroxaban) treated patients (RR 0.90), and a significantly decreased risk of intracranial bleeding (RR 0.49).[2] For venous thromboembolic (VTE) use similar results are found comparing DOACs with VKAs, i.e. DOACs are equally effective and have a lower risk for major bleeding including gastrointestinal and intracranial bleeding.[3,4] It is still questioned whether the data of the large DOAC studies performed in both in atrial fibrillation and VTE patients are dependent upon the quality of monitoring VKA treatment. In the RELY study, the time in therapeutic range (TTR) in the VKA-treated group was relatively low, which may lead to a more beneficial outcome for the DOACs.[5] In the GARFIELD registry, an increased survival was shown in patients using VKAs with a TTR above 60%, compared with those with a lower TTR.[6] However, recent studies reported that a strong dose relationship in outcome was also seen for the dabigatran concentration in plasma.[5] It has even been suggested to monitor these levels to improve the outcome of DOACs, thereby taking away one of the major advantages of DOACs over VKAs.[7]

Given these potential advantages mentioned above, is there also a down side to DOACs?

Less monitoring of anticoagulant treatment might lead to reduced patient adherence. In several recent reports the reduction of adherence seems to be minimal.[8] The costs of the DOACs compared with VKA treatment are much higher. Patients may experience gastrointestinal side

effects, such as nausea. For dabigatran, a slightly increased risk of gastrointestinal bleeding has been reported compared with VKA,[9] although this was not observed in a meta-analysis of patients treated for venous thrombosis.[4]
A major limitation of DOACs is the lack of a specific antidote for immediate reversal of the anticoagulant effect in case of bleeding or emergency surgery. Recently, antidotes have been developed, both for the direct thrombin inhibitor dabigatran and the direct Xa inhibitors.[10,11] Idarucizumab completely blocks the anticoagulant activity of dabigatran and prevented further bleeding complications.[10] Other antidotes are still under investigation, for instance andexanet alpha for Xa inhibitors and ciraparantag for all DOACs.[12] Hopefully, they will be swiftly approved if the currently ongoing studies show that they are indeed effective and safe. Until approval, doctors have to rely on other haemostatic agents, including 4-factor prothrombin complex concentrate (PCC),[13] activated PCC and/or recombinant factor VIIa, depending on national and/or local hospital guidelines.[14]
Another limitation of DOACs is the potential accumulation in patients with renal failure, due to the renal clearance of DOACs. The current guideline on using DOACs in the Netherlands recommends to be careful with DOACs in patients with a creatinine clearance between 31-50 ml/min and not to use DOACs in case of a clearance of < 30 ml/min.[14]

The major questions that remain are: Should patients who are currently treated with VKA switch to a DOAC?
In this issue Boom et al. present data from a patient questionnaire which show that 57% of the patients who are taking VKA would switch to a DOAC, if this removes the need for regular laboratory monitoring. Even more patients would switch if DOAC use were to lead to less bleeding (65%).[1] It should be remembered that also patients on DOAC will need some follow-up, for instance to check their renal function at regular intervals. Unfortunately, the authors did not include the issue of the lack of an antidote for the DOACs in their survey. Would this preference have been different if a patient is aware that bleeding cannot be counteracted by a direct-acting antidote? In addition, the authors did not take into account whether the increasing number of patients who are self-monitoring or even self-dosing share this opinion.
A patient who is motivated and fit, has no other major comorbidities, such as chronic renal insufficiency (creatinine clearance < 30 ml/min) or hepatic impairment, gastrointestinal bleeding history, is using no other interacting drugs (inhibitors of CYP3A4 and P-gp), could be an appropriate candidate to switch from VKA to a DOAC. If a patient is comfortable with self-monitoring or self-dosing or if there is any uncertainty about compliance, switching is not advised.

Should the decision to switch be a joint patient-clinician decision?
Primarily, it is a physician's choice, as he can oversee the patient's past medical history, concomitant medication and determine if the patient is truly motivated for the right reasons. The clinician prescribing anticoagulant drugs should be familiar with the use of DOACs. Many DOAC guidelines are currently available: how to use,[15] how to switch,[16] and how to reverse in emergencies.[13] The hospital team and the clinician should be able to work according to these guidelines at all times and have a protocol for DOAC use in their hospital.
Finally, when both clinician and patient are comfortable in making the switch from VKA to DOAC, they can proceed in being a part of the future of this exciting anticoagulation world.

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REVIEW

Review of current and emerging treatment options in acromegaly

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ABSTRACT

In almost every patient, acromegaly is caused by a growth hormone secreting pituitary adenoma. Clinical features are the result of excessive growth hormone secretion and the consecutive excess in insulin-like growth factor I levels. This results in somatic overgrowth and metabolic disturbances with a higher morbidity and mortality than in the general population. With optimal disease management, mortality can be reduced to that seen in the general population. The current treatment of acromegaly is based on a combination of surgery, radiotherapy and medical therapy. This review provides an overview of the current and upcoming therapies with a focus on medical therapy.

KEYWORDS

Acromegaly, treatment, somatostatin analogues, cabergoline, pegvisomant, pasireotide, oral octreotide

INTRODUCTION

Acromegaly is a rare disease characterised by excessive growth hormone (GH) secretion almost exclusively caused by a benign pituitary adenoma.[1] Clinical features are the result of chronic GH and insulin-like growth factor-1 (IGF-I) hypersecretion leading to soft tissue enlargement, excessive skeletal growth, metabolic disturbances, a reduced life expectancy and a reduced quality of life (QoL).[1,2]. Incidence of acromegaly is estimated to be around 2.8-6 cases per million per year.[3-8] However, this is an underestimation because many cases go unrecognised, as data from a detailed population-based study in Belgium reported that the true incidence of acromegaly might be 1 case per 8000 population, which suggests that acromegaly is more prevalent than previously considered.[9,10] Many signs and symptoms develop insidiously and are often subtle, particularly in the early stages before the characteristic physical changes become visible. Historically, the treatment delay from first symptoms to diagnosis is 7-10 years, although in younger patients the delay seems to be shorter.[11]

Optimal management of acromegaly is based on three pillars: control of GH and IGF-I hypersecretion, tumour size control and optimisation of QoL by comprehensive management of the comorbidities commonly associated with acromegaly, such as diabetes mellitus, hypertension, obstructive sleep apnoea and dyslipidaemia. Surgical, medical and radiotherapy modalities are available to treat acromegaly. An optimal treatment approach should be chosen depending on the size, localisation of the pituitary adenoma and patient characteristics.

This article will review the current therapies with a focus on the recent significant advances in the medical treatment of acromegaly.

DIAGNOSIS AND ASSAY PITFALLS

The clinical manifestations of acromegaly depend on the progression of the disease and patients may not always manifest with clear diagnostic features. Clinicians should be aware of the possibility of acromegaly in patients with two or more of the following comorbidities: new-onset diabetes, diffuse arthralgias, new-onset or difficult-to-control hypertension, cardiac disease including biventricular hypertrophy and diastolic or systolic dysfunction, fatigue, headaches, carpal tunnel syndrome, sleep apnoea syndrome, diaphoresis and loss of vision.[12]

The biochemical diagnosis of acromegaly is made by measurement of serum IGF-I which, because its half-life is longer than that of GH, serves as an integrative marker of GH secretion. Another advantage of a single IGF-I over a single GH measurement is that IGF-I can be assessed

independent of the time of day and food intake. In cases that are not clear-cut, i.e. with IGF-I levels just above or around the upper limit of normal, confirmation is frequently needed by showing a lack of suppression of GH to less than 1 µg/l following documented hyperglycaemia during an oral glucose tolerance test.[12] In acromegaly patients with poorly controlled diabetes mellitus, the oral glucose tolerance test is not reliable and serum IGF-I levels should be re-assessed when glycaemic control has been established. Systemic illnesses, hepatic or renal failure, malnutrition, diabetes mellitus and oral oestrogens may decrease IGF-I levels which might result in false-negative interpretations.[12-14] False-positive elevated IGF-I levels can occur during pregnancy. Accurate measurement of GH and IGF-I is important for diagnosis and monitoring of acromegaly. In an illustrative paper, the same GH sample was measured in 104 centres and an IGF-I sample in 23 centres across the UK using different assays. The results varied more than threefold for GH and about 2.5 fold for IGF-I.[15] Even when using the same automated immunoassay, significant intraindividual variability still existed. It is, therefore, imperative that when assessing serum IGF-I levels, the values should be interpreted against the clinical background rather than by the absolute IGF-I values alone. An overview of the current treatment modalities is shown in *table 1*.

Surgery

Transsphenoidal surgery is the primary treatment for patients with small and, therefore, curable tumours or for large adenomas causing impingement of the optic chiasm.[16,17] Surgical results depend on preoperative GH and IGF-I levels, tumour invasiveness and surgical skills. Surgery is the treatment of choice for microadenomas (diameter ≤ 1 cm) and well-defined intrasellar macroadenomas. In these cases experienced surgeons can achieve remission rates of about 80%, defined as postoperative normalisation of IGF-I levels and suppression of GH levels to < 1 mg/l after an oral glucose load. These rates drop to 20-30% for macroadenomas (diameter ≥ 1 cm). For macroadenomas that are not entirely surgically resectable (e.g., those with cavernous sinus extension) surgery may be considered with the goal of debulking the tumour mass.

Debulking seems to increase the efficacy of postoperative treatment with long-acting somatostatin analogues (LA-SSAs),[18-20] although conflicting data have been reported as well.[21] Preoperative treatment of macroadenomas with LA-SSAs has been shown to improve surgical outcome.[22-25] Successful surgery is accompanied by a rapid fall in GH and IGF-I levels and the costs are relatively low compared with life-long drug therapy, although the efficacy of surgery might be overestimated as the data on surgical outcome are almost exclusively reported from high specialist centres. For instance, in the UK, for all centres, an efficacy rate for microadenomas < 37% and for macroadenomas < 20% has been reported.[26]

Radiotherapy

Although radiotherapy has been used for decades, nowadays it is considered a third line of treatment for acromegaly in most centres.[27-29] For conventional radiotherapy, remission rates of around 50% after a follow-up of ten years have been reported. However, these remission rates are accompanied by an increased risk of hypopituitarism as 50-80% of patients develop pituitary insufficiencies after a mean follow-up period of ten years.[30,31] Another drawback is that it sometimes takes years before radiotherapy induces biochemical remission, which is associated with a negative impact on quality of life.[32] Analysis of the UK acromegaly database showed that radiotherapy was associated with an increased mortality risk, and cerebrovascular disease as the main cause of death.[33] Additionally, studies assessing QoL observed a lower QoL in patients treated with radiotherapy that further decreased during follow-up.[32,34,35] Joint problems are important factors affecting the QoL after radiotherapy.[34] In patients in whom an increase in tumour size is observed despite surgery and medical therapy, radiotherapy should be considered. Very rarely, pituitary adenomas still increase in size after radiotherapy.

Pharmacotherapy

Somatostatin analogues

Somatotroph (i.e. GH secreting) adenomas predominantly express somatostatin receptor sub-type 2 (SSTR2) and 5 (SSTR5). Octreotide long-acting release (Sandostatin LAR™) and lanreotide (Somatulin autosolution™) are long-acting analogues of somatostatin (growth hormone inhibitory hormone) that inhibit GH secretion by predominantly binding to SSTR2. Both formulations are on the market as monthly injections and equivalent in terms of efficacy, but differ in their mode of administration; lanreotide is available in pre-filled syringes injected deep subcutaneously and octreotide LAR requires reconstitution before being injected intramuscularly.[36,37] Biochemical normalisation of IGF-I and GH levels can be obtained in about 40% of treatment-naïve patients with LA-SSAs.[38,39] Tumour shrinkage is frequently observed (40-63%) during LA-SSA treatment and the decrease in GH levels generally occurs within the first four months.[39-43] LA-SSAs have a good safety and tolerability profile. Relatively few side effects occur; in the first few weeks transient self-limiting gastrointestinal symptoms such as abdominal discomfort, nausea and fat malabsorption occur in most patients.[44] Asymptomatic gallbladder stones or bladder sludge can develop in the first 18 months in up to 20% of patients.[45] Although current guidelines do not

Table 1. *Advantages and disadvantages of the current treatment modalities*

	Therapy	Advantages	Disadvantages
Surgery	Transsphenoidal selective adenectomy	Inexpensive Rapid reduction in IGF-I and GH	Remission rate 20-80% Recurrence rate of 3-10% over 5 years Postoperative hypopituitarism
Radiotherapy	External beam radiosurgery	Inexpensive	High frequency of hypopituitarism Remission rate 50% Decreased quality of life Potentially increased incidence of cardiovascular events
Pharmacological	Cabergoline	Inexpensive Oral administration	IGF-I normalisation 30% GH and IGF-I normalisation < 20%
	Somatostatin analogues (Octreotide LAR and Lanreotide autosolution)	Remission rate 40% 42% tumour shrinkage No additional hypopituitarism	Expensive (€20,000/year) Monthly muscular injection
	Pasireotide LAR	Remission rate 31%	Price to be determined Hyperglycaemia
	Pegvisomant monotherapy	60-90% normalisation IGF-I	Expensive (€50,000/year)
	Combination LA-SSAs and weekly pegvisomant	> 90% normalisation in IGF-I (with 50% lower PEG-V dose) Tumour shrinkage No additional hypopituitarism Possibly improved quality of life in some patients	At least cost-neutral compared to pegvisomant monotherapy

yet recommend the use of preoperative LA-SSAs, there is clear evidence from a meta-analysis and three randomised controlled trials indicating that LA-SSAs can improve the efficacy of surgery in macroadenomas.[46,47] However, there is limited evidence that LA-SSAs improve surgical outcome. LA-SSA pretreatment is a good option for patients with macroadenomas and for patients on a waiting list for neurosurgery, as it can reduce signs and symptoms.

Dopamine agonists

Until the 1980s, dopamine agonists were the only class of pharmaceutical agents available for acromegaly. Cabergoline is an oral second-generation dopamine agonist with a high affinity for dopamine receptor type 2 and has been used as monotherapy and in combination with somatostatin analogues.[48] It is usually well tolerated with few side effects and is inexpensive.[49] Because cabergoline alone has a modest efficacy of about 30% in normalising IGF-I levels, it is recommended as an add-on therapy in patients who have not reached biochemical remission on somatostatin analogues alone, and for patients with no access to pegvisomant.[48,50] However, the efficacy of cabergoline to control IGF-I and GH is probably below 20%.[48]

Pegvisomant

Pegvisomant (Somavert®) is a genetically modified analogue of human GH that binds to and blocks the GH receptor, acting as a competitive growth hormone receptor antagonist.[51] It is currently used as a second-line therapy in patients who are inadequately controlled with LA-SSA monotherapy.[27] Treatment with pegvisomant results in a rapid reduction in IGF-I serum levels which causes a paradoxical rise in serum GH levels, due to the negative feedback loop via the hypothalamus and the pituitary gland.[52,53] Cross-reactivity between pegvisomant and endogenous GH in commercial assays disables proper assessment of the endogenous GH levels.[54] For these reasons GH cannot be reliably assessed in patients treated with pegvisomant, unless specific assays are used.[55] The key biomarker during the treatment of pegvisomant, therefore, is the serum IGF-I level along with clinical signs and symptoms.

To date, pegvisomant is the most effective drug to normalise IGF-I levels in acromegaly.[51,53,56] Reports from clinical studies demonstrated that more than 90% of patients with acromegaly achieved normalised IGF-I levels.[53,56] Because pegvisomant is a competitive blocker, virtually all patients with acromegaly can be controlled providing treating physicians adequately titrate the dose of pegvisomant. However, in observational registries lower efficacy rates of around 60% were reported.[57-60] The lower efficacy might be explained by the relatively low doses of pegvisomant that were recorded in these registries. To achieve efficacy rates of above 90% with pegvisomant

monotherapy, the average expected weekly dose is probably above 120 mg. Efficacy rates of pegvisomant as a single agent and in combination with LA-SSAs are equally high. However, the advantage of co-administration of pegvisomant with LA-SSAs is the much lower (around 50%) required weekly dose of pegvisomant.[52] Because LA-SSAs inhibit the secretion of GH, pegvisomant meets less competition from endogenous GH around the GH receptor, meaning a lower dose of pegvisomant is needed to block all GH receptors during combination therapy and additionally reduces the number of GH receptors on the hepatocytes.[52,61,62] Although LA-SSA treatment decreases hepatic IGF-I production, GH action in peripheral tissues remains too high. This may lead to insufficient control of disease activity in peripheral tissues despite biochemical control. Blocking peripheral GH action using pegvisomant can therefore be useful in treating extrahepatic acromegaly.[63] Improvement in quality of life was previously observed in acromegaly patients who had normalised IGF-I during LA-SSA therapy.[64] Pegvisomant therapy has also been shown to have beneficial effects on glucose metabolism by several mechanisms.[65-70]

Pegvisomant is also an expensive drug. A median dose of 120 mg per week comes at an annual price of around € 62,000. Combining pegvisomant with LA-SSAs, therefore, might significantly reduce medication costs. The most common side effect associated with the use of pegvisomant is a transient elevation of liver transaminases.[52,58,60-62] The incidence of this temporary increase in transaminases was reported to be higher in patients on a combination with LA-SSAs. Although many risk factors have been suggested, the underlying pathophysiology of the development of a pegvisomant-induced transient elevation of liver transaminases remains unclear.[61,62,71,72] There is no clear evidence that pegvisomant directly promotes tumour growth, but ongoing vigilance is required by repetitive imaging to monitor tumour size.[58] The high efficacy of pegvisomant in acromegaly can only be achieved in experienced centres that treat a high volume of patients with pegvisomant.[52]

Pasireotide

Pasireotide LAR (Signifor®) is a novel multireceptor somatostatin analogue with broader somatostatin receptor binding affinity for SSTR1, SSTR3 and SSTR5. It is available as monthly subcutaneous injections. Because of the broader binding profile compared with octreotide and lanreotide, it may provide additional therapeutic benefits. Pasireotide LAR has recently been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of acromegaly in patients in whom surgery is not an option or is not curative and who are inadequately controlled on treatment with first-generation somatostatin analogues.[73] In a prospective, randomised, double-blind head-to-head superiority study in medically naïve acromegaly patients, biochemical control after 12 months was significantly higher in the pasireotide LAR compared with the octreotide LAR treated patients (31.3% vs. 19.2%). However, hyperglycaemia-related adverse events were more common in the pasireotide LAR treated group (57.3% vs. 21.7%).[74] Recently, the efficacy and safety of pasireotide LAR was addressed in acromegaly patients refractory to octreotide LAR or lanreotide autosolution. Inadequately controlled acromegaly patients on the currently available somatostatin analogues were randomised to pasireotide LAR 40 mg, pasireotide LAR 60 mg or continued treatment with octreotide LAR 30 mg or lanreotide autosolution 120 mg (active control). After 24 weeks, biochemical control was achieved in 15% of patients in the pasireotide LAR 40 mg group, 20% in the pasireotide LAR 60 mg group and no patients in the active control group. IGF-I normalisation was reported in about 25% of patients in both pasireotide LAR groups, while no patients receiving active control achieved normal IGF-I concentrations.[75] Glycosylated haemoglobin levels increased in the pasireotide group within 12 weeks and remained elevated throughout the study. Because somatostatin receptors are also expressed on pancreatic islet cells, somatostatin analogues may also affect glucose homeostasis. Several studies have demonstrated that pasireotide is associated with a higher frequency and severity of hyperglycaemia. Mechanistic studies in healthy volunteers have suggested that the hyperglycaemic effect of pasireotide is related to decreases in insulin secretion and incretin hormone response, but with no effect on insulin sensitivity. Pasireotide-induced hyperglycaemia can be managed with standard antidiabetic treatment with a possible additional beneficial effect of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists.[76,77] Owing to the hyperglycaemic side effects the EMA has currently advised to limit the use of pasireotide LAR as a second-line agent for patients inadequately controlled with first-generation LA-SSAs.

Oral octreotide

Recently a new oral octreotide formulation (Octreolin®) has been developed which enables intestinal absorption of octreotide with limited intestinal bioavailability. The results of a phase III multicentre trial on the efficacy of oral octreotide showed that switching from injectable LA-SSA to the oral formulation can effectively maintain biochemical control in 65% of cases after 13 months.[78]

In conclusion, optimal care of acromegaly patients should be achieved by a tailored treatment approach that is based on pituitary tumour characteristics, GH and IGF-I levels and patient comorbidities plus the availability of a multidisciplinary team of experts in experienced centres.

Serum IGF-I and GH levels should be measured by a validated assay in a dedicated endocrine laboratory, and clinicians should be aware of the various assay pitfalls. Currently, long-acting somatostatin analogues are the first line of medical treatment for acromegaly and surgery is the primary treatment option when the tumour is resectable, provided an experienced neurosurgeon is available. In case of a lack of response to a combination of LA-SSA, dopamine agonists and surgery, treatment with pegvisomant should be initiated. Pegvisomant is the most effective drug in achieving IGF-I normalisation to date, with or without co-treatment with LA-SSAs.

The recently introduced second-generation multireceptor somatostatin analogue pasireotide seems to have a higher efficacy compared with the first-generation analogues octreotide and lanreotide, but a significantly higher incidence in hyperglycaemia has been reported during pasireotide treatment.

DISCLOSURES

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ORIGINAL ARTICLE

When do patients prefer a direct oral anticoagulant over a vitamin K antagonist?

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ABSTRACT

Background: The reasons for patients to change their usual vitamin K antagonist (VKA) treatment to a direct oral anticoagulant (DOAC) are unexplored.

Method: A random sample of 200 patients treated with VKAs for the indication of atrial fibrillation from the Thrombosis Service in Amsterdam was selected. A survey, using the treatment trade-off technique, was sent to participants. The trade-off included four scenarios: 1 (no need for laboratory controls); 2 (less bleeding); 3 (less interactions); 4 (more effective).

Results: Under scenario 1, 57% of the patients would have made the switch, with a further increase to 65% with scenario 2 (trend value, p = 0.006, 95% CI 1.11-1.85). In addition, in each scenario patients who were less satisfied with their current treatment were more likely to switch to a DOAC compared with satisfied patients. The variables duration of treatment, gender, age and educational level did not affect the preference for a DOAC.

Conclusion: Patients considered no requirement for regular laboratory control and a lower risk of bleeding the most important arguments to switch to a DOAC.

KEYWORDS

Atrial fibrillation, direct oral anticoagulants, DOAC, vitamin K antagonists, VKA

What was known on this topic?

Treatment with vitamin K antagonists (VKAs) requires frequent laboratory control and dose adjustments. Direct oral anticoagulants (DOACs) form a new class of drugs that can be given in a fixed dose.

What does this add?

Patients consider the lack of frequent laboratory controls to be the major reason to change to a DOAC. Patient satisfaction about their VKA treatment and the reason for this satisfaction are essential in the decision process to switch from VKA to DOAC.

INTRODUCTION

Currently around 400,000 persons are treated with a vitamin K antagonist (VKA) in the Netherlands. The indications for use include atrial fibrillation, venous thrombosis and artificial heart valves.[1]

Considering the disadvantages of VKA, such as a small therapeutic window, requirement of frequent laboratory testing and interaction with food and medication, there is a need for an alternative. Therefore, direct oral anticoagulants (DOACs) were developed and recently introduced clinically. In contrary to a VKA, DOACs act directly on the coagulation system. Currently four DOACs are available: dabigatran, rivaroxaban, apixaban and edoxaban. Large phase III studies have been completed for these four compounds, for the indication of atrial fibrillation, as well as for venous thromboembolism.[2]

A lot of research has been done on the efficacy and safety of DOACs, but the view of the user, the patient, has not been explored. That is why the opinion of patients with

atrial fibrillation about DOACs in comparison with their usual VKA is investigated in this study. Furthermore, the influence of different variables such as age, education and treatment satisfaction are analysed to better understand the preferences for treatment.

METHOD

Study population

In this investigation the opinions were analysed of a random sample of 200 patients who are treated with VKA for the indication of atrial fibrillation at the Thrombosis Service in Amsterdam, the Netherlands. This was achieved by a questionnaire, which was sent by post and also included a return envelope and a recommendation letter from the director of the Thrombosis Service. After three weeks all 200 patients received a reminder.[3]

Survey format

The survey was designed according to the treatment trade-off technique, a method that offers the opportunity to compare the therapy preference between two different options.[4] The trade-off included four consecutive scenarios: 1 (no need for laboratory controls); 2 (less bleeding); 3 (less interactions); 4 (more effective). In each scenario one variable was changed and the patient was asked what their preference would be for each scenario: stay on VKA or change to a DOAC.[5,6]

The scenarios were developed in a way in which a proven statement for a DOAC is added for the following scenario. Using this approach it can be tested which statement the patient finds most important in his/her consideration for switching to a DOAC. In scenario 1 the efficacy and risks of VKA and DOAC are the same; the only difference is that the absence of the need for laboratory control for DOACs is mentioned. Scenario 1 is used as the baseline. In scenario 2, the additional statement indicates that the DOAC may be associated with a lower risk of severe bleeding. In scenario 3 it is made clear that a DOAC is less influenced by food and other medication. Finally, in scenario 4 it is stated that a DOAC is more effective. For each scenario the patient had to choose between 5 options; from 1: 'definitely stay on VKA' to 5: 'definitely switch to a DOAC'.

Feedback on the clarity and content of the questionnaire was obtained from different sources prior to constructing the final version of the survey. One of these sources was a large market and opinion company in Amsterdam with the aim to find the best way of communication to patients. A pilot survey was presented to 20 persons without atrial fibrillation to check the comprehensibility. Finally, information from six in-depth interviews with patients of the Thrombosis Service in Amsterdam was used to complete the design of the survey.

Statistical analysis

We set the minimum value of the response rate at 50%, with a target value of 70%. The data were analysed with a chi-square test. If this test was significant (p-value < 0.05) a generalised estimating equation was performed.[7] The generalised estimating equation takes into account that the preferences of all individuals are correlated in each single scenario. The chi-square test measures whether the percentage of patients that have a certain preference is equal over the whole study population.

The fourth and fifth option 'I would probably switch to a DOAC' and 'I definitely would switch to a DOAC' are merged for the present analyses. Certain variables were studied for the scenario preferences, i.e. age as dichotomous (≤ 65 and > 65 years) and quartiles, gender as men and women, education as highly educated (higher professional education and university) and other (all other levels of education). These variables were also tested with three groups and higher general continued education and pre-university education (HAVO, HBS and VWO) was used as the average education level group. The duration of current VKA treatment was analysed as < 4 years or > 4 years and in quartiles. The satisfaction level about current treatment was divided into three options: completely satisfied, satisfied and not satisfied/neutral.

RESULTS

Study population and response

In total 120 patients responded with a completed survey and were included in the analysis (response rate 60%, *figure 1*). The characteristics of the respondents are detailed in *table 1*. The average age was 75 years and half of the respondents had been treated with VKA for their atrial fibrillation for over four years. A total of 75% of respondents indicated that they were satisfied with their current treatment.

Preference

First the preference of the whole population per scenario between DOAC and VKA (*figure 2*) was analysed. In scenario 1, where it is detailed that a DOAC does not require laboratory investigations, slightly more than half (57%) of the respondents would switch to DOAC. When, in scenario 2, it is added that the risk of severe bleeding is decreased with a DOAC, this preference rises to 65% (trend value; p = 0.006, CI: 1.11-1.85). The advantage of no interactions with food or medication or greater efficacy of a DOAC did not result in noteworthy changes in the preference.

Variables preference

The variables age, gender, education and duration of treatment did not influence the preference for treatment. The satisfaction of the patient with the VKA treatment played a critical role.

Data were available for 118 respondents (*figure 3*). In the group of the respondents who are completely satisfied with their current VKA treatment, approximately a quarter (27%) preferred a DOAC over VKA in scenario 1, which increased to 41% in scenario 2. In contrast, in the group

Figure 1. *Response percentage process*

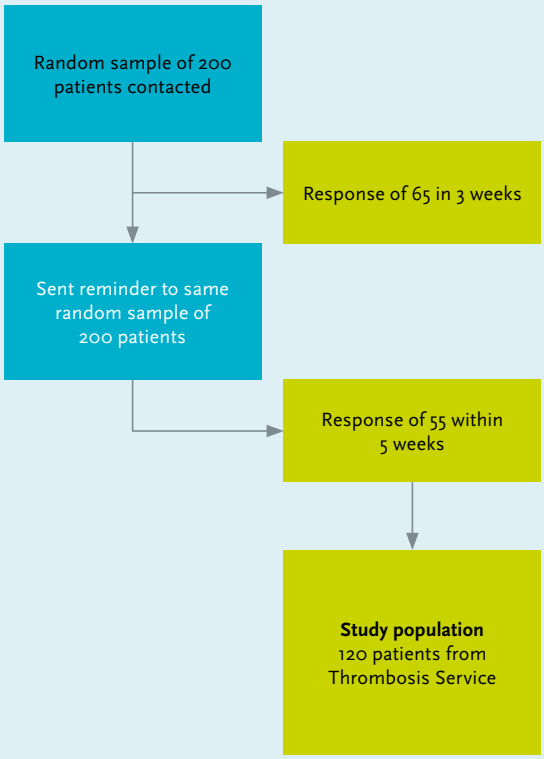
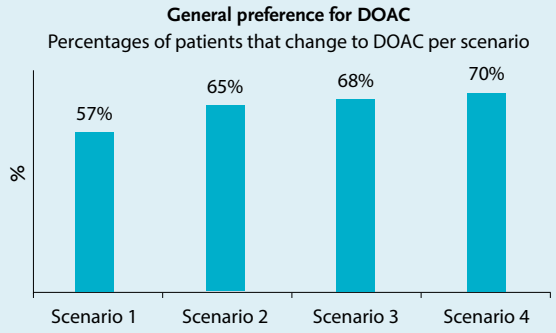


Table 1. *Characteristics of the 120 respondents*

Patient characteristics	
Age	
• Average ± 1 SD; years	75 ± 9.5
• ≤ 65 years (%)	16
Gender	
• Men (%)	57
Education	
• High*(%)	38
Duration of treatment with VKA	
• Average ± 1 SD; years	5.4 ± 4.4
• < 4 years (%)	48
Satisfaction level†	
• Completely satisfied (%)	28
• Satisfied (%)	47
• Neutral/not satisfied (%)	25

*Higher professional education and university; VKA = vitamin K antagonist; †about the VKA treatment.

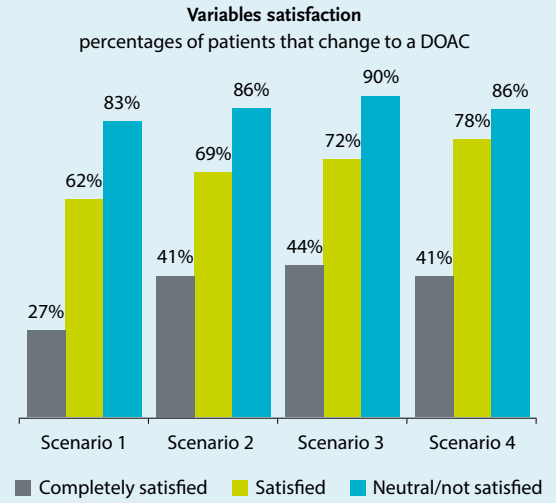
Figure 2. *General preference for a DOAC over a VKA*



DOAC = direct oral anticoagulants; **VKA = Vitamin K antagonist.

In scenario 1 the advantage of not requiring check-ups was mentioned for DOACs. In scenario 2 also the possible lower chances of severe bleeding are shown. In scenario 3 also the less interactions with food and medication is outlined. In the last scenario it is also mentioned that a DOAC is more effective.

Figure 3. *The correlation per scenario between the variables satisfaction and preference for a DOAC*



The completely satisfied group comprised 28% (n=34) of the respondents, the satisfied group 47% (n=55) and the neutral/not satisfied group 25% (n=29). The advantage in scenario 1 was no check-ups required for a DOAC, in scenario 2 the lower risk of serious bleeding, in scenario 3 less interactions with food or medication and in the last scenario the better efficiency.

who indicated not to be satisfied or to be neutral regarding their current therapy, which encompasses a quarter of the study population, 83% preferred a DOAC in scenario 1.

Medical recommendation

A relevant recommendation for medical practice is that besides including the patient's opinion in changing the type of anticoagulation, physicians should determine patient satisfaction about the current treatment. It appears to be the most important component in the decision to switch to a DOAC. The results show that in the category 'satisfied about current VKA treatment' already 55% would prefer a DOAC over VKA, only on the basis of no requirement for laboratory checks. A reason to prefer a DOAC to a VKA is the lack of laboratory visits despite satisfaction with the VKA treatment.

DISCUSSION

The most striking finding is that slightly more than half of the whole study population would already prefer a DOAC if only the need for regular blood checks is eliminated. This is a scenario that reflects the reality of DOAC treatment. When a small decrease in the risk of severe bleeding is added, this preference rises to two-thirds of the study population. These two factors seem to have the largest influence on the preference of the studied patients. An interesting fact is that the advantages that are thought to be of great importance by physicians, i.e. less interaction and possible greater effectiveness, are barely of importance to the patient.

Surprisingly, the studied variables age, education level and duration of treatment did not seem to have an influence on the preference, although results did show that satisfaction about current treatment played a significant role. There is a clear difference between the 'completely satisfied' and the 'neutral/not satisfied' group of patients, 27% and 83% respectively in the first scenario. It can be concluded that it is meaningful to be aware of the satisfaction level of the patient if a switch to a DOAC is considered.

As mentioned earlier, large trials on safety and efficacy have been completed for each DOAC, but the opinion of the patient should be explored more clearly.

In Germany, investigators are currently developing an instrument for doctors to identify the preference of a patient, thereby increasing compliance as well. By means of this instrument patients are asked to participate in the choice of anticoagulants to improve therapy outcome. From this it appears that patient preference plays an important role.[8]

Some of the aspects of our study require comment. First, the size of the study sample of 200 atrial fibrillation patients is limited. However, the study population is a random sample and representative for the atrial fibrillation patients seen at the Thrombosis Service of Amsterdam. Second, the response rate of 60% was moderate, though not unusual for postal questionnaires. This percentage is between our earlier fixed margins.

We used methods to make the response rate as high as possible, such as sending it by post with a recommendation letter from the director of the Service and a return envelope.[3] The observed response rate may affect generalisation of the findings of the present study. Third, it should be realised that, at present, specific antidotes for DOACs are lacking in case of major bleeding. The importance of this for the choice of the patient was not assessed in this study.

Furthermore the scenarios in the questionnaires sent out were all presented in the same order. Possible bias due to the influence of the scenario mentioned earlier cannot be investigated in this way and is not included in the analysis. The average high age of the study population increases the chance of not having a computer; the choice of a postal version eliminated this limitation.

Comments are conceivable on the structure of the survey. The treatment trade-off technique has a certain complexity, which is not universally understood.[4] On the other hand per scenario a possible advantage for a DOAC is added; this can give the impression that this will influence the opinion of the patient. However, we believe that this is not the case, since each added statement is supported by findings from clinical studies. The only expectation is in scenario 4, the possible better efficacy of a DOAC; however, this scenario hardly influenced the preference of the patient. The goal was to investigate what the patient considers to be important in switching to another medicine and which reasons would determine that switch. That is why efficacy had to be one of the statements.

CONCLUSION

Patients considered the lack of the need for regular laboratory control and the lower risk of serious bleeding important arguments to switch to a DOAC, even for patients who are satisfied about their current VKA treatment. Efficacy was considered less important. Less satisfied patients were more likely to prefer a DOAC over a VKA.

DISCLOSURES

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ORIGINAL ARTICLE

No accumulation of a prophylactic dose of nadroparin in moderate renal insufficiency

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ABSTRACT

Background: Low-molecular-weight heparins (LMWHs) have been shown to accumulate in patients with renal insufficiency, especially in therapeutic dosages. Although no appropriate studies have been conducted for prophylactic dosages of nadroparin, dose reduction is sometimes recommended, especially for high prophylactic dosages. We assessed accumulation of a prophylactic dose of 5700 IU subcutaneous nadroparin once daily in patients with renal insufficiency.

Methods: We conducted a prospective cohort study and measured peak anti-Xa activity four hours after subcutaneous nadroparin injection on day 1, 3, 5 and if possible day 10 in adults with and without renal insufficiency defined as a glomerular filtration rate (GFR) below or above 50 ml/min/1.73 m^2. Patients with a GFR below 10 ml/min/1.73 m^2 were excluded.

Results: We included 14 patients in each group. In the group with renal failure 12 patients had a GFR between 30 and 50 ml/min/1.73 m^2. Peak anti-Xa activity showed a high interindividual variability, but was fairly constant within each patient. There was no rise in peak anti-Xa activity on day 3 and 5 after consecutive administration. In the group with normal renal function, peak anti-Xa activity declined on day 5 compared with day 1 ($p = 0.005$).

Conclusion: Prophylactic dosages of nadroparin showed no accumulation in patients with a GFR between 30-50 ml/min/1.73 m^2. Dose reduction in this group could lead to suboptimal thromboprophylaxis. Due to underrepresentation of patients with a GFR < 30 ml/min/1.73 m^2 ($n = 2$), we cannot give recommendations for this group.

KEYWORDS

Kidney disease, low-molecular-weight heparin, nadroparin, pharmacokinetics

INTRODUCTION

Low-molecular-weight heparins (LMWHs) are at least as effective as unfractionated heparin (UFH) in the treatment and prevention of venous thromboembolism (VTE) and do not cause more bleeding complications.[1-6] LMWHs have many practical advantages, such as subcutaneous administration, higher bioavailability, longer half-life (permitting once or twice daily administration), a more predictable anticoagulant response and dose-dependent elimination.[7,8] A disadvantage is the possible accumulation in patients with renal insufficiency.

Several LMWHs are on the market, and they vary in mean molecular weight, elimination half-life and anti-Xa/IIa activity ratio.[9,10] LMWHs are mainly excreted by the kidney and as a consequence they can accumulate in patients with renal insufficiency, putting these patients at risk for haemorrhage.[11,12] Due to the differences described above, data on accumulation cannot easily be converted from one LMWH to another. For instance, accumulation has been found for therapeutic and prophylactic dosages of enoxaparin, certoparin and bemiparin in patients with renal insufficiency, but not for tinzaparin.[12-22] Information on prophylactic dosages of nadroparin is lacking.[23]

Nadroparin is a widely used LMWH with a mean molecular weight of 4300 Dalton, a bioavailability above 89% and an elimination half-life of 3.7 hours.[6,10] Nadroparin showed accumulation in a therapeutic dosage.[24] However, although no proper studies have been conducted to assess accumulation of prophylactic nadroparin, dose reduction is sometimes recommended, especially for high prophylactic dosages.[6,8,23,25,26] We chose to study the high prophylactic dosage of 5700 IU since the patients at high risk of VTE who are eligible for this dosage are of most interest, and lack of accumulation can be translated to lower dosages.[27]

The aim of this study was to assess accumulation of a prophylactic dosage of nadroparin 5700 IU by measuring

peak anti-Xa activity in patients with normal renal function and in patients with renal insufficiency.

MATERIALS AND METHODS

Study design

We conducted a prospective observational cohort study in medical and surgical patients at the Erasmus MC Rotterdam (a large university hospital) from March until August 2014. We did not interfere in nadroparin prescription, and included only patients in whom nadroparin was started by the treating physician. For every new prescription of once daily subcutaneous nadroparin 5700 IU (Fraxiparine®, GlaxoSmithKline, Zeist, the Netherlands) an alert was sent automatically to the research team by the electronic prescription system, after which the patient was screened for eligibility. The study was approved by the medical ethics committee and all patients gave written informed consent.

Patients

Eligible patients were 18 years or older with a recent creatinine measurement (not older than one month without an indication that it could have changed due to onset of new medical conditions) and a glomerular filtration rate (GFR) above 10 ml/min/1.73 m^2. A further requirement was the expectation that they would be on nadroparin 5700 IU for at least five days during hospitalisation. Furthermore, patients were not eligible if they had severe liver failure, were pregnant, had used LMWH prior to inclusion and if nadroparin was started in the intensive care unit (ICU). Enrolled patients were excluded if they left the hospital or if the nadroparin 5700 IU dose was stopped or changed.

Nadroparin administration and measurement of peak anti-Xa activity

Nadroparin was administered subcutaneously every day at the same time. To study peak anti-Xa activity, blood samples were taken four hours after nadroparin injection. Samples were taken on day 1, 3, 5 and if possible on day 10. Times of administration and blood sampling were registered by the nurse. If a blood sample could not be taken on these days for logistic reasons, blood sampling was performed the next day, four hours post injection. Blood samples were obtained in a 3.2% sodium citrate anticoagulated tube and sent immediately to the hospital haemostasis laboratory. Anti-Xa activity was measured by using a validated chromogenic assay (Sysmex CS-5100) and was expressed in international units per millilitre (IU/ml). The minimum anti-Xa activity that could be measured was 0.10 IU/ml.

Glomerular filtration rate

GFR was calculated using the Modification of Diet in Renal Diseases (MDRD) equation: GFR (ml/min/1.73 m^2) = 186 x (serum creatinine (µmol/l) / 88.4)-1.154 x age (in years)–0.203 x 0.742 (for women) and multiplied by 1.21 for negroid patients (which was not the case for any of the patients).

Outcomes

Primary outcomes were peak anti-Xa ratio on day 5 compared with day 1. Secondary outcomes were peak anti-Xa ratio on day 3 compared with day 1, bleeding complications, VTE and mortality within 30 days. Bleeding complications were classified as major bleeding, clinically relevant non-major bleeding and minor bleeding as suggested earlier.[28]

Statistical analysis

Based on studies on other LMWHs and on clinical relevance, we defined the statistical detection threshold as 30% (i.e. percentage increase of peak anti-Xa activity considered to be accumulation).[25] Six patients per group needed to be included for a power of 0.80 using an alpha of 0.05. We aimed for six patients in GFR groups of > 50 ml/min/1.73 m^2, 40-50 ml/min/1.73 m^2, 30-40 ml/min/1.73 m^2, 20-30 ml/min/1.73 m^2, and 10-20 ml/min/1.73 m^2. We used a paired t-test for the primary outcome, an unpaired t-test for continuous baseline characteristics and chi-square for categorical variables. A p-value below 0.05 was considered significant.

RESULTS

Patient characteristics

We included 36 patients in the study. Eight were excluded from statistical analyses because they had less than two peak anti-Xa measurements which restricted the analysis to 28 patients. No patients with GFR 10-20 ml/min/1.73 m^2 were included and only two with GFR 20-30 ml/min/1.73 m^2. The group of GFR 30-40 ml/min/1.73 m^2 consisted of five patients and the group of GFR 40-50 ml/min/1.73 m^2 of 7 patients. We pooled the data into two groups for analysis: normal renal function (GFR > 50 ml/min/1.73 m^2) and moderate renal insufficiency (GFR 20-50 ml/min/1.73 m^2) (*figure 1*).

Table 1 shows the baseline characteristics. While GFR was stable in the group with normal renal function, it was more variable in the group with moderate renal insufficiency: In four patients, GFR improved to > 50 ml/min/1.73 m^2 during follow-up (on day 3, 4 or 5), while in one patient the GFR did improve but remained below 50 ml/min/1.73 m^2. GFR decreased in one patient, and only one measurement was available in four patients.

Primary outcomes: peak anti-Xa activity

Table 2 shows the mean peak anti-Xa activity on day 1, day 3 and day 5 and the ratios of day 3 and 5 to day 1, while *figures 2A and 2B* show the peak anti-Xa activity for all patients during follow-up including measurements on other days than included in the calculations.

Table 1. *Patient characteristics*

Characteristics	GFR 20-50 n=14	GFR >50 n=14
Age	69 (3.3)	68 (2.2)
Female	10 (71%)	6 (43%)
Weight	79 (4.4)	72 (3.1)
Surgery	8 (57%)[1]	13 (93%)[1]
GFR at start day	39 (2.4)	75 (4.0)
Follow up days*	5.0 (0.6)	5.9 (0.7)
Number of measurements	2.7 (0.2)	2.9 (0.2)

Numbers are given as mean (standard error) or number (%); [1]p = 0.029 between groups; *mean length between first and last measurement; GFR = glomerular filtration rate (ml/min/1.73 m²).

Patients with GFR > 50 ml/min/1.73 m² (n = 14) on average had a lower peak anti-Xa activity after daily nadroparin administration during follow-up than on day 1, but this was only significant when day 5 was compared with day 1 (ratio 0.7; p = 0.005).

In the group with GFR 20-50 ml/min/1.73 m² average peak anti-Xa peak activity did not change after daily nadroparin administration (*table 2*).

If the target range of peak anti-Xa activity for optimal thromboprophylaxis is considered to be between 0.2-0.5 IU/ml, 13 patients had suboptimal peak anti-Xa activity at some point during the study, while only one measurement was above the suggested target range: 0.54 on day 3, in a patient with GFR 70 ml/min/1.73 m².[29]

In a large number of patients peak anti-Xa activity decreased after repetitive administrations (*figure 2*), which seemed to correlate with undergoing surgery (p = 0.023). The administration of nadroparin was not interrupted in any of the cases.

Secondary outcomes: bleeding complications and death

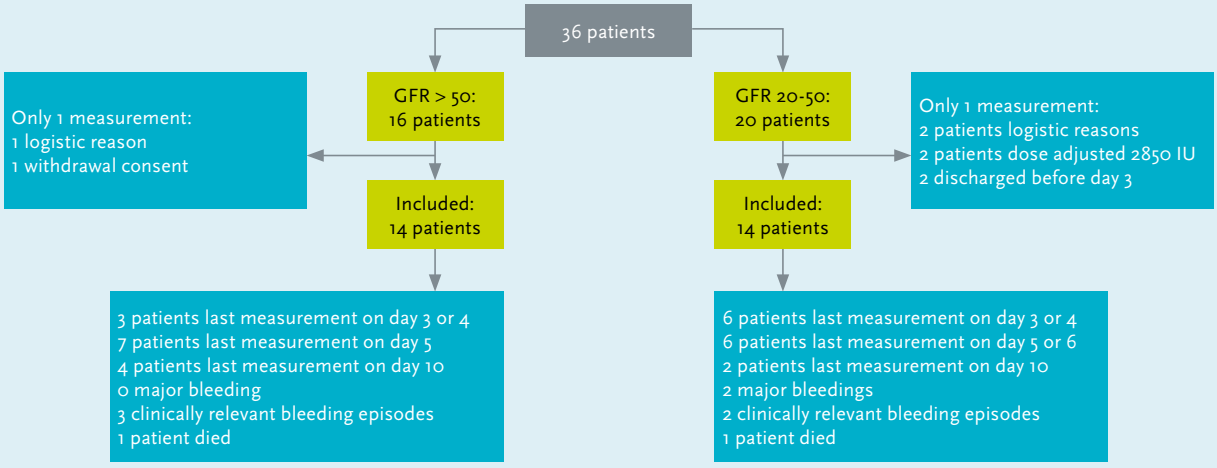
During the study, seven patients developed bleeding complications, of which four were in the group with impaired renal function (more details in *figure 1*). In both

Table 2. *Anti-Xa activity*

GFR[a]	Day 1	Day 3	Day 5	Ratio day 3/day 1	Ratio day 5/day 1
GFR >50	0.34 (0.03) n=13	0.27 (0.04) n=12	0.24 (0.02)[1] n=11	0.78 (0.11) n=11	0.70 (0.09) n=10
GFR 20-50	0.28 (0.02) n=11	0.27 (0.03) n=12	0.22 (0.01) n=7	1.01 (0.05) n=9	0.78 (0.07) n=4

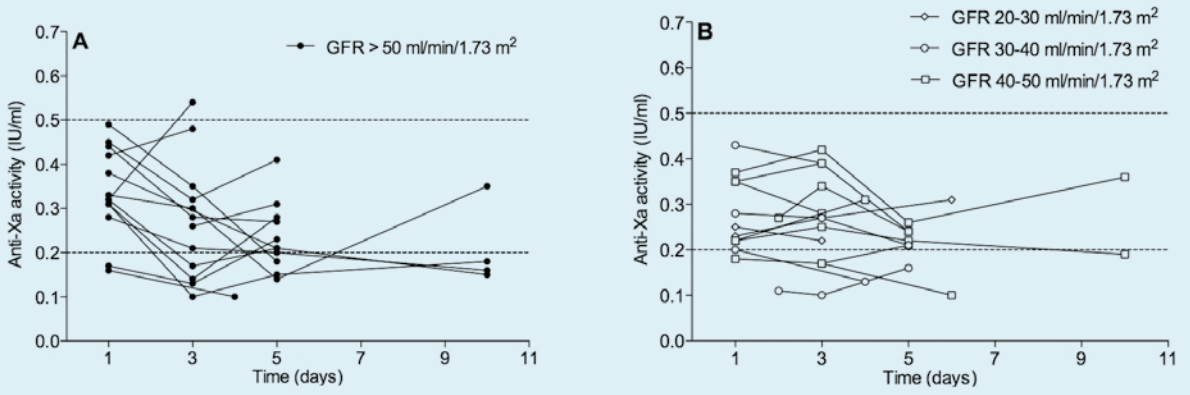
Values are mean (standard error);[1]p = 0.005 for difference with day 1; GFR = glomerular filtration rate (ml/min/1.73 m²).

Figure 1. *Flow diagram*



Numbers are given as mean (standard error) or number (%); [1]p = 0.029 between groups; *mean length between first and last measurement; GFR = glomerular filtration rate (ml/min/1.73 m²).

Figure 2. *Peak anti-Xa activity. 2A. Peak anti-Xa activity in GFR > 50 ml/min/1.73 m². 2B Peak anti-Xa activity in GFR 20-50 ml/min/1.73 m²*



groups, one patient died due to other reasons than bleeding or VTE. Although our sample size is not large enough to find significant differences, there were no correlations between clinical outcomes and renal function or peak anti-Xa activity. For instance, one major bleed was detected on day 6 while peak anti-Xa activity on day 4 was 0.13 IU/ml and the patient was switched to 2850 IU on day 5 due to a further decrease of GFR. In the other patient with major bleeding, severe liver failure including low levels of coagulation factors (including factor V) likely attributed to bleeding, since peak anti-Xa activity was normal on day 3 and nadroparin was terminated in advance of the bleeding.

DISCUSSION

We found no accumulation of a prophylactic dosage of 5700 IU nadroparin in patients with moderate renal insufficiency with a GFR between 30-50 ml/min/1.73 m² during a mean follow-up of five days. Peak anti-Xa activity appeared to be lower on day 5 than on day 1 in a large number of patients, especially in patients who underwent surgery. Although the correlation between anti-Xa activity and clinical outcomes is not unambiguous, it is the best available test to measure LMWH activity, and we therefore conclude that a high prophylactic dosage of nadroparin is safe in patients with GFR 30-50 ml/min/m².[1,30-34] Due to underrepresentation of patients with a GFR < 30 ml/min/1.73 m² we cannot give a conclusion for this group.

Our results are in accordance with a small earlier multiple-dose study.[35] This study in six patients with nephrotic syndrome with a GFR above 30 ml/min did not find nadroparin accumulation. An earlier single-dose study did find a prolonged half-life and a higher area under the curve in renally impaired patients compared with healthy participants, but no significant differences in peak anti-Xa activity.[25] Although a prolonged half-life after a single dose does not necessarily lead to clinically significant accumulation, this single-dose study seems to be the basis for the currently recommended prophylactic dose reductions in patients with a GFR below 50 ml/min.[6,8,25,26,36,37]

It is surprising that in a large number of patients peak anti-Xa activity decreased after repetitive administrations (*figure 2*), which seemed to correlate with undergoing surgery (p = 0.023). We confirmed administration of nadroparin on all days including the day of surgery. Earlier studies that reported a decrease of peak anti-Xa activity mainly included patients on the ICU and decrease of peak anti-Xa activity could be explained by ICU-related factors such as multi-organ failure and vasopressin use.[38-42] We cannot explain the observed changes in anti-Xa activity. This finding does not affect our conclusion, because significantly more patients in the group with normal renal function underwent surgery. This might be due to the fact that in patients with normal renal function surgery will more often be the reason for hospitalisation while patients with renal insufficiency had more comorbidity leading to hospitalisation for other reasons.

We found that peak anti-Xa activity showed a high interindividual variability, while the intraindividual variability was low in each patient. The high interindividual variability suggests there are other patient factors besides renal function that influence LMWH pharmacokinetics. This was also reported by other authors, except for tinzaparin.[20,22,25,26,36,37,43] We found a significant correlation between anti-Xa activity measurements and body weight. For instance, for the first measurement the Pearson correlation coefficient was -0.439 (p = 0.019). There was no significant correlation between age and anti-Xa activity. Therefore, the high interindividual anti-Xa variability could be partly explained by body weight, probably due to differences in volume of distribution. These findings did not influence our results, since ratios based on measurements within the same patient were used for analyses (*figure 2*).

The strength of this study is that we used several consecutive days of dosing and multiple peak anti-Xa activity measurements in each patient, enabling us to objectively observe nadroparin accumulation. Second, we classified the patients in groups with GFR below and above 50 ml/min/1.73 m², because it has become common practice to consider nadroparin dose reduction in GFR < 50 ml/min. Therefore our conclusion is directly applicable.[6,8,25,26]

The observational study design caused some limitations, including changes in renal function while patients were already included in the study. We decided to classify groups based on GFR at inclusion. Of the four patients with renal insufficiency at baseline in whom peak anti-Xa activity increased on the last day, two patients had a GFR that had increased > 50 ml/min/1.73 m². Since this study aimed to define whether dose adjustment is necessary, we think this observation further supports the findings that it is not necessary to adjust the starting dosage of prophylactic nadroparin.

A second possible limitation is that with 28 evaluable patients the sample size was small. However, the study was powered to detect significant differences if present and is comparable with other LMWH accumulation studies.[24,25,35,37]

Another limitation is that we were not able to include patients with a GFR < 20 ml/min/1.73 m². This is probably due to pre-emptive dose adjustment in patients with severe renal insufficiency. This is a major limitation, since this is the group of most interest: if any accumulation occurs it will be in this group. Earlier studies showed both an increased bleeding risk and a more than twofold VTE risk in patients with severe renal insufficiency.[45-51]

In conclusion, in patients with moderate renal insufficiency no accumulation of high prophylactic dosages of nadroparin could be detected. Therefore no dose adjustment is necessary when GFR is 30-50 ml/min/1.73 m².

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DISCLOSURES

All authors declare they have no conflict of interest.

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CASE REPORT

Acute episode of cyclic vomiting syndrome preceded by arterial hypertension – Case presentation and review

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ABSTRACT

Cyclic vomiting syndrome (CVS) is a functional disorder with recurrent episodes of vomiting. Between these episodes patients recover to well-being. Lack of awareness often leads to a delay in making the diagnosis. The diagnosis is based on a typical medical history and exclusion of other causes. We present a case report of a middle-aged patient who had recurrent episodes of vomiting for 12 years coinciding with hypertension. After excluding other causes, CVS was diagnosed. The episodes of acute vomiting were stopped by administration of antiemetic and sedative drugs and urapidil reduced the hypertension. Treatment with sedatives stops vomiting caused by the emetic centre of the central nervous system.

KEYWORDS

Cyclic vomiting syndrome, CVS, vomiting, hypertension, amitriptyline, smoking

INTRODUCTION

Cyclic vomiting syndrome (CVS) is a functional disorder, which comprises recurrent and stereotypical episodes of nausea and vomiting, lasting for hours or even days[1-17] and intervals of well-being with absence of symptoms between the vomiting episodes, lasting days to months.[1-7,9-15,17,18]

CVS is a rare disease that can occur in all age groups, but has its onset predominantly in childhood.[1,5,8, 11-15] Adults typically develop CVS in middle age.[1,5,9,19,20] Prevalence is about 2% in childhood and the disease is less frequent in adults.[2,3,7,10,14,18,21]

CVS comprises four phases.[1,5,14,15] Phase I is defined as the symptom- and nausea-free interval between episodes of vomiting and nausea.[5,6,15] If symptoms of CVS occur as prodromes with nausea and indisposition these indicate the next phase.[3,5,15,17,22] Increasing nausea and the start of vomiting characterise phase III, often accompanied by abdominal pain.[1,5,14,15] Vomiting episodes are in most cases stereotypical in manner and duration. The vomiting episodes occur on average 6-12 times per year and last several hours to 7 days.[1-14,21,23-25] The frequency of vomiting in patients with CVS can reach 20 times per hour.[5,7,14] As soon as the vomiting stops, the recovery period (phase IV) begins, which individually lasts between minutes to days. After phase IV, CVS returns to the symptom-free phase I.[5,15,17,25]

Frequently reported triggers of CVS vomiting episodes are stress, tiredness, infections, asthmatic attacks, hypoglycaemia or hyperglycaemia, and even chocolate or cheese.[1,4,5,7-10,14]

Little is known about the pathogenesis of CVS.[4, 7-11,13-16,21,23] It has been suggested that CVS is a functional disorder with strong associations towards migraine.[2,5,7-9,11,13-15] Moreover, familial clustering of CVS has been reported.[8,16]

To date, there is no specific test to diagnose CVS.[9,15,17] The diagnosis of CVS requires a typical accurate anamnestic report, fulfilment of specific diagnosis criteria and most importantly the exclusion of other disorders that are associated with recurrent vomiting.[12,15,16] The ROME III diagnosis criteria of 2006 comprise recurrent, self-limiting, stereotypical episodes of high-intensity vomiting lasting less than seven days without an organic cause.[1,5,10,13-15,17] The frequency of vomiting episodes must exceed two episodes in the last year.[13-15]

Typical symptoms of CVS as nausea, vomiting and abdominal pain are highly unspecific and can also occur

in many other diseases. Therefore, and because of a lack of awareness, making the correct diagnosis of CVS is often delayed for months or even years.[1,4,5,14,17,18,26,27]

Important differential diagnoses of acute or recurrent vomiting of CVS are gastroenteritis, gastroesophageal reflux, gastric and duodenal ulcers, appendicitis, cholecystitis, pancreatitis, hepatitis and other infections, porphyria and other metabolic disease, pyelonephritis, medication side effects, drug use, endometriosis, abdominal angina, gastric stenosis, neurological disease, gastroparesis or vestibular factors.[5,14,15,17,23]

To date, neither treatment of acute vomiting episodes nor prophylaxis of CVS is evidence based.[11,15]

Symptomatic acute treatment comprises antiemetic medications (e.g. ondansetron, granisetron, dimenhydrinate), sedatives (e.g. lorazepam) and antimigraine therapy (e.g. sumatriptan, zolmitriptan).[1,2,4,7,8,10-14,21,23,24,28] Moreover hypovolaemia should be corrected and use of proton-pump inhibitor has been recommended.[4,5,7,10,14,17] Hypovolaemia is associated with a risk of collapse as well as thromboembolic events.

Prophylactic treatment consists of avoidance of triggering factors for vomiting episodes with sufficient sleep, physical exercise and adequate nutrition.[13,18] A medical prophylactic therapy of CVS is worth considering, especially if the frequency of vomiting episodes exceeds once a month.[1,4,7,18] Prophylactic treatment with amitriptyline and propranolol has been the best studied and the efficacy of both medications has been proven.[1-5,7,9-14,17,19,20,29] Amitriptyline at a dose of 5-25 mg per day currently represents the standard prophylactic treatment of CVS.[2,7] Beside these two drugs, a large number of other drugs have been tested for prophylaxis of CVS, with varying degrees of success.[1,2,4,7,10-12,14,19,21,24,30,31]

The prognosis of CVS is good. Diet, trigger factor avoidance and medical prophylaxis are beneficial in most CVS patients.[5,15]

CASE REPORT

A 56-year-old woman presented to our emergency department with hypertensive crisis and nausea. The patient's blood pressure was elevated up to 205/140 mmHg. Restlessness was another symptom.

She reported having recurrent episodes of vomiting for 12 years. These vomiting episodes occurred up to twice a week and lasted about 12-16 hours with more than two vomiting attacks per hour. The vomiting attacks were almost stereotypical and between them she fully recovered to a sense of well-being. During and before vomiting episodes, she did not have headaches. The symptom-free intervals varied in duration between days and several months. She reported that hypertensive blood pressure was common during the vomiting episodes. In the intervals free from symptoms, her blood pressure was normal to low with systolic blood pressure values of 100-120 mmHg. Arterial hypertension was not known.

On several occasions she had been under the care of a physician due to vomiting attacks, but mostly without success. Several examinations were performed to find the cause of the patient's recurrent episodes of vomiting. She underwent multiple endoscopies and ultrasounds, which showed no pathological findings. The last oesophago-gastro-duodenoscopy was performed about three months ago. Moreover, she was examined by a neurologist, who performed a cranial computer tomogram which was again without pathological findings. Antiepileptic drugs and antidepressants such as topiramate and desipramine were unable to prevent the recurrence of the episodes of vomiting. As a result, the recurrent vomiting led to a significant psychological strain with social alienation and conflicts in her professional and private life. The patient denied drug abuse such as cannabis or cocaine.

During the hypertensive crisis on the day of admission, the patient took her husband's antihypertensive drugs (nifedipine and clonidine) which did not sufficiently lower her blood pressure. Physical examination demonstrated a good general condition and no pathological findings. The blood pressure was elevated up to 225/105 mmHg. We admitted the patient with the tentative diagnosis of hypertensive crisis within the context of arterial hypertension and CVS.

We started antihypertensive therapy with urapidil for acute treatment of her hypertensive crisis and ramipril and thiazide for long-term antihypertensive therapy. In this way, her blood pressure could be reduced towards the normal range. Standard ECG and 24-hour ECG showed no pathological findings. The 24-hour blood pressure examination showed a good blood pressure profile under the started antihypertensive treatment. The highest systolic blood pressure was 145 mmHg. We detected a non-dipper finding associated with the patient's restlessness in the night hours. Transthoracic echocardiography showed a normal left ventricular ejection fraction, concentric hypertrophy of the left ventricular myocardial muscle and no pathological valve findings.

During the hospital stay her blood pressure was well adjusted in the first two days. Then, the blood pressure increased once again and the patient reported increasing nausea. Her heart rate was also accelerated. Although we started to treat the patient's nausea with dimenhydrinate, her restlessness with oral lorazepam and the hypertensive crisis with oral nifedipine, the patient soon developed recurrent vomiting associated with increasing restlessness and persistent hypertensive crisis.

Abdominal ultrasonography showed a status post cholecystectomy with normal width of the bile duct and

no further pathological findings. Laboratory examinations, including hepatitis screening, were without pathological findings. Especially the inflammation markers were in the normal range.

We diagnosed an acute episode of CVS combined with a hypertensive crisis. Antiemetic treatment did not decrease the frequency of the vomiting attacks. The blood pressure increased once again up to 230/120 mmHg. Intravenous sedation was started with lorazepam to interrupt the vomiting episode. Furthermore, hypovolaemia was corrected by intravenous administration of isotonic NaCl fluid, and pantoprazole was injected intravenously to prevent gastric or oesophageal lesions. We administered urapidil intravenously to reduce the blood pressure in the context of a hypertensive crisis.

The vomiting episode was interrupted when the patient was sedated. The blood pressure dropped due to cessation of the vomiting and intravenously administered urapidil. The patient fully recovered after eight hours of sleep.

Therefore, we confirmed our tentative diagnosis of CVS with a concomitant hypertensive crisis. Moreover we concluded that the hypertensive crisis might have triggered the vomiting episode. The diagnosis of CVS and the suggested trigger was explained to the patient. We recommended identification and avoidance of triggering factors for the vomiting episodes as well as consideration of a pharmaceutical prophylaxis with amitriptyline or propranolol.

DISCUSSION

Our case report presents a typical history of a CVS patient. The patient had been under the care of physicians several times due to vomiting attacks without finding the correct diagnosis. Making the correct diagnosis of CVS was delayed for more than ten years, although extensive examinations were performed by physicians, gastroenterologists and neurologists. Without a correct diagnosis, treatment was symptomatic and ineffective. Because of the highly unspecific symptoms of nausea, vomiting and abdominal pain, it is not uncommon that patients with undiagnosed CVS undergo surgery for suspected appendicitis or acute cholecystitis. Treatment with sedatives stops the vomiting caused by the emetic centre of central nervous system.

It is important that physicians become more aware of CVS. CVS should be recognised and identified early in the course of disease and adequate treatment for the acute phase and prophylaxis should be started, if necessary.

During a CVS episode, concomitant hypertensive crisis and tachycardia are recognised in about 20% of all CVS patients.[5] In this context, hypertensive crisis and tachycardia occur at the beginning of the vomiting episode and are primarily caused by stress during the episodes of vomiting.

The 56-year-old woman in our case report presented with hypertensive blood pressure values both during the vomiting phase of CVS, but also before the prodromes with nausea had started. Therefore, we suggest that the hypertensive crisis was not only a concomitant symptom of an acute vomiting episode in CVS, but may also be a triggering factor for CVS vomiting episodes. It is well known that gastrointestinal symptoms can occur with severe hypertensive crisis.[32] It could be hypothesised that these patients with an elevated blood pressure and tachycardia response in an acute episode of vomiting have a higher sympathetic level than those CVS patients without this response. These patients seem to be more prone and receptive to sympathetic triggers with an earlier response. Interestingly, in our patient, we found typical echocardiographic signs of a hypertensive heart disease with left ventricular hypertrophy, without a known history of arterial hypertension. Therefore, arterial hypertension could have been present – unnoticed – for a longer period of time.[33] We diagnosed arterial hypertension and started antihypertensive treatment.

Of peculiar interest in the treatment of hypertensive crises related to CVS is the fact that antihypertensive treatment of the hypertensive crises during the vomiting episode with intravenous urapidil was successful, while nifedipine therapy was not. Nifedipine is an antihypertensive drug with a peripheral effect on the vascular system, while urapidil acts on the peripheral postsynaptic α-receptors as well as on the central serotonin receptors.

In irritable bowel syndrome, serotonin (5-HT) has been described as an important neurotransmitter and paracrine signalling molecule in the gastrointestinal tract.[34] 5-HT is released from enterochromaffin cells, which initiate peristaltic, secretory, vasodilatory, vagal and nociceptive reflexes.[34] The enteric nervous system is a semiautonomous effector system connected to the central autonomic nervous system.[34] Activation of parasympathetic and sympathetic nerve systems modulates the enteric nervous system via afferent and efferent communications.[34] Bidirectional brain–gastrointestinal tract interactions involve 5-HT pathways.[34] 5-HT is one of the major signalling molecules in the central nervous system with influence on diverse systems and physiological functions, including mood, appetite, nausea, sleep, memory and the learning process and homeostasis.[34] 5-HT modulators have been successfully used to treat many disorders including anxiety, migraine, nausea, chronic pain and hypertension.[34] Therefore, 5-HT could be the pathomechanistic link between arterial hypertension and CVS vomiting episodes.

Avoidance of CVS trigger factors is primarily beneficial in the prophylaxis of further CVS vomiting episodes[5,15] and

may also be beneficial in reducing the severity of vomiting and nausea in the acute vomiting phase, but in most cases a vomiting episode cannot be terminated exclusively by trigger avoidance, which is also the case with an acute migraine attack. Therefore the treatment of hypertensive crisis within a CVS vomiting episode should be helpful and supportive but not be crucial to terminate an acute CVS vomiting episode.

CONCLUSION

These described facts lead to the hypothesis that sympathetic activation and 5-HT modulation have an impact on the vomiting episodes of CVS in some CVS patients.

CONFLICTS OF INTEREST

None.

DISCLOSURES

None.

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CASE REPORT

Non-myeloablative allogeneic stem cell transplantation: a new treatment option for acquired angioedema?

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ABSTRACT

Introduction: Acquired angioedema is a rare disorder causing recurrent life-threatening angioedema, due to decreased activity of C1 esterase inhibitor.

Case report: A 57-year-old man presented to our hospital with recurrent swelling of the hands, lips, tongue, scrotum and throat. Lab examination showed the presence of an IgM kappa monoclonal antibody. Additional analysis showed that in the IgM fraction autoantibody activity against C1 esterase inhibitor was present. This confirmed the diagnosis of acquired angioedema in the presence of lymphoplasmacytic lymphoma.

Despite standard therapy, there was an increase in the episodes of laryngeal oedema. Therefore it was decided to perform a non-myeloablative allogeneic haematopoietic stem cell transplantation, with his HLA-identical brother as donor. The post-transplantation course was without complications. Five years following alloSCT he is in complete remission without symptoms and with increased C1 esterase inhibitor activity.

Discussion: In this case all other known treatment options for severe acquired angioedema failed. This is the first case describing treatment of severe acquired angioedema, caused by lymphoplasmacytic lymphoma, with an alloSCT.

KEYWORDS

Acquired angioedema, allogeneic stem cell transplantation, treatment

What was known on this topic?

Acquired angioedema is a rare disorder causing recurrent life-threatening angioedema due to decreased activity of C1 esterase inhibitor.

What does this add?

Many or probably all patients are effected by altered B cell proliferation control which, in case of failure of standard treatment options, might be controlled or may be cured by a non-myeloablative allogeneic stem cell transplantation.

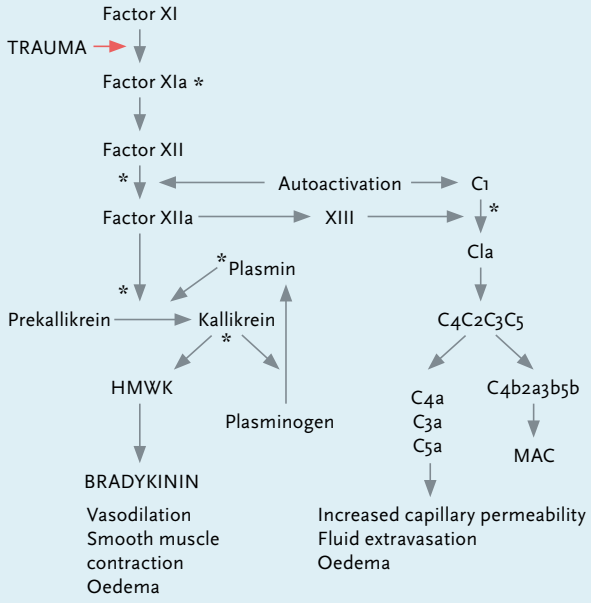
INTRODUCTION

Acquired angioedema is a rare disorder, characterised by recurrent attacks of non-itching, self-limiting subcutaneous oedema (or angioedema) and can present with life-threatening airway obstruction or with abdominal symptoms that mimic an acute abdomen, as upper respiratory tract and gastrointestinal tract are sites that are most often affected. Deficiencies in the inhibitor of the first component of human complement (C1-Inh) leading to angioedema can be either acquired or hereditary.[1]

In acquired angioedema the activity of C1-Inh is decreased and, subsequently, serum complement factors 4 (C4) and 1q (C1q) are low. Due to decreased levels of C1-Inh there is a continuous autoactivation of C1 leading to unrestrained activation of the classical pathway of the complement system. C1-Inh also inhibits factor XIIa and kallikrein, proteases belonging to the contact pathway. Increased vascular permeability due to massive bradykinin release via the contact pathway is thought to be the primary cause of symptoms in acquired angioedema (*figure 1*).[2]

Mechanisms causing acquired C1-Inh deficiency have been broadly investigated. Historically, acquired angioedema was defined as a constellation of syndromes, due to the many associated conditions such as lymphoproliferative diseases, systemic lupus erythematosus, primary

Figure 1. *Pathogenesis of angioedema*



* C1 esterase inhibitor – site of action; Cla = complement activation; HMWK = high-molecular-weight kininogen; MAC = membrane attack complex.

myelofibrosis, autoimmune haemolytic anaemia, cryoglobulinaemia and liver hydatidosis.[3] In 1986, Jackson *et al.*[4] first described an IgG autoantibody inactivating C1-Inh demonstrating an autoimmune mechanism to be the cause of the C1-Inh deficiency in otherwise healthy patients. Acquired angioedema was divided into two types: type I, associated with lymphoproliferative disorders developing anti-idiotyping antibodies directed against the M-component. This immune complex causes activation of C1 and consumption of C1-Inh. Type II is primarily due to direct autoantibodies, impairing the activity of C1-Inh. Now it is becoming clear that there is an overlap between these two groups, since there are patients with lymphoproliferative diseases who also have anti-C1 inhibitor antibodies.[5-7] Thus, the division of acquired angioedema into these two types has been abandoned. Subsequent work revealed that acquired angioedema usually arises in the setting of an uncontrolled clonal proliferation of B lymphocytes. However, the mechanism by which clonal B cell disorders lead to depletion of C1-Inh and angioedema remains incompletely understood.

CASE REPORT

A 57-year-old male presented to our hospital with recurrent swelling of the hands, lips, tongue, scrotum and throat. He had no allergies, no urticarial rash, and was not on any medication known to provoke angioedema. Physical examination was normal. Laboratory tests showed the presence of an IgM kappa monoclonal antibody (2.76 g/l), with decreased activity of C1-Inh and consistent C1q and C4 consumption. CT scan of the thorax and abdomen showed no abnormalities. Bone marrow examination showed an increase in B-lymphocytes (24%), which were monoclonal. Immunophenotyping showed a monoclonal B lymphocyte population of 6%, positive for CD19, CD20, CD22, CD79a and expressing IgM kappa, compatible with a lymphoplasmacytoid malignant lymphoma (also frequently called Waldenström's disease, however this term is not part of the current lymphoma classification). Additional analysis showed that in the IgM fraction autoantibody activity against C1-Inh was present (Professor M. Cicardi, Milan). This confirmed the diagnosis of acquired angioedema as a result of an IgM antibody directed against C1-Inh (type II).

Treatment was started with danazol and tranexamic acid. During the subsequent years his symptoms worsened, requiring high-dose purified human C1-Inh (15,000 units Cetor®/month). Despite this treatment he developed recurrent episodes of life-threatening laryngeal swelling, necessitating artificial ventilation. The M-protein was stable and there were no signs of osteolytic lesions or lymphadenopathy. Several courses of immunosuppression (high-dose prednisone, cyclophosphamide, azathioprine, mycophenolate mofetil and rituximab) were given with temporary relief of symptoms but recurred during maintenance therapy with prednisone, danazol and low-dose immunosuppression with prophylactic infusion of high-dose purified C1-Inh. In fact, he showed an increase in episodes of life-threatening laryngeal oedema. Two courses of rituximab, cyclophosphamide, vincristine and prednisone were given, again without a decrease in symptoms. C1-Inh activity at that time was only 7%. To treat the IgM-producing clone directly, we performed a non-myeloablative alloSCT, with his HLA-identical brother as donor. Awaiting the transplantation, he received two courses of rituximab, fludarabine, cyclophosphamide and mitoxantrone, again without response. Pre-transplant conditioning consisted of fludarabine and total body irradiation. The post-transplantation course was without complications. Immunosuppression consisted of mycophenolate mofetil until day +85 and tacrolimus until day +180. At day +100 chimerism was 97% donor and he was free of symptoms. To date (now year +5 after transplant) he is still in clinical remission with a C1-Inh activity of 75% and no clinical symptoms. There are no signs of graft versus host disease.

DISCUSSION

Here, we show successful treatment of acquired angioedema with a non-myeloablative alloSCT. The patient had very frequent and severe attacks of angioedema

requiring high doses of Cetor®. After transplantation there was complete resolution of symptoms. Hereby, we provide evidence that alloSCT can suppress the antibody-producing clone resulting in an increase of C1-Inh activity with a subsequent resolution of symptoms. Whether this patient is cured of the underlying M-protein producing clone remains to be seen since C1-Inh activity has not yet completely normalised.

Acquired angioedema is frequently associated with lymphoproliferative disorders, developing anti-idiotyping antibodies and/or autoantibodies. Autoimmunity and lymphoproliferation are closely connected in acquired angioedema. Different forms of B cell disorders coexist and/or evolve into each other, and seem to be dominated by alterations in the control of B cell proliferation. Blocking autoreactive or neoplastic B cell proliferation is probably essential in the treatment of acquired angioedema in these cases.[2] Levi *et al.*[8] and Ziakas *et al.*[9] both described patients who were cured after treatment with anti-CD20 monoclonal antibody rituximab. There are data available supporting the efficacy of alloSCT in IgM-producing lymphoplasmacytic lymphoma. Kyriakou et al.[10] described the outcome of alloSCT in 86 patients using either myeloablative (MAC; n = 37) or reduced-intensity conditioning (RIC; n = 49): the three-year non-relapse mortality rate was 33% for MAC and 23% for RIC, five-year overall survival rate was 62% for MAC and 64% for RIC and five-year progression-free rate was 56% for MAC and 49% for RIC. Gilleece *et al.*[11] described the outcome of alloSCT in the setting of lymphoplasmacytic lymphoma patients in the UK. In nine allografted patients transplant-related mortality at 12 months was 44%.

Acquired angioedema can be treated with androgenic steroids, such as danazol. The underlying mechanisms are not yet clear, but it is believed to work either by stimulating the production of C1-Inh in the liver, increasing levels of aminopeptidase P, an enzyme that inactivates kinins, or by additional undetermined mechanisms.[12] Antifibrinolytics, such as tranexamic acid, inhibit the conversion of plasminogen to plasmin and also inhibit activated plasmin. These steps in fibrinolysis are also inhibited by C1-Inh (*figure 1*).[13] Administration of purified C1-Inh is also used in the treatment of acute attacks of acquired angioedema. Patients with acquired angioedema usually need much higher doses than patients with hereditary angioedema (20 units/kg).[7] The bradykinin B2-receptor antagonist icatibant is suggested to be of value, based on its characteristic to antagonise the bradykinin B2 receptor (*figure 1*).[14,15] At the time of treatment of this patient, no published data were available on the use of icatibant in patients with acquired angioedema. In addition, as we consider this patient to have a type 1 disease, we choose to treat the underlying disease by performing a non-myeloablative alloSCT.

In conclusion, to our knowledge, this is the first case to be described of acquired angioedema that was successfully treated with alloSCT. Five years after transplantation the patient is still in complete remission with no episodes of angioedema. Although further studies are warranted, this indicates that alloSCT may be a treatment option for acquired angioedema in case other known treatment options fail.

DISCLOSURE

The authors have declared that they have no conflict of interest.

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PHOTO QUIZ

A patient with right-sided deep venous thrombosis and lymphadenopathy on ultrasound

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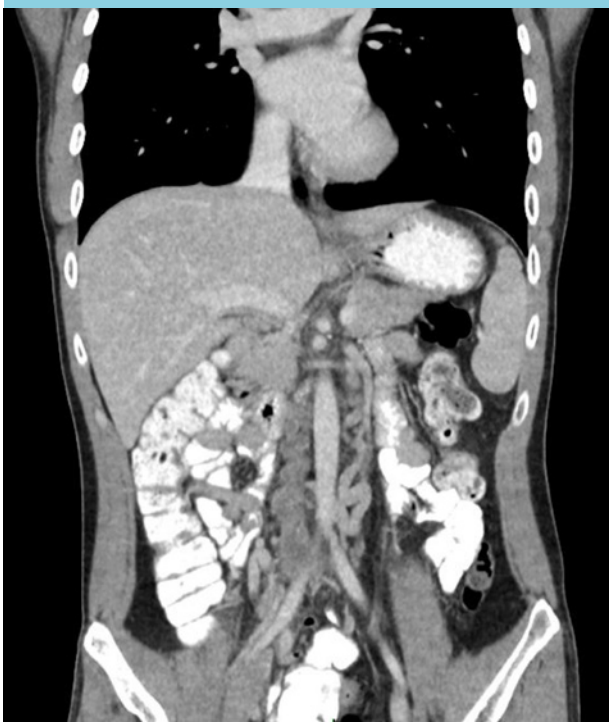
CASE REPORT

A 27-year-old male without a medical history went to the general practitioner complaining of back pain which radiated to the groin. The general practitioner referred the patient to the radiologist for an ultrasound of the groin and lower abdomen. The radiologist confirmed a deep venous thrombosis (DVT) of the right popliteal vein to the femoral vein and para-aortal lymphadenopathy. No provocative factors for the DVT were found. The patient was not on any medication. He did not smoke or do drugs and only drank alcohol socially. His family history was positive for a brother with testicular cancer and a grandmother on his mother's side had a DVT in puerperium. The family history was negative for clotting or congenital disorders.
On suspicion of a germ cell tumour, a testicular ultrasound was performed that showed no pathological testicular masses. The tumour markers beta-human chorionic gonadotropin and alpha-fetoprotein were not elevated.
Since a malignant origin for the DVT and para-aortal lymphadenopathy was suspected a CT scan was performed.

Figure 1. *CT-scan showing para-aortal vascular anomalies*



WHAT IS YOUR DIAGNOSIS?

See page 387 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 386)

A PATIENT WITH RIGHT-SIDED DEEP VENOUS THROMBOSIS AND LYMPHADENOPATHY ON ULTRASOUND

DIAGNOSIS

DVT as a result of an obstructed vena cava inferior (IVC; *figure 2* no. 1) which is most likely to be congenital since there is extensive azygous and hemiazygous circulation (*figure 2* no. 2). DVT has a multifactor aetiology which includes a state of hypercoagulability or venous stasis. The incidence of DVT increases with age. The incidence of DVT in patients younger than 40 is estimated at 1 per 10,000. In patients younger than 40 years an IVC anomaly is present in 5-6.7% of the cases.[1,2] These anomalies include absence of the suprarenal or infrarenal segment or a double IVC with suprarenal anomalies.[3,4] Formation of the IVC is a complex process which consists of fusion and regression of the three paired veins comprising the supracardinal, posterior cardinal and subcardinal veins. Anomalies of the IVC is a result of impaired fusion and regression of these three paired veins.[4] In patients with a congenital IVC anomaly a prominent azygos and hemiazygos system is present to assure blood flow from the distal extremities to the heart. However, blood flow in these collateral systems is inadequate thereby predisposing to DVT. In 35.4-50% the DVT is bilateral compared with 10% in patients without an IVC anomaly. More than half of the patients with DVT and an IVC anomaly also had a thrombophilic defect (such as deficiency of antithrombin, protein C, or protein S, antiphospholipid antibody syndrome, a factor V Leiden mutation or a prothrombin gene mutation), thereby adding to the risk of developing DVT and suggesting an interaction between IVC anomaly and thrombophilic defects in the pathogenesis of DVT.[2,3] However, literature is lacking on this hypothesis.

Our patient had bilateral DVT, which was more extensive in the right leg than in the left. Besides the obstructed IVC, CT images did not show any other vascular anomalies. It is suspected that the back pain was caused by growth of a pre-existing DVT which occurred as a consequence of the insufficient blood flow in the collateral systems, thereby predisposing to DVT. Unfortunately, no radiological images were taken at a younger age. The patient was treated with a vitamin K antagonist and compression stockings. Ten days after starting the initial treatment the back pain faded and was absent a month later. Since the DVT is very extensive, treatment with a vitamin K antagonist will be continued for at least two years after which an even longer treatment will be considered. The patient has refused analysis for thrombophilic defects for the moment since it would not have any consequences for now.

In our hospital it is protocol to treat patients with a DVT with vitamin K antagonists. However recently new oral anticoagulants (NOAC) are also being used and studied for the purpose of extended treatment of DVT. Studies show that NOACs are non-inferior compared with vitamin K antagonists in treating DVT and have less adverse complications such as bleeding.[5] Therefore DVT could also be treated with a NOAC. However, there is no antidote for NOACs as there is for vitamin K antagonists.

Figure 2. *An obstructed vena cava inferior (1) most likely congenital since there is an extensive collateral system (2) present*

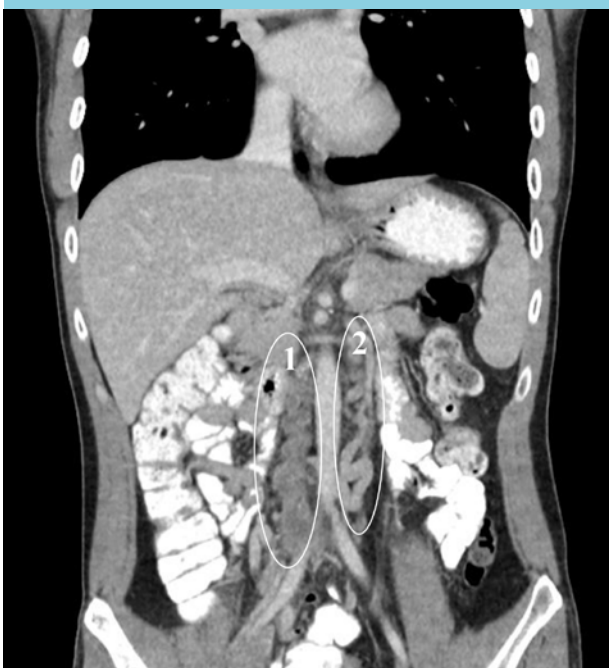


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PHOTO QUIZ

Hypertension at a young age: beware of the unexpected

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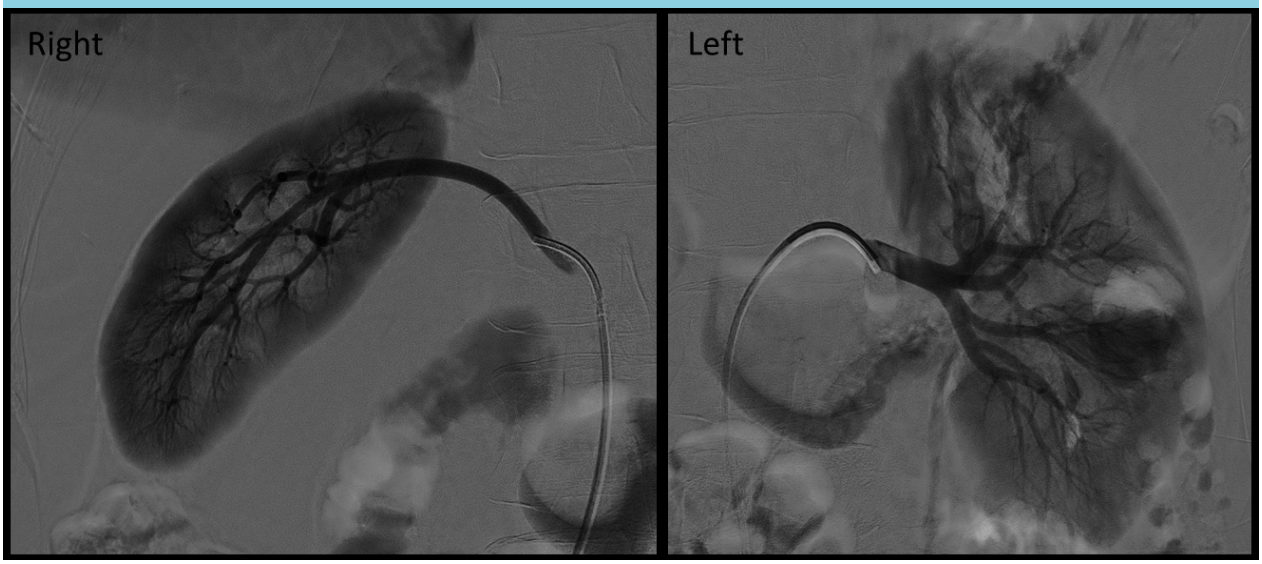
CASE REPORT

A 25-year-old man with a clear medical record was referred because of accidentally discovered hypertension. He had a normal lifestyle and body mass index (20.4 kg/m^2) and was not using any medication or other substances. A thorough physical examination was normal, except for high blood pressure (220/95 mmHg). Although 24-hour ambulatory blood pressure measurements showed a white coat effect, his blood pressure was nevertheless elevated: 151/101 mmHg. Routine laboratory tests, including serum potassium level, were normal and the estimated glomerular filtration rate was 85 ml/min/1.73m^2. As echocardiography revealed left ventricular hypertrophy, treatment with valsartan 80 mg daily was initiated, resulting in a decrease in the blood pressure to 130/75 mmHg. Given his young age and the presence of left ventricular hypertrophy, we suspected renovascular hypertension (e.g. due to fibromuscular dysplasia) and performed an invasive renal digital subtraction angiography (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 389 for the answer to this photo quiz.

Figure 1. *Selective digital subtraction angiography of the right and left kidney*



ANSWER TO PHOTO QUIZ (PAGE 388)

HYPERTENSION AT A YOUNG AGE: BEWARE OF THE UNEXPECTED

DIAGNOSIS

The renal angiography showed no signs of renal artery stenosis or fibromuscular dysplasia. However, the right kidney appears hypoplastic and displaced with a somewhat curved renal artery. Because of this uncommon deformity, we performed a computed tomography (CT) scan (*figure 2*). This revealed a 9 by 10 cm large retroperitoneal tumour compressing and displacing the kidney. Fine-needle biopsy demonstrated benign neural cells, corresponding to a schwannoma. Distant metastases were excluded with an MRI-PET scan. As the patient had no symptoms, his blood pressure was well controlled, and removal of this non-malignant lesion required major surgery (probably including removal of the kidney and inferior caval vein), a wait-and-see policy was followed with regular radiological follow-up.

DISCUSSION

We describe a very uncommon secondary cause of hypertension in a patient in whom the kidney was compressed by a schwannoma. A schwannoma is a benign nerve sheet tumour which is often found in neurofibromatosis, but can also occur sporadically as in this patient.[1] As malignant transformation is rare, radiological surveillance without surgical resection is safe.[1] Previously, other tumours inducing hypertension by compression of the renal artery have been described, including leimoyosarcomas, pheochromocytomas, and papillary carcinomas.[2] Presumably, compression of the kidney and displacement of the renal artery decreased renal perfusion, resulting in increased renin secretion and, subsequently, an increase in blood pressure.

Given the young age of onset we initially suspected renal artery fibromuscular dysplasia, an often curable form of renovascular hypertension.[3] Although the renal arteries appeared normal (i.e. no signs of fibromuscular dysplasia or renal artery stenosis), other abnormalities on the renal angiogram pointed us to compression of the renal artery by an adjacent tumour. This illustrates that physicians should be aware of uncommon secondary causes of hypertension in young patients.

Figure 2. *Arterial phase computed tomography (CT) scan of the abdomen, showing a 9 by 10 cm large retroperitoneal mass (arrow) compressing and displacing the right kidney*

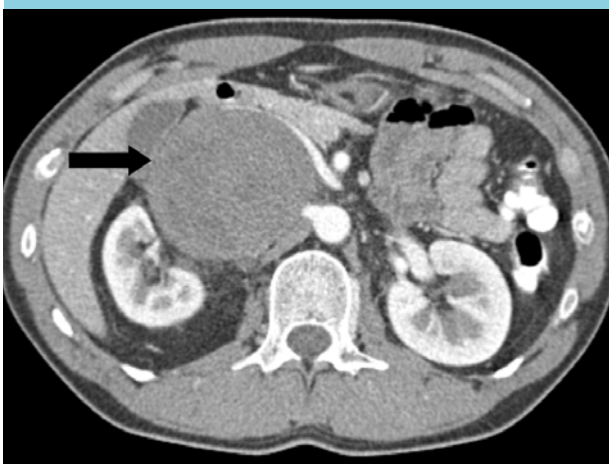


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PHOTO QUIZ

Chronic diarrhoea and repeated bowel obstruction in an 84-year-old woman

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CASE REPORT

An 84-year-old woman was admitted for diarrhoea and weight loss occurring over the past six months. She described an attack of abdominal pain and bowel obstruction five months previously. Oral intake was stopped and she was switched to intravenous fluids. A laparotomy failed to define the cause of obstruction at that time. The obstruction disappeared after the operation, but her diarrhoea (up to 9 to 10 times daily, watery) recurred, although stool investigations remained negative. An abdominal MRI was negative.

She was admitted with another episode of bowel obstruction. On this admission, a plain X-ray showed multiple air-fluid levels (*figure 1*) and an abdominal CT revealed distal ileal dilatation of 5.5 cm. Laboratory studies showed iron deficiency anaemia. Her blood urea nitrogen, creatinine, transaminase, glucose and electrolyte levels were normal. Oral feeding was stopped and intravenous fluid was initiated. The obstruction improved within two days without any intervention.

A gastroduodenoscopy was performed and duodenal biopsies showed active enteritis with partial subtotal atrophy and increased intraepithelial lymphocytes (*figure 2*). CD3 staining confirmed an increased number (> 25 per 100 enterocytes) of lymphocytes in the intestinal epithelium. Bone-mineral density showed severe osteoporosis.

Figure 1. *Plain X-ray showing multiple air-fluid levels (arrows)*

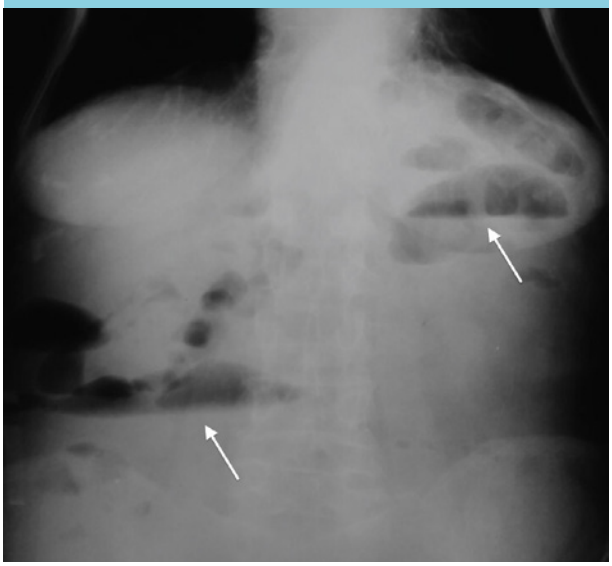
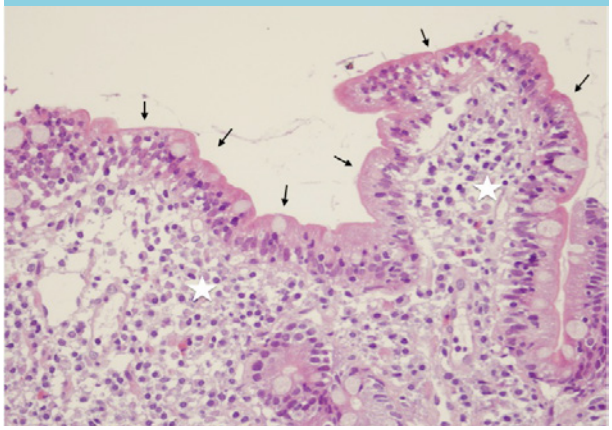


Figure 2. *Duodenal biopsy showing blunt and shortened villi (arrows) and increased intraepithelial lymphocytes (stars) (Haematoxylin and Eosin, x 400)*



WHAT IS YOUR DIAGNOSIS?

See page 391 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 390)

CHRONIC DIARRHOEA AND REPEATED BOWEL OBSTRUCTION IN AN 84-YEAR-OLD WOMAN

DIAGNOSIS

Anti-gliadin IgG (39.3 U/ml), anti-gliadin IgA (>300 U/ml), anti-tissue transglutaminase IgG (>300/ml), and anti-tissue transglutaminase IgA (> 300/ml) were strongly positive. Her ileus improved within two days of stopping oral nutrition and switching to parenteral fluids. She was diagnosed with coeliac disease and started on a gluten-free diet, osteoporosis treatment, and iron replacement therapy. Her diarrhoea improved within five days.

Two weeks later, she was doing well and a repeated coeliac serology showed a decrease of the following antibodies: anti-gliadin IgG 20.5 U/ml, and anti-tissue transglutaminase IgG 59.3 U/l. After 12 months, she was symptomless under the gluten-free diet.

Chronic diarrhoea, characterised as three or more loose stools per day lasting for at least four months, is caused by inflammatory bowel disease, irritable bowel disease, malabsorption syndromes, chronic infections, food, and drugs. Coeliac disease, another cause of chronic diarrhoea, is a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals. The inflammation and intestinal mucosal damage may cause a wide spectrum of gastrointestinal symptoms, nutritional abnormalities, and systemic complications including anaemia and osteoporosis, secondary autoimmunity and malignancy.

This disease was once considered a disease of children and was thought to rarely occur in the elderly. In fact, the peak age of diagnosis is in the fourth and fifth decades of life[1] and some evidence shows an increased rate of diagnosis among adults and the elderly.[2] Overall, 19 to 34% of newly diagnosed coeliac disease patients are over 60 years of age.[3] The incidence rates are increasing among all age groups, including the elderly.[3]

Coeliac disease presents a spectrum of clinical features that range from severe malabsorption with nutritional deficiencies to presentation with a single symptom, such as anaemia, osteoporosis or osteomalacia. Intestinal symptoms are less prominent in elderly coeliac patients than in younger ones. Some elderly patients may present with acute complications such as intestinal obstruction or perforation. Although the exact mechanism of obstruction is not known, it is suggested to originate from electrolyte deficiency due to primary malabsorption or increased faecal loss or both or from disturbed motility of the gastrointestinal system due to gluten-driven mucosal inflammation. Motor abnormalities may present radiologically with a decreased number of jejunal folds, an increased number of ileal folds, small bowel dilatation, and intussusception. Our patient's obstruction and ileal dilatation improved after withholding gluten. Our patient presented twice with intestinal obstruction and her clinical picture was improved inadvertently by stopping oral nutrition.

Intestinal lymphoma is rarely associated with coeliac disease. The diagnosis may be difficult since it may be multifocal. Our endoscopic biopsy did not show any evidence of lymphoma. Imaging studies were negative for any involvement for the extranodal sites. The clinical course may exclude lymphoma: during gluten-free follow-up of 12 months, she was doing well; in lymphoma, however, overall survival is 7-10 months despite chemotherapy.[4]

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PHOTO QUIZ

Severe abdominal pain three weeks after a hemi-hepatectomy

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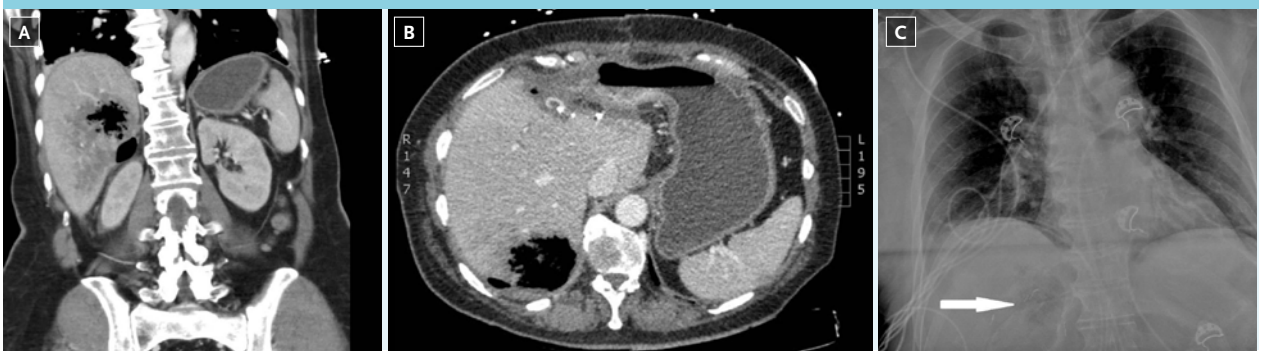
CASE REPORT

A 71-year-old woman presented with severe upper abdominal pain and vomiting for one day. She had undergone a left-sided hemi-hepatectomy due to liver metastases of a neuroendrocrine tumour of an unknown primary three weeks earlier. One week later, she received a percutaneous biliary drain due to a bile leak, and underwent endoscopic retrograde cholangiopancreatography (ERCP) with stent placement. Her medical history included cerebral vascular accident, appendectomy and mild pancreatitis. At presentation, the physical examination showed tachypnoea, direct and rebound tenderness of the right upper quadrant of the abdomen and normothermia. Laboratory analysis showed haemoglobin 6.6 mmol/l (reference range 7.5-10.0 mmol/l), leucocytes 40.1 x 10^9/l (reference range 4-10 x 10^9/l), neutrophils 37.9 x 10^9/l (reference range 1.5-9 x 10^9/l), bilirubin 179 µmol/l (reference range < 17 µmol/l), lactic acid 5.0 mmol/l (reference range 0.5-2.2 mmol/l), creatinine 119 mmol/l (67 mmol/l two weeks earlier) (reference range 50-90 µmol/l) and free haemoglobin 358 µmol/l (reference range < 0.16 µmol/l); due to massive haemolysis, liver enzymes and lactate dehydrogenase could not be measured. Haptoglobin was unfortunately not available either. The biliary drain produced some pus, but no bile. Blood cultures were drawn, an chest X-ray and a computed tomography (CT) scan of the abdomen were performed (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 393 for the answer to this photo quiz.

Figure 1. *A and B: Computed tomography of the abdomen in axial (A) and coronal (B) slicing shows a gaseous configuration in the liver, as seen in infections with gas-forming bacteria such as C. perfringens, C: On the chest radiograph an air configuration in the liver can be seen*



ANSWER TO PHOTO QUIZ (PAGE 392)

SEVERE ABDOMINAL PAIN THREE WEEKS AFTER A HEMI-HEPATECTOMY

DIAGNOSIS

CT scan of the abdomen revealed a gas-forming pyogenic liver abscess, indicating an infection with anaerobic bacteria such as *Clostridium perfringens*. The other symptom which was strongly indicative of a *C. perfringens* infection was massive intravascular haemolysis. Our patient was immediately started on piperacillin/tazobactam and within two hours a percutaneous drain was inserted and pus was evacuated. Blood cultures showed both *C. perfringens* and *Enterococcus faecium*. Abscess cultures showed *C. perfringens, E. faecium* and *Klebsiella oxytoca*, therefore vancomycin intravenously and locally via the abscess drain were added.

Hyperbilirubinaemia and high serum free haemoglobin suggested haemolysis and possibly bile duct obstruction. The biliary drain became productive again so re-ERCP with stent replacement was performed and successful. Surprisingly, our patient has not been haemodynamically or respiratorily compromised. However, she did develop acute tubular necrosis secondary to the haemolysis and was started on continuous venovenous haemofiltration and eventually intermittent haemodialysis. After one month in hospital, our patient was discharged.

C. perfringens bacteraemia is a rare but well-known cause of massive haemolysis and a fulminant – often fatal – infection. Van Bunderen *et al.* reviewed 40 cases; most cases involved immunocompromised patients with underlying malignancy or diabetes and about 80% of these patients did not survive (median survival was only eight hours).[1] However, liver abscesses due to *C. perfringens* infection have only been sparingly described. A patient similar to ours, although without a history of invasive procedures, died within hours.[2] More recently, Kurasawa *et al.* wrote a case report about a diabetic patient with a fatal *C. perfringens* liver abscess and also reviewed 124 cases of *C. perfringens* septicaemia and 30 cases of *C. perfringens* liver abscesses, whereas in the first group 50 patients and in the latter group only three patients survived. All survivors underwent some form of abscess drainage.[3] In conclusion, *C. perfringens* septicaemia is a rare but very serious disease were early recognition is of the utmost importance. In all septic patients with signs of massive haemolysis and/or gas-forming abscesses, *C. perfringens* infection should be considered and treated rapidly with adequate antibiotic coverage and aggressive drainage.

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LETTER TO THE EDITOR

Is hyperhomocysteinaemia a minor risk factor for venous thrombosis or subject to publication bias?

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To the Editor,

In the editorial by Lugthart[1], we were surprised to find hyperhomocysteinaemia being classified as a known risk factor for venous thrombosis. The consensus now is that hyperhomocysteinaemia is not a risk factor for venous thrombosis. The lack of dissemination of this in the general field of medicine might have to do with several findings. First, patients with cystathionine β-synthase deficiency (CBSD), leading to homocystinuria, have a high risk of thrombosis.[2] Reduction of homocysteine levels with B vitamins in these patients led to a spectacular decrease of 80% in the absolute cumulative risk of any thrombosis in one landmark study.[2] However, homocysteine levels in patients with CBSD are much higher than 100 µmol/l, while homocysteine levels in the normal population are much lower. Therefore, translating treatment of homocystinuria in patients with CBSD to a normal population needs to be done with caution. Indeed (second reason), trials with vitamin B in individuals without CBSD have not shown a decrease in risk of venous thrombosis.[3,4]

A third reason why it has been believed that hyperhomocysteinaemia is a cause of venous thrombosis is due to Mendelian randomisation studies. Individuals with the MTHFR C677T mutation, who have genetically higher levels of homocysteine, are at increased risk of venous thrombosis according to the latest meta-analysis on this issue, conducted in 2005.[5] However, the authors did not exclude the possibility of publication bias. To do so, we drew a funnel plot on the data of this meta-analysis[5] including 52 of 54 studies (data not retrievable for 2). As shown in *figure 1*, potential publication bias cannot be excluded, i.e. smaller studies or studies of lower quality reporting against an association might be underrepresented. Moreover, in 2007 Bezemer et al.[6] found no association between MTHFR C677T genotype and venous thrombosis (see diamond in *figure 1*), providing further evidence that the association between hyperhomocysteinaemia and venous thrombosis is probably biased.

Altogether, hyperhomocysteinaemia appears to be a very minor risk factor for venous thrombosis in general, based on evidence that might have been subject to publication bias, without the possibility to intervene on the attributable risk. In accordance, it is no longer mentioned in the list of risk factors for venous thrombosis in acknowledged guidelines (American College of Chest Physicians,[7] National Clinical Guideline Center from the UK[8]). We appeal for a consistent and similar policy in the general field of medicine in order to prevent further misperception on this topic.

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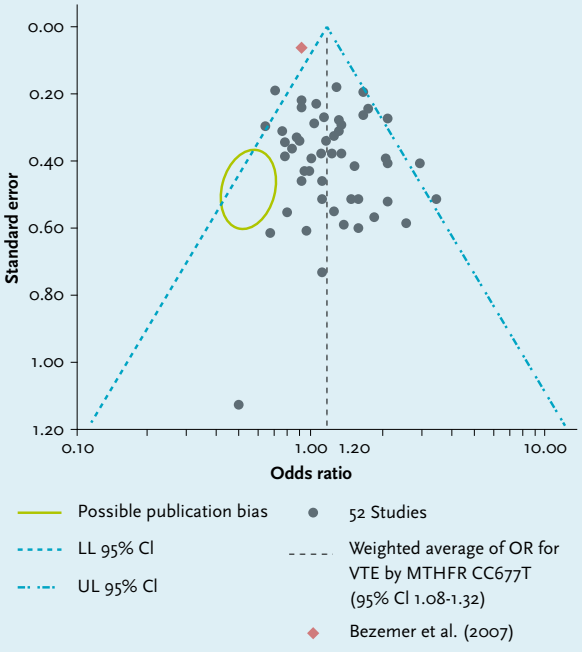
Figure 1. *Funnel plot with pseudo 95% confidence intervals (dotted-dashed lines). We see the precision of a study (estimated by the standard error of the effect) plotted against its reported odds ratio (estimate of the relative risk of VTE by the MTHFR CC677T mutation). In general, the precision of a study increases with its size and when it approaches the 'true' effect size (dashed line). Possible publication bias can be identified when a 'gap' between the dashed line and a 95% confidence interval line is observed (i.e. the funnel plot is not symmetric). Often, this concerns small studies (low precision) supporting the 0-hypothesis, which might be the case here (indicated by the green circle)*



LL = lower limit of pseudo 95% confidence interval; UL = upper limit of pseudo 95% confidence interval; VTE = venous thromboembolism.

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