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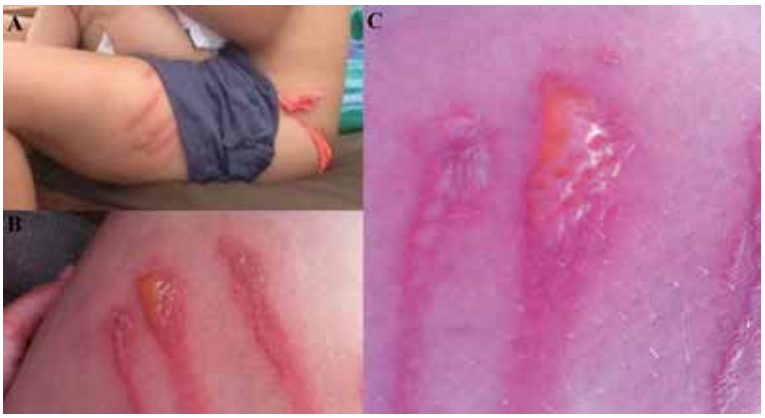

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EDITORIAL

Bariatric surgery: a metabolic solution or a paradigm for novel treatment options?

E.F.C. van Rossum

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The prevalence of obesity has increased substantially, afflicting approximately 10% of the world's population.[1] Obesity has important negative physical, psychosocial and economic consequences.

In general, quality of life in morbid obesity is decreased, which is well demonstrated by the findings that patients seeking weight loss surgery are on average willing to accept a 13% risk of death to achieve their most desired health or weight state. Social stigma or public distress, and the interference of role functioning due to physical limitations, are reported to be the major determinants of their lower quality of life.[2] Worldwide, a large number of patients undergo bariatric surgery to mitigate obesity-related complications. Metabolic surgery, as bariatric surgery is also called, has indeed been demonstrated to significantly improve or resolve cardiometabolic complications of obesity, such as type 2 diabetes (T2D), hypertension, and dyslipidaemia, as well as sleep apnoea and psychological disturbances.[3] With respect to T2D, a recent meta-analysis showed that the overall T2DM remission rate in the first 12-24 months after surgery is 63.5%.[4]

An intriguing aspect of bariatric surgery is that it greatly improves glycaemic control, often within days after surgery, and out of proportion to postoperative weight loss.[5] Therefore, in the clinical practice of bariatric surgery for patients with insulin-dependent T2D, the dosages of insulin used should be reduced to prevent postoperative hypoglycaemia. Cruijsen *et al.* show in their study in this issue of the Netherlands Journal of Medicine that an insulin dose reduction of 75% may be safe, as shown by the observations that no hypoglycaemic events occurred in the early postoperative phase, and 26% of all glucose measurements on the day of surgery and only 4% of the measurements one week after discharge were above 15 mmol/l.[6] This type of studies are valuable to provide practical tools to physicians involved in bariatric care. At present not all underlying mechanisms of the fast T2D remission have been revealed. However, elucidation of these mechanisms is of paramount importance, since they may yield improvement of surgical techniques or novel noninvasive anti-diabetic treatment strategies.

In this context, it has been shown that vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) induce changes in the regulation of intestinal hormones leading to decreased appetite and increased satiation.[5] Remission of T2D occurs more frequently after VSG and RYBG than after laparoscopic adjustable gastric banding (LAGB). After all these types of surgical procedures, hepatic insulin sensitivity increases rapidly, and in a later phase insulin sensitivity also increases in the peripheral tissues. In addition, VSG and RYBG are also associated with improved beta cell function and an exaggerated postprandial secretion of glucagon-like peptide 1, which is attributed to the altered transit of nutrients. The vagal pathway is also suggested to be involved in the neurohumoral regulatory pathways controlling post-bariatric glucose homeostasis and appetite. Although the exact mechanisms are not yet clear, it has recently been suggested that alterations in the gut microbiota, as well as changes in bile acid concentrations, may contribute to post-bariatric improved glucose and lipid metabolism.[5]

For these reasons, metabolic surgery to treat T2D, rather than targeting obesity per se, is receiving growing attention. At present, on average, it is the most effective treatment for these conditions.[7] It should be noted, however, that the potential benefits have to weighed against the still problematic short-term and long-term risks of surgery. These risks consist of complications (17%), reoperation (7%), and death (0.31% after 30 days).[7] In the long term, nutritional complications frequently occur, which can be attributed to several causes: preoperative malnutrition, decreased food intake and inadequate nutrient supplementation. The last-mentioned can be due to poor compliance or insufficient types of supplements, malabsorption, or inadequate professional nutritional support by long-term follow-up.[8] Standard multivitamin supplementation is often not sufficient to prevent nutritional deficiencies after RYGB. It was shown that two

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years after RYGB, 98% of the patients required at least one specific supplement (e.g. calcium, vitamin D, vitamin B-12, iron) in addition to the multivitamin supplementation.[8] Also, deficiencies of other nutrients such as copper and zinc can lead to adverse consequences such as poor immunity, anaemia, hair loss, and neuromuscular dysfunctioning.[9]

The effects of bariatric surgery beyond decreasing BMI and improving T2D are expected to be stabilisation or improvement of cardiovascular, renal, retinal, peripheral nervous, reproductive and hepatic end-organ damage. However, most of these outcomes have not yet been studied with randomised controlled clinical trials comparing bariatric surgery with non-surgical interventions.[10] These trials are needed to better evaluate whether the risks of surgery outweigh the significant benefits for end-organ outcomes. This is in particular important considering also the risk of weight recidivism post-bariatric surgery.

PREDICTORS OF SUCCESSFUL POST-BARIATRIC WEIGHT LOSS

It has been extensively demonstrated that bariatric surgery is highly effective as a weight loss treatment for a large number of patients.[7] With non-surgical weight loss programs the problem is often to maintain the lost weight in the long term. New insights into the well-known yo-yo effect after dietary restriction have recently been obtained. This was demonstrated by a study by Sumithran *et al.* showing that one year after a ten-week very-low-energy diet, the levels of circulating mediators of appetite that stimulate weight regain do not revert to baseline values.[11] This biological drive towards weight regain may also exhibit similarities with a subgroup of post-bariatric patients who experience weight regain. The rate of post-bariatric weight regain is reported to range from 5-39% with a mean of 21%.[12] The causes can be categorised as patient-related or operation specific. The reported major patient-related determinants are loss of dietary control with grazing behaviours (consumption of smaller amounts of food over extended periods of time) and poor diet quality, physical inactivity and uncontrolled mental disorders, e.g. binge eating, depression, alcoholism or psychiatric diagnosis.[13] Importantly, endocrine and metabolic imbalances have been reported to be associated with weight regain, such as increased plasma ghrelin levels, low peptide YY and altered glucose regulation, as shown by glucose tolerance testing with reactive hypoglycaemia at 1-2 hours after the glucose load.[14] These alterations also seem to be related to increased hunger and maladaptive eating behaviour. The major surgery-related determinants of weight regain are stomal dilation and pouch length and type of surgery with more weight regain after adjustable gastric band procedures.[13]

In the ideal world we would be able to exactly predict in advance which patients will benefit from bariatric surgery and which patients will achieve a long-term weight loss. This, of course, also applies to other anti-obesity treatments such as lifestyle interventions with diet and exercise, cognitive behavioural therapy, EndoBarrier, vagal blocking or medical therapy. Unfortunately, at present this is not the case. However, some first attempts have been made with respect to metabolic surgery outcomes. The non-surgical baseline predictors for unsuccessful weight loss or T2D remission which have been identified are: impulsive behavioural traits,[15] older age, more severe and longer duration of T2D and lower C-peptide levels,[16] higher preoperative BMI and personality disorders.[17] Greater post-bariatric benefit was reported for patients with higher educational status, Caucasian or Hispanic ethnicity, non-shift-work working patterns, female gender and social support, as well as increased levels of preoperative physical activity and an absence of binge eating behaviour.[18,19]

Most of the studies investigating predictive factors of post-bariatric weight loss comprise a relatively short follow-up, while studies with long-term follow-up are scarce. Importantly, the majority of these studies do not take into account potentially relevant other biological factors, such as genetic factors, resting energy expenditure or endocrine factors (e.g. appetite and metabolism regulating hormones). Holistic pre-treatment phenotyping of obese patients is of great importance, not only to detect underlying diseases, but also to determine which type of patients are the good responders in the long term. Considering the invasive procedures and lifelong follow-up to treat the long-term complications, which is all accompanied by high costs, it is essential to be able to predict which patients will benefit. Studies addressing all these various contributing factors to obesity simultaneously are urgently needed. This can lead to a way of personalised medicine and improve efficacy of all types of anti-obesity treatments.

Thus, bariatric surgery is indeed a solution for obesity-related metabolic disturbances for many, but not all, severely obese patients. In addition, the effects of metabolic surgery yield important new insights into the regulation of body weight and metabolism and may therefore also lead towards novel non-surgical treatment options.

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REVIEW

Disseminated intravascular coagulation as clinical manifestation of colorectal cancer: a case report and review of the literature

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ABSTRACT

We describe the case of a 65-year-old woman, known with ulcerative colitis, who presented with progressive headaches, haematomas and rectal bleeding which turned out to be the initial manifestation of disseminated intravascular coagulation (DIC) associated with colorectal cancer. The presentation posed as a general medicine case but turned out to be a rare oncological complication. The patient revealed possible carcinocythaemia and bone marrow infiltration with signet ring-like cells, as indicators of advanced adenocarcinoma. Treatment of the underlying disease resolved the DIC and contributed to prolonged survival. Subsequently, we reviewed the English literature since 1990 on similar cases and demonstrated that this association is extremely rare and is associated with a poor prognosis. Prompt recognition and treatment of the underlying disease is confirmed to be of utmost importance to prolong (progression-free) survival.

KEYWORDS

Carcinocythaemia, colorectal neoplasm, disseminated intravascular coagulation

INTRODUCTION

Disseminated intravascular coagulation (DIC) is a clinicopathological syndrome characterised by the occurrence of bleeding, thrombosis, or both, in patients with laboratory evidence of activation of the clotting and fibrinolytic systems.[1] Underlying diseases causing DIC include haematological malignancies, infection, sepsis, and trauma.[1] The relation with solid tumours is uncommon. We present the case of a patient who presented with a coagulation disorder as a result of DIC accompanying metastasised colorectal cancer and review similar cases published since 1990.

CASE

A 65-year-old woman, known with ulcerative colitis, was admitted to the emergency department because of a sudden increase of headache, spontaneous haematomas, and rectal bleeding. One month before presentation she had experienced continuous headaches and an increased stool frequency accompanied by rectal bleeding, which she thought was an exacerbation of her inflammatory bowel disease. She also mentioned malaise and weight loss. Her ulcerative colitis was diagnosed in 2007 in another hospital, and she had withdrawn from follow-up, partly due to fear of having to undergo colonic endoscopies. At presentation her body temperature was 37.7 °C, blood pressure 165/90 mmHg, pulse 101 beats/min and respiratory rate 18/min. Physical examination revealed several haematomas of different sizes and age on the patient's legs. The lungs were clear, and the heart sounds were regular with no murmurs. The examination of the abdomen revealed an enlarged liver. There were no palpable lymph nodes and the rest of the physical and neurological examination was without abnormalities. Laboratory evaluation showed haemolytic anaemia with a haemoglobin concentration of 9.8 g/dl, haematocrit of 30%, mean corpuscular volume of 85 fl, reticulocyte count of 256 x 10^3/ml, lactate dehydrogenase concentration of 891 U/l (normal range: 10-450 U/l), total bilirubin concentration of 0.9 mg/dl (normal range: 0.1-0.9 mg/dl), and haptoglobin concentration less than 10 mg/dl (normal range: 30-200 mg/dl). Furthermore, thrombocytopaenia of

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136 x 10^3/ml and leukocytosis of 14.1 x 10^3/m were found. The prothrombin time was 19.2 seconds (normal range: 11-13 seconds), activated partial thromboplastin time was 29 seconds (normal range: 25-33 seconds), fibrinogen concentration of 50 mg/dl (normal range: 200-400 mg/dl), and D-dimer concentration of 14.45 µg/ml (normal range: 0-0.55 µg/ml), which indicated DIC. Examination of the peripheral blood smear excluded haematological malignancies but revealed limited leukoerythroblastosis, some fragmented erythrocytes and a sporadic atypical cell of unknown origin, resembling a seal ring (*figure 1*). An MRI of the cerebrum was performed and showed multiple cerebral infarctions. A bone marrow aspiration and biopsy demonstrated grouped mucin-forming atypical cells, positive for staining with CAM 5.2, an epithelial marker, indicating the possibility of an adenocarcinoma. Computed tomography (CT) of the thorax and abdomen revealed pathological thickening of the colon wall along more than 10 cm and pathological lymphadenopathy (mediastinal and para-aortic) (*figure 2*). The biopsy of the abnormality found by imaging, obtained through colonic endoscopy, confirmed the presence of a mucin-forming adenocarcinoma of the sigmoid. The patient started palliative chemotherapy three days after admission, consisting of XELOX: capeticabine 1000 mg/m^2 twice daily and oxaliplatin 130 mg/m^2 every three weeks, which she tolerated well despite of minor neuropathy after the second cycle. DIC was successfully suppressed after starting chemotherapy with clinically diminishing haematomas and resolution of her headache and with normalisation of platelet count, clotting times and rise in coagulation proteins after ten days. The patient was discharged 15 days after admission. The tumour marker carcinoembryonic antigen decreased after one month and CT scan after the third cycle of chemotherapy showed regression of the pathological lymph nodes. After eight cycles of chemotherapy disease progression occurred. Laboratory tests confirmed a new episode of DIC. The patient received a gift of FOLFIRI (folinic acid, fluorouracil and irinotecan), which did not improve her symptoms. She died eight months after the diagnosis of colorectal cancer due to disease progression. On autopsy, the colonic tumour invaded surrounding tissue and disseminated to the peritoneal cavity and bone marrow. Extended leptomeningeal carcinomatosis was found. There were no macrometastases in other visceral organs. An infarction of the spleen was present.

Figure 1. *Peripheral blood smear demonstrating some fragmented erythrocytes and a sporadic atypical cell of unknown origin, resembling a seal ring*

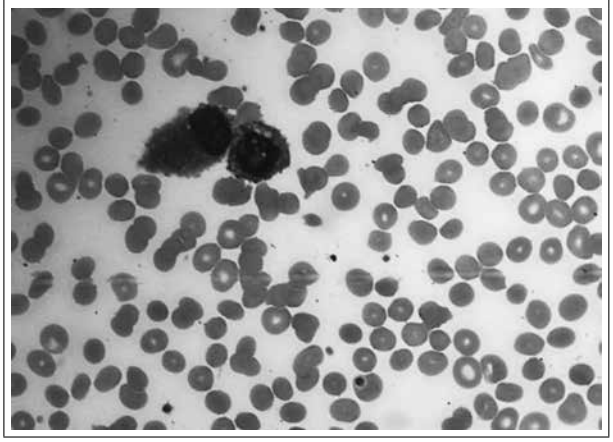
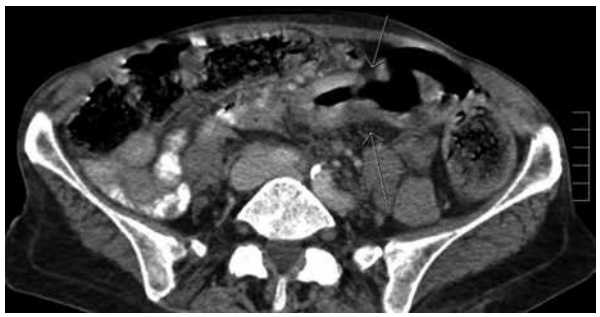


Figure 2. *Computed tomography of the abdomen revealing pathological thickening of the colon wall and pathological lymphadenopathy*



RESULTS AND DISCUSSION

The association of DIC and solid tumours is rare but has been known for decades. In 10-15% of patients with metastasised solid tumours there is evidence of DIC.[2] In a study by Sallah *et al.*[3] of 1117 patients with solid tumours, 6.8% were diagnosed with DIC. In a multivariate analysis, older age, male gender, advanced malignancy, breast cancer and the presence of necrosis in the tumour specimen emerged as independent factors significantly related to the occurrence of DIC. Patients diagnosed with DIC had a reduced survival, even when grouped by tumour stage, compared with patients without DIC. Nevertheless, the exact mechanism of DIC in patients with solid tumours remains unclear.[1] The initiation of widespread activation of the coagulation system could be based on the abnormal expression of procoagulant tissue factor on tumour cells and/or the vessel surface that leads to activation of the extrinsic coagulation pathway through a complex binding with factor VII.[2] For the treatment of DIC supportive measures, consisting of anticoagulants, platelets and plasma, coagulation inhibitors, or antifibrinolytic agents, may be necessary, although no consensus regarding optimal therapy exists at this time.[1] The widespread activation of coagulation can ultimately lead to thrombotic occlusion of small and middle sized vessels. At the same time, the use and subsequent depletion of platelets and

coagulation proteins may induce severe bleeding. Bleeding can complicate decisions about anticoagulant treatment. Our patient demonstrated multiple cerebral infarctions, but without functional abnormalities. Next to that, blood loss in her stools was substantial and red blood cell transfusion was needed twice. Therefore, no anticoagulant therapy was administered.

This case demonstrates a rare presentation of advanced colorectal cancer. Reviewing the English literature published since 1990 on DIC and colorectal carcinoma revealed only five cases (*table 1*).[4-8] Including our case, patient age at diagnosis ranged from 50-79 years. Four out of six patients were male. DIC was the presenting symptom in all but two cases. In these two cases DIC occurred after initial surgery,[7] or chemotherapy.[4] The cases were associated with a pathological diagnosis of poorly/moderately differentiated or signet ring-like cell adenocarcinoma. Bone marrow invasion was described in four out of the six cases reviewed.[6-8] In five of the six cases the patients died with a survival, after the diagnosis of DIC, ranging from 12-210 days. In one case the patient died after 83 days of pneumonia, unrelated to DIC or tumour progression.[7] Supportive treatment for DIC was administered in four cases but did not really seem to affect outcome.[4,6-8] However, in the three cases where chemotherapy was initiated, the survival times were longest (83, >120, 210 vs. 12, 25, 30 days). Due to the limited number of cases statistical analyses could not be conducted. Overall, identification of the underlying disease and prompt treatment seemed essential for the effective management of DIC and (progression-free) survival. The underlying cause of our patient's coagulation disorder was diagnosed rapidly and chemotherapy was administered within three days after admission. She responded well with normalisation of several laboratory values after ten days, and eventually a decreasing tumour marker within one month. She had a progression-free survival of almost eight months, with good quality of life. However, after this period her disease progressed rapidly, leading to death within several weeks. At presentation, our patient had demonstrated an atypical cell in the peripheral blood smear. Carcinocythaemia, introduced by Carey *et al.*,[9] is known as a unique form of cancer metastasis in which the cancer cells can be detected in the peripheral blood, generally occurring in a far advanced stage of certain neoplasms, mostly breast cancer. Gallivan *et al.*[10] describe a mean time between detection of carcinocythaemia and death to be five weeks (median two weeks) reflecting the fact that it is generally a terminal event. The coincidence of DIC and carcinocythaemia is extremely rare and has been published only thrice to date.[6,10,11]

Table 1. *Cases of disseminated intravascular coagulation and colorectal carcinoma published since 1990*

Author	Year	Sex	Age (year)	Platelet count (x10³/μl)	APTT (sec)	PTT (sec)	Fibrinogen (mg/dl)	D-dimer (μg/ml)	Carcinocythaemia	Marrow carcinomatosis	Histology	(Progression-free) survival (days)	Therapy
Yoshioka et al.[8]	1992	M	62	71	44	13.3	142	x	x	Yes	Moderately differentiated adenocarcinoma	12, died	Anti-DIC
Huang et al.[7]	2005	M	79	58	41	21.1	233.8	1.05	x	Yes	Moderately differentiated adenocarcinoma	83, died*	Anti-DIC, 5-FU, leucoverin
Misawa et al.[6]	2008	M	51	129	x	x	95.2	0.615	Yes	Yes	Signet ring-like cell carcinoma	25, died	Anti-DIC
Kato et al.[5]	2010	F	72	23	29	36.6	381	0.063	x	x	Poorly differentiated adenocarcinoma	30, died	x
Mizota et al.[4]	2011	M	50	18	x	x	31.4	1.352	x	x	Poorly differentiated adenocarcinoma	>120	Anti-DIC, FOLFOX, bevacuzimab
Van Bunderen et al. (present study)	2014	F	65	127	29	19.1	500	14.45	Yes	Yes	Signet ring-like cell carcinoma	210, died	XELOX, FOLFIRI

Sec=seconds; APTT=activated partial thromboplastin time; PTT=prothrombin time; M=male; x=not reported; anti-DIC=treatment for disseminated intravascular coagulation; F=female; FOLFOX=folinic acid, fluorouracil, oxaliplatin; 5-FU=fluorouracol, XELOX=capecitabine, oxaliplatin; FOLFIRI=folinic acid, fluorouracil, irinotecan. *Patient died of pneumonia without signs of DIC or tumour progression.

In conclusion, we report an unusual presentation of the association of DIC and colorectal cancer. This case, supported by a review of the literature, illustrates that DIC in advanced colorectal cancer is rare, but can be managed with prompt diagnosis and immediate chemotherapy, consequently prolonging survival.

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REVIEW

Pheochromocytoma: A review on preoperative treatment with phenoxybenzamine or doxazosin

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ABSTRACT

Background: During surgical treatment of pheochromocytoma, haemodynamic instability may occur. To prevent this, patients receive preoperative treatment with an alpha-blocker. Nowadays, some centres use phenoxybenzamine, while others use doxazosin. The purpose of this review is to analyse the current evidence of the benefits and risks of phenoxybenzamine and doxazosin in the preoperative treatment of pheochromocytoma.

Methods: The literature was reviewed by searching PubMed using the following search terms: pheochromocytoma, phenoxybenzamine, doxazosin and alpha-blockade. The filter was set on English language.

Results: No randomised controlled trials were found. Five follow-up studies comparing phenoxybenzamine and doxazosin in the treatment of pheochromocytoma were retrieved and analysed. There was a trend that systolic arterial pressure is slightly better controlled by phenoxybenzamine. However, this resulted in more pronounced postoperative hypotension as well. The use of an alpha-blocker was often accompanied by other vasoactive agents. Phenoxybenzamine was often accompanied by a beta-blocker to control reflex tachycardia, while patients on doxazosin received significantly more additional antihypertensive medicines. Most of the studies showed that the use of vasoactive drugs and fluid infusion does not differ significantly between the two drugs. Phenoxybenzamine caused significantly more orthostatic hypotension, oedema and complaints of a stuffy nose.

Conclusion: On the basis of the current evidence, there is no evidently superior alpha-blocker for the pretreatment of patients with pheochromocytoma. Perioperative haemodynamics seem to be slightly better controlled with phenoxybenzamine, at the cost of more pronounced postoperative hypotension. Side effects occurred less often in the doxazosin group.

KEYWORDS

Pheochromocytoma, phenoxybenzamine, doxazosin, alpha-blockade

INTRODUCTION

Pheochromocytoma is a rare tumour originating from the catecholamine-producing chromaffin tissue in the adrenal medulla or the extra-adrenal paraganglia.[1] Incidence among the general population is about 0.8 per 100,000 person-years, and is estimated to be 0.1-0.6% in the hypertensive population.[2,3] Diagnosis usually takes place in patients aged 40-50 years.[4] However, hereditary variants, such as multiple endocrine neoplasia type 2, Von Hippel-Lindau disease, neurofibromatosis type 1 and the pheochromocytoma-paraganglioma syndrome, can present earlier.[5] A history of episodic tachycardia, sweating, headache and signs of paroxysmal hypertension is classic.[6,7] These symptoms arise as a consequence of excessive catecholamine release. Between episodes blood pressure can be normal. However, clinical presentation can differ, depending on the catecholamine-releasing profile of the tumour. A tumour predominantly secreting epinephrine is usually associated with paroxysmal hypertension, while the norepinephrine-secreting variant is associated with sustained hypertension.[8,9] Pheochromocytoma is diagnosed by biochemical testing: plasma or 24-hour urinary fractionated metanephrines, further imaging and pathological confirmation.[10] The imaging consists of an abdominal or pelvic CT scan, MRI or even 123I-MIBG scintigraphy and FDG-PET to determine the exact site of the tumour.[11,12] The only definitive treatment consists of surgical resection. During manipulation of the tumour, dangerous amounts of catecholamines can be released in the circulation,

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resulting in life-threatening events, including hypertensive crises, cardiac arrhythmias, myocardial infarction or ischaemia, pulmonary oedema and multiorgan failure.[13-16] Furthermore, the rapid decrease of catecholamines after surgery may result in severe hypotension.[16,17]

To prevent these life-threatening events from happening, preoperative management has been recommended. One of these therapies is the use of alpha-adrenoceptor blockers, which can counter the adrenergic effects of catecholamines.[18] In addition, alpha-blockade permits intravascular volume expansion.[19] Nowadays, some centres use the non-selective alpha-blocker phenoxybenzamine, while others use the selective alpha-blocker doxazosin.[20] Although both compounds have been used for a long time and proved to result in reduction in operation mortality, neither of them is officially registered for the preoperative management of pheochromocytoma.[20-24]

PHARMACOLOGICAL PROPERTIES

Phenoxybenzamine is a non-competitive, long-acting, alpha-1- and alpha-2-adrenoceptor antagonist.[20,23,25] The usual starting dose is 10 mg twice daily per os and can be increased until control of blood pressure (<160/90 mmHg) or orthostatic hypotension arises.[3,18,20] The hypothetical advantage of the non-competitive action is that even when excessive amounts of catecholamines reach the circulation, alpha-blockade is still effective. A disadvantage is the high incidence of reflex tachycardia, due to the inhibition of the alpha-2 adrenoceptors localised in the presynaptic membrane. Stimulation of these presynaptic receptors inhibits norepinephrine release. Blockade results in a disturbance of the negative feedback loop and, as a consequence, an increase in chronotropic activity.[9,20] Therefore, a beta-blocker is often added to phenoxybenzamine therapy in order to decrease chronotropic activity. Moreover, phenoxybenzamine causes central sedation, headaches and is long acting, which may cause prolonged hypotension postoperatively.

Doxazosin is a competitive, short-acting, selective alpha-1-adrenoceptor antagonist.[20,24,25] These properties offer some possible advantages. Doxazosin does not cause reflex tachycardia and has a relatively short duration of action because of its competitive inhibition, possibly shortening the hypotensive period postoperatively. Although it is relatively short-acting, the plasma half-life is 22 hours; therefore it can be dosed once daily. The starting dose is usually 1 mg per os, with a recommended maximum of 16 mg a day. Furthermore, doxazosin does not cause central signs – unlike phenoxybenzamine it does poorly pass the blood-brain barrier – or peripheral oedema.[26] As a consequence of its competitive property, blockade may be ineffective during high plasma concentrations of catecholamines, for example occurring during tumour handling.

No consensus about the optimal regimen has been reached so far.[20] The purpose of this review is to analyse the current evidence of the benefits and risks of phenoxybenzamine and doxazosin in the preoperative management of pheochromocytoma, in order to find out whether there is an optimal regimen concerning intraoperative haemodynamics. Secondary outcomes are side effects and amount of fluid and vasoactive drug administration.

METHODS

The literature was reviewed by searching PubMed using the following search terms: pheochromocytoma, phenoxybenzamine, doxazosin and alpha-blockade. The filter was set on English language. No randomised controlled trials directly comparing the two compounds were found. Five follow-up studies comparing phenoxybenzamine and doxazosin in the treatment of pheochromocytoma were retrieved and analysed.

RESULTS

An overview of the retrieved studies is presented in *table 1*.

Prys-Roberts *et al.*

Prys-Roberts *et al.*[26] compared phenoxybenzamine versus doxazosin in the preoperative treatment of pheochromocytoma. Thirty-five patients diagnosed with pheochromocytoma or paraganglioma were included in this prospective follow-up study. Between 1990 and 1992, eight patients were included for the phenoxybenzamine group, receiving 20-120 mg per day. Doses were increased until orthostatic hypotension occurred or the patient complained of a stuffy nose. All eight patients received additional beta-receptor blockade therapy with propranolol (n=4), metoprolol (n=2), labetalol (n=1) or atenolol (n=1). Between 1993 and 2001, 27 patients received doxazosin 2-16 mg per day, the maximum dose depending on the blood pressure and mild orthostatic hypotension. The first four patients and five out of the subsequent 23 patients received additional beta-receptor blockade. These five patients had tachycardia as a result of an epinephrine-secreting tumour. Heart rate (HR), systolic (SAP) and diastolic arterial pressure (DAP) were continuously measured perioperatively. The amount of vasoactive drugs used and side effects were monitored as well.

Table 1. *Overview of the retrieved studies*

Reference	Study type	Number of patients	Intervention		Outcome				Bias
			Phenoxybenzamine	Doxazosin		PXB	DOX	Significance (P<0.05)	
Prys-Roberts, 2002	Prospective follow-up study	PXB n=8 DOX n=27 Patients diagnosed with pheochromocytoma or paraganglioma (n=3)	Daily dose 20-120 mg (in three times daily) β-blocker (n=8, (100%))	Daily dose 2-16 mg β-blocker (n=9, (24%))	Preoperative SAP (mmHg) DAP (mmHg) HR (beats/min)	 162±17.7 92±15.3 71±12.6	 148±21.1 78±13.6 72±11.5	 ns 0.029 ns	No randomisation, small sample size. Patients in PXB group were selected between 1990 and 1992, whereas DOX patients were treated from 1993 until 2001 The last 9 patients in the DOX group underwent laparoscopic surgery No correction for tumour size or excretion profile
					During anaesthesia SAP (mmHg) DAP (mmHg) HR (beats/min)	 98±5.9 59±7.6 51±3.7	 97±6.9 52±6.5 59±5.0	 ns 0.049 0.003	
					Peak during tumour handling SAP (mmHg) DAP (mmHg) HR (beats/min)	 185±32.5 102±14.4 94±9.7	 178±29.9 95±17.3 78±13.9	 ns ns 0.013	
					Postoperative SAP (mmHg) DAP (mmHg) HR (beats/min)	 100±11.9 55±7.1 61±6.9	 116±14.8 64±8.5 71±10.1	 0.004 0.007 0.010	
					Vasoactive drugs Phentolamine (mg) Labetalol (mg)	 96±6.8 33.1±8.4	 11.1±7.6 15.8±8.2	 ns ns	
					Side effects Orthostatic hypotension (%) Oedema (%) Fluid retention (ml) Stuffy nose (%)	 n= 8 (100) n= 7 (88) 4794±2474 n= 8 (100)	 n= 2 (7.4) n= 1 (4) 2828±1386 n= 0	 0.025 	
Kocak, 2002	Retrospective follow-up study	PXB n=21 DOX n=17 (Prazosin n=11) Patients diagnosed with pheochromocytoma or paraganglioma (n=3)	Mean daily dose 105.7 mg (range 40-120 mg)	Mean daily dose 11.8 mg (range 4-32 mg)	Time for preparation (weeks)	3.7 (R 2-6)	4.1 (R 2-6)	ns	No randomisation, small sample size. Different periods of inclusion, no patient selection The last 6 patients in DOX group underwent laparoscopic surgery. Absence of baseline table
					Preoperative blood pressure	No data	No data	ns	
					No. of patients with hypertension during surgery	17 (81%)	14 (82%)	ns	
					Hypertensive attacks during tumour manipulation (SAP>180 mmHg)	~80%	~80%	ns	

					No. of patients with postoperative hypotension (SAP <100 mmHg)	6 (28%)	5 (29%)	ns
					Mean intraoperative fluid replacement (ml)	4328 (R 1700-6450)	4504 (R 2250-7000)	ns
					Mean postoperative fluid replacement (ml)	4697 (R 2100-6000)	3853 (R 1800-6000)	ns
Yu Zhu, 2010	Retrospective follow-up study	PXB n=31 DOX n=36 Unilateral pheochromocytoma largest diameter <6 cm No severe injury in the heart, lung or kidney	Daily dose 20-60 mg (two or three times daily) β-blocker (n=24, (77%)) Additional antihypertensive therapy (n=5, (16%))	Daily dose 4-16 mg (one to three times daily) β-blocker (n=4, (11%)) Additional antihypertensive therapy (n=14, (39%))	Preoperative SAP (mmHg) DAP (mmHg)	125±13.2 78±11.5	123±15.9 77±8.7	ns ns
					Haematocrit Before therapy After therapy	0.41 ± 0.039 0.37 ± 0.040	0.39 ± 0.045 0.36 ± 0.044	ns ns
					Before anaesthesia SAP (mmHg) DAP (mmHg)	132±20.6 82±12.3	145±16.3 86±13.1	<0.01 ns
					During anaesthesia SAP (mmHg) DAP (mmHg)	91±16.2 65±15.1	110±15.6 70±14.0	<0.01 ns
					During tumour handling SAP (mmHg) DAP (mmHg)	162±19.2 100±15.1	169±24.7 98±13.4	ns ns
					Removal of tumour SAP (mmHg) DAP (mmHg)	74±8.8 52±7.5	96±10.8 53±6.3	<0.01 ns
					Postoperative SAP (mmHg) DAP (mmHg)	111±13.1 71±10.0	112±14.1 72±9.2	ns ns
					Δ Blood pressure SAP (mmHg) DAP (mmHg)	88±10.4 48±12.2	73±15.7 47±11.7	<0.01 ns
					Preoperative period (days)	25±3.2	11±3.6	<0.001
					Estimated blood loss (ml) Blood transfusion (ml) Crystal solution infusion (ml) Colloidal solution infusion (ml)	270±181 282±56 2549±279 2100±247	260±188 252±51 2580±260 2083±254	ns ns ns ns

Table 1. *Overview of the retrieved studies*

Reference	Study type	Number of patients	Intervention		Outcome				Bias
			Phenoxybenzamine	Doxazosin		PXB	DOX	Significance (P<0.05)	
Weingarten, 2010	Retrospective follow-up study	PXB n=50 Alpha 1 group n=37	Mayo Clinic Phenoxybenzamine (n=49, (98%)) Daily dose unknown β-blocker (n=39, (78%)) Calcium channel blocker (n=11, (22%)) Metyrosine (n=3, (6%)) Oral sodium chloride (n=30, (60%)) Hydration iv (n=4, (8%))	Cleveland Clinic Selective alpha 1 antagonist (n=24, (65%)) Daily dose 2-10 mg Phenoxybenzamine (n= 6, (16%)) 7 patients received no treatment with alpha-blockade β-blocker (n=17, (46%)) Calcium channel blocker (n=11, (30%)) Oral sodium chloride (n=33, (89%))	Preoperative SAP (mmHg) Mean (mmHg) DAP (mmHg) Intraoperative peak SAP (mmHg) Mean (mmHg) DAP (mmHg) SAP ≥30% baseline (min) SAP ≥200mmHg (min) Lowest intraoperative SAP (mmHg) Mean (mmHg) DAP (mmHg) SAP ≤30% baseline (min) SAP ≤30% baseline (% anaesthesia time) Greatest HR (beats/min) HR ≥100 beats/min (min) Lowest HR (beats/min) HR ≤50 beats/min (min) Estimated blood loss (ml) Intraoperative crystalloid (L) Intraoperative colloid (L) Vasoactive drugs Nitroprusside (%) Nitroglycerin (%) β-blocker (%) Labetalol (%) Phenylephrine (%)	 139±22 99±18 83±12 187±30 136±20 109±18 2 (IQ 0-11) 0 (IQ 0-2) 73±14 55±11 46±9 28 (IQ 6-62) 15.7 (IQ 3.3-24.9) 104±28 0 (IQ 0-1) 47±10 2 (IQ 0-11) 75 (IQ 25-250) 3.0 (IQ 2.0-3.1) 0 62.0 2.0 52.0 24.0 56.0	 139±22 93±19 73±17 209±44 151±30 114±26 5 (IQ 0-22) 0 (IQ 0-7) 78±15 56±10 43±9 13 (IQ 3-49) 5.1 (IQ 0.9-16.0) 105±18 0 (IQ 0-1) 51±10 0 (IQ 0-7) 100 (IQ 82-250) 5.0 (IQ 3.4-6.4) 1.00 (IQ 0.5-1.0) 67.6 46.0 27.0 40.5 27.0	 ns ns ns 0.011 0.004 ns ns ns ns ns ns ns 0.026 ns ns ns ns 0.010 <0.001 <0.001 <0.001 ns <0.001 0.027 ns 0.009	No randomisation, small sample size. Surgery during different periods and in different clinics. BMI in Cleveland Clinic patients was significantly greater. Amount of catecholamines measured in plasma is unknown Not all patients with selective alpha-1 blockade received doxazosin

Bruynzeel, 2010	Retrospective follow-up study	PXB n=31 DOX n=42 Patients diagnosed with pheochromocytoma or paraganglioma (10%)	Daily dose 60 mg (20-210 mg) Propranolol (n=25, (81%)) NaCl 0.9%, 2l/day	Daily dose 24mg (8-56 mg) Propranolol (n=37, (88%)) NaCl 0.9%, 2l/day	At presentation SAP (mmHg) Mean (mmHg) DAP (mmHg)	140 (R 90-230) 100 (R 70-178) 80 (R 55-152)	150 (R 105-240) 108 (R 80-180) 90 (R 64-150)	ns <0.05 <0.05	No randomisation, small sample size. Patients in PXB group were selected between 1995 and 2003, whereas DOX patients were treated from 2003 until 2007 No correction for tumour size. Plasma norepinephrine is significantly greater in DOX group; no correction
					After α-blockade SAP (mmHg) Mean (mmHg) DAP (mmHg)	130 (R 97-183) 98 (R 67-137) 80 (R 48-113)	129 (R 95-178) 95 (R 70-127) 76 (R 55-105)	ns ns ns	
					Postoperatively SAP (mmHg) Mean (mmHg) DAP (mmHg)	125 (R 90- 180) 90 (R 60- 133) 72 (R 45- 110)	120 (R 71- 170) 81 (R 64- 127) 61 (R 40- 106)	ns <0.01 ns	
					Fluctuations MAP <60 mmHg (min) SAP >160mmHg Episodes Minutes	5 (R 0- 150) 1 (R 0- 9) 3 (R 0- 165)	10 (R 0- 85) 1 (R 0- 4) 13 (R 0- 70)	ns ns ns	
					Fluid administration	No data	No data	ns	
					Vasoactive drugs Esmolol (mg) Phenylephrine Nitroglycerine Norepinephrine Phentolamine	314-5 No data No data No data No data	95 No data No data No data No data	<0.05 ns ns ns ns	

PXB = phenoxybenzamine; DOX = doxazosin; SAP = systolic blood pressure; DAP = diastolic blood pressure; HR =; heart rate; NS =; not significant; IQ = interquartile range; R = range.

Preoperatively SAP and HR did not differ significantly between the phenoxybenzamine and the doxazosin groups. In the doxazosin group DAP was significantly lower. During anaesthesia all values were significantly lower than preoperatively. HR was significantly lower in the phenoxybenzamine group (51 vs. 59 beats/min, p=0.003), while DAP remained higher (59 vs. 52 mmHg, p=0.049). During tumour handling, blood pressure and HR rose significantly, but only HR was significantly higher in the phenoxybenzamine group (94±9.7 vs. 78±13.9, p =0.013). Postoperatively SAP, DAP and HR were significantly lower in the phenoxybenzamine group. Moreover, the alpha-blockade by phenoxybenzamine persisted significantly longer. There were no significant differences in the administration of phentolamine or labetalol during surgery. All patients in the phenoxybenzamine group complained of orthostatic hypotension and dizziness on standing, in contrast to 7% (n=2) in the doxazosin group, who had mild orthostatic hypotension. Oedema due to colloid infusion occurred more often in the phenoxybenzamine group (88% vs. 4%) and fluid retention was significantly higher (p=0.025).

Limitations of this study are non-randomisation and small sample size. Furthermore, the therapy between the groups was not similar: the phenoxybenzamine patients received significantly more beta-blockers and the last nine patients in the doxazosin group underwent laparoscopic surgery. Tumour handling might be different during laparoscopic surgery. Moreover, the operations in the phenoxybenzamine group took place during the early 1990s, while the doxazosin group were treated until 2001. Although they used the same lateral extraperitoneal approach, one can expect better equipment and surgery conditions during the last operations. Tumour size was not analysed in this study. Therefore, it is uncertain whether tumour size in the two groups is comparable. If not, tumour manipulation would be more difficult and catecholamine secretion might be greater, resulting in more unstable haemodynamics. Because of the different diagnostics in the first five patients in the phenoxybenzamine group, there is no catecholamine excretion profile or plasma concentrations of catecholamines. Even so, the authors did not correct for differences in profile. Particularly the latter can influence the intraoperative haemodynamics.

Kocak *et al.*

Kocak *et al.*[27] retrospectively analysed the preoperative preparation of 49 patients treated for pheochromocytoma (n=46) or paraganglioma (n=3) between 1985 and 2000. Non-selective alpha-blockade with phenoxybenzamine was given before 1994 in 21 cases. The mean final daily dose was 105.7 mg (range 40-120 mg). Selective alpha-blockade was given in the form of prazosin (n=11) between 1994 and 1997 and doxazosin (n=17) between 1997 and 2002. Mean daily doses were 14.2 mg (4-28 mg) and 11.8 mg (4-32 mg), respectively. All patients were dosed until they had no hypertensive episodes and blood pressure was lower than 150/90 mmHg for one week. None of the patients received additional beta-blockade. All patients underwent laparotomy, except for six patients in the doxazosin group; they underwent laparoscopic adrenalectomy. Outcomes were the time elapsed for preparation with alpha-blockade and the perioperative records of blood pressure, volume replacement and supplemental adrenergic agents.

Time elapsed for preparation varied between 2 to 6 weeks and did not differ significantly between groups (p>0.05). At induction of anaesthesia, none of the patients had hypertension. Hypertension during surgery did not differ significantly between groups. It occurred in 81% (n=17) of patients in the phenoxybenzamine group, 73% (n=8) in the prazosin group and 82% (n=14) in the doxazosin group. During tumour manipulation hypertensive crises were measured in approximately 80% of patients in all three groups. Hypertensive crisis was defined as a SAP >180 mmHg and/or the need for sodium nitroprusside infusion. Postoperative hypotension was defined as a SAP <100 mmHg. This occurred in 28% (n=6), 27% (n=3) and 29% (n=5) in the phenoxybenzamine, prazosin and doxazosin groups, respectively and did not differ significantly (p>0.05). The use of inotropic agents was not required. Crystalloid fluid infusion both intraoperatively and postoperatively did not differ significantly between all three groups (p>0.05).

A strong point of this study is the monotherapy given to each patient; comparison between the two alpha-blockers is therefore more reliable. Limitations are the small sample size and non-randomisation. Furthermore, baseline characteristics are not given; it is uncertain whether the groups are comparable. The phenoxybenzamine group were treated during an entirely different period and the last six patients in the doxazosin group were treated by laparoscopy. The potential differences in outcome are therefore not the sole effect of the alpha-blockers. Moreover, values of blood pressure are not given; the quantitative effect of alpha-blockade on blood pressure cannot be compared with the other studies in this review. This could be the result of a retrospective study where data were retrieved going back to 1985.

Yu Zhu *et al.*

This retrospective follow-up study[16] compared the effects of phenoxybenzamine versus doxazosin in the preoperative treatment of pheochromocytoma. Originally there were 142 patients with pheochromocytoma, of whom 67 were included. Inclusion criteria were: 1) symptomatic pheochromocytoma, 2) diagnosis confirmed both biochemically and by MRI or CT, 3) unilateral adrenal

gland localisation, 4) largest diameter of tumours <6 cm, 5) without concomitant hypertensive encephalopathy or injury to heart, lung or kidney, 6) operation through retroperitoneal 11th intercostal incision. Between 2003 and 2005, 31 patients were pretreated with phenoxybenzamine, while 36 patients treated between December 2005 and 2008 received a preoperative treatment with doxazosin. Phenoxybenzamine was dosed between 20-60 mg in two or three gifts daily. Doxazosin was given at between 4-16 mg a day; in both groups doses were adjusted according to blood pressure. Beta-blockers were added when tachycardia occurred, this happened in 77% (n=24) of cases in the phenoxybenzamine and 11% (n=4) of cases in the doxazosin group. Only three cases from the phenoxybenzamine group had a predominantly epinephrine-secreting tumour, whereas all four patients receiving beta-blocker in the doxazosin group had one. Additional antihypertensive drugs were added when the blood pressure remained >160/100 mmHg (phenoxybenzamine 16% (n=5) vs. doxazosin 39% (n=14)). The main outcomes were perioperative haemodynamics. An intra-arterial catheter was used to continuously measure the perioperative blood pressure. Secondary outcomes were haematocrit, time till optimal preoperative condition, estimated blood loss and fluid infusion.

During the entire treatment DAP did not differ significantly between the two groups, baseline SAP was similar in both groups. However, the SAP before anaesthesia, during anaesthesia and after tumour removal was significantly lower in the phenoxybenzamine group. Postoperatively, there was no significant difference in blood pressure. The fluctuations in SAP, measured during surgery, were significantly greater in the phenoxybenzamine group: 88±10.4 mmHg versus 73±15.7 mmHg (p<0.01), but there were no significant differences in peak SAP. The difference in fluctuation between groups is caused by the higher SAP directly after tumour removal in the doxazosin group, suggesting the intraoperative haemodynamics were more stable. The time till achievement of optimal preoperative condition was longer in the phenoxybenzamine group; 25 days versus 11 days (p<0.001). Haematocrit did not differ significantly between the groups. However, there was a significant decrease after drug therapy in both groups (phenoxybenzamine 0.41± 0.039 before treatment vs. 0.37±0.040 after treatment, doxazosin 0.39± 0.045 before treatment vs. 0.36±0.044 after treatment, p<0.05). Concerning the estimated blood loss and fluid infusion, there were no significant differences between the two groups.

Limitations of this study include non-randomisation and being completely unmasked. Furthermore, the sole effect of phenoxybenzamine and doxazosin was not analysed; there were significant differences in the use of beta-blockers and other antihypertensive agents. However, one could state that this does follow clinical practice. Moreover, because of more recent surgery in the doxazosin group results might be influenced. There was no correction for tumour excretion profile.

Weingarten *et al*.

In this retrospective study[28] patients were selected after laparoscopic treatment for pheochromocytoma in the Mayo or Cleveland Clinic. During 2003-2006, 50 consecutive patients from the Mayo Clinic were treated preoperatively for pheochromocytoma; their records were analysed. The records of 37 consecutive patients treated between 2005 and 2009 in the Cleveland Clinic were reviewed as well. In the Mayo Clinic 49 (98%) patients were treated with phenoxybenzamine till orthostatic hypotension was achieved, 39 (78%) patients received an additional beta-blocker and 11 (22%) received a calcium channel blocker. Three (6%) patients received metyrosine, a catecholamine synthesis inhibitor. Furthermore, 30 (60%) patients received oral sodium chloride and four intravenous hydration. In Cleveland Clinic, there was no predominant treatment regimen: 65% (n=24) of patients received selective alpha-blockade (2-10 mg per day) and 16% (n=6) phenoxybenzamine, seven patients did not receive preoperative treatment with alpha-blockade. In 46% of cases a beta-blocker was added, as were calcium channel blockers in 30% of cases. Oral sodium chloride was given to 33 patients (89%). Primary outcome was the perioperative haemodynamics. Fluid administration, estimated blood loss and vasoactive drugs were secondary outcomes.

Preoperative blood pressure values were comparable between groups. The maximum intraoperative values of SAP and MAP were significantly lower in the phenoxybenzamine group of the Mayo Clinic. However, Mayo Clinic patients spent a relatively longer time in a hypotensive state during surgery (≤30% baseline SAP/ anaesthesia time). Estimated blood loss was lower in the Mayo Clinic: 75 ml (25-150) versus 100 ml (82-250), as was fluid infusion. The use of the vasopressor phenylephrine during surgery was significantly greater in the Mayo Clinic: 56% (n=28) versus 27% (n=10).

Limitations are the non-randomisation and retrospective nature of the study. Moreover, the treatment regimens were highly variable, especially the ones in the Cleveland Clinic. Furthermore, not every patient received doxazosin, some received prazosin. The use of additional antihypertensive therapy and vasoactive agents during surgery differed considerably as well. There is no explanation why different time periods were chosen to compare groups. Furthermore, the body mass index in the Cleveland group was significantly greater (29.8±7.1 vs. 26.5±4.6, p=0.009). For these reasons it is difficult to extract a reasonable conclusion out of these data.

Bruynzeel *et al.*

Bruynzeel *et al.*[29] compared the effectiveness of phenoxybenzamine versus doxazosin in the pretreatment of pheochromocytoma or paraganglioma (10%). In this retrospective follow-up study 73 patients were included. Between 1995 and 2003, 31 patients received phenoxybenzamine (median 60 mg per day, range 20-270 mg) and in 25 cases (81%) propranolol was added. Whereas between 2003 and 2007, 42 patients were pretreated with doxazosin (median 24 mg per day, range 8-56 mg) and propranolol (88%, (n=37)). All patients received preoperative volume expansion by infusion of NaCl 0.9% 2 litres a day, for two days. Laparoscopic surgery was performed in 39% (n=12) of the phenoxybenzamine group and 52% (n=22) of the doxazosin group on the following conditions: tumour size was ≤6 cm and no suspicion of malignancy. Outcomes were the perioperative blood pressure, use of vasoactive drugs and amount of fluids administered during surgery. Secondarily they analysed the influence of an additional beta-blocker on haemodynamics as well.

Blood pressure at presentation – before the start of doxazosin treatment – was higher in the doxazosin group. However, after alpha-blockade blood pressures were comparable. There were no significant differences in blood pressure fluctuations between groups. Furthermore, MAP postoperatively in the phenoxybenzamine group was significantly higher. Concerning the vasoactive drugs, only esmolol was administered significantly more in the phenoxybenzamine group. Use of phenylephrine, nitroglycerin and phentolamine was comparable, as was fluid infusion. There was no significant difference in intraoperative or postoperative blood pressure instability when comparing therapy with or without an additional beta-blocker.

Limitations of this study were non-randomisation, retrospective study design and the different periods during which the two groups were treated. Furthermore, it is not clear whether the results were corrected for tumour size or excretion profile. Plasma norepinephrine was significantly higher in the doxazosin group. This might explain the higher blood pressure at presentation and the lower blood pressure postoperatively; a higher dose of alpha-blockade was required, consequently leading to a more pronounced decrease in blood pressure postoperatively.

DISCUSSION

On the basis of the five studies analysed in this review, one can state that both phenoxybenzamine and doxazosin are capable of perioperative blood pressure control in patients with pheochromocytoma. There seems to be a trend, although not reaching statistical significance in some studies, that SAP is slightly better controlled by phenoxybenzamine. However, this seems to result in more pronounced postoperative hypotension as well. Monotherapy is rarely an adequate management. Phenoxybenzamine often has to be accompanied by a beta-blocker to control reflex tachycardia, while patients receiving doxazosin received significantly more additional antihypertensive medicines, such as calcium channel blockers or ACE-inhibitors, to control blood pressure. The use of vasoactive drugs and fluid infusion does not differ significantly among most studies. Only Prys-Roberts reviewed the side effects of both alpha-blockers. Phenoxybenzamine caused significantly more orthostatic hypotension, oedema and complaints of a stuffy nose.

Most results of the analysed studies were consistent. SAP during anaesthesia and surgery did not differ significantly between groups, only Yu Zhu – during anaesthesia – and Weingarten – during surgery – found a significantly greater SAP in the doxazosin group. This could be an effect caused by the phenoxybenzamine itself, but the treatment regimens between the two groups in the study by Weingarten have many irregularities. It is therefore difficult to attribute this difference to the influence of phenoxybenzamine alone.

Prys-Roberts found that postoperative blood pressure was significantly lower in the phenoxybenzamine group and Weingarten stated that patients in the phenoxybenzamine group spent relatively more time in a hypotensive state. The postoperative blood pressures did not differ significantly in the studies by Kocak and Yu Zhu. Although the postoperative SAP was similar in Yu Zhu's study, it was significantly higher in the doxazosin group directly after tumour removal. In contrast, the results of Bruynzeel *et al.* show a significantly higher MAP in the phenoxybenzamine group postoperatively. This might be the result of significantly higher plasma norepinephrine levels in the doxazosin group, resulting in higher alpha-blockade doses and a greater decrease of plasma catecholamines after surgery.

As a result of comparable SAP before and during surgery, and lower blood pressure postoperatively, one can hypothesise that fluctuation of blood pressure intraoperatively is greater in the phenoxybenzamine group. This was analysed in the study by Yu Zhu, confirming this hypothesis. Bruynzeel *et al.* found no significant difference in blood pressure fluctuation, possibly as a consequence of the different tumour excretion profiles, rendering the postoperative MAP in the doxazosin group rather low. Although this slightly more pronounced decrease in blood pressure in the phenoxybenzamine group is something to be aware of, it has not been reported by the analysed studies as being clinically relevant.

The use of vasoactive drugs did not differ significantly in three out of the five studies. The difference in the study by Weingarten is explained by other first choice intraoperative vasoactive agents between hospitals. They did, however, use the vasopressor phenylephrine significantly more in the phenoxybenzamine group, possibly to compensate for the more pronounced perioperative hypotension. Bruynzeel *et al*. found a significantly greater use of esmolol in the phenoxybenzamine group, possibly the result of more frequent episodes of tachycardia related to the use of phenoxybenzamine.

Another mode of action of alpha-blockade is preoperative volume expansion by vasodilatation. Yu Zhu measured the difference in haematocrit before and after treatment with both compounds and found that there was a significant decrease, but no significant difference in decrease of haematocrit between the groups. This suggests that the effects of the two compounds are similar concerning volume expansion. Fluid administration during surgery was similar in both groups in the studies by Kocak, Yu Zhu and Bruynzeel. Weingarten found a greater use of intraoperative crystolloids in the Cleveland or doxazosin group. This might be the consequence of more blood loss during surgery, instead of smaller preoperative volume expansion. Since the groups in Weingarten *et al*.'s study are very hard to compare, it may be safe to conclude that volume expansion and the use of intraoperative fluids is similar in both compounds.

Side effects were only analysed in the study by Prys-Roberts. Although both groups consisted of a small number of patients, the results seem to be evident. Patients in the phenoxybenzamine group had significantly more complaints about orthostatic hypotension, oedema and stuffy nose, as was expected, considering the phenoxybenzamine dose was increased until signs of orthostatic hypotension and stuffy nose occur. This does not, however, explain the oedema. One possibility could be a greater amount of fluid infusion postoperatively, because of the lower blood pressures.

Limitations of this review are the filter settings on English language, possibly missing relevant literature in other languages. However, they are mainly derived from the used studies themselves. Nevertheless, all retrieved articles were used.

None of the used studies were randomised controlled trials. Therefore comparison between the two groups can prove to be difficult, as will be discussed later. Second, patients, doctors and researchers were not blinded for the treatments and research question. However, due to the retrospective nature of four out of five of the studies and the objective continuous measurement of blood pressure, we regard the effects of an unmasked study on the primary outcomes as minimal. Some of the data had to be retrieved from 1985, possibly resulting in information or recall bias. This might be the case in the study by Kocak *et al*. where the baseline table and quantitative data of blood pressure perioperatively are absent. Third, sample sizes in the studies were small, most likely the result of the low incidence of pheochromocytoma. This was especially the case in the studies by Prys-Roberts and Kocak. The first study included only eight patients receiving preoperative treatment with phenoxybenzamine, while the second included 21 and 17 patients in the phenoxybenzamine and doxazosin groups, respectively. As a consequence, the power of these studies is rather low. The influence of a selection effect on the results is considered low, due to the absence of loss to follow-up. Four out of the five studies included all patients being prepared with alpha-blockade during a certain period. Only the study by Yu Zhu used inclusion criteria to select patients, excluding the patients most at risk for hypertensive crises, possibly to diminish the effect of outliers concerning the haemodynamics. Therefore these results could be used when treating an average patient with pheochromocytoma.

There are several confounding factors that were not corrected for. First of all, it is often not the sole effect of alpha-blockade that was measured, but the effect of additional antihypertensive treatment as well. Only the study by Kocak used monotherapy preoperatively. Other studies often combined phenoxybenzamine with a beta-blocker, possibly enhancing the blood pressure controlling effects of phenoxybenzamine. One can state, however, that phenoxybenzamine and a beta-blocker are often used together in daily clinical practice. It is therefore not illogical to measure the effect of both when both are considered necessary. Moreover, Bruynzeel found no difference in perioperative haemodynamics with or without an additional beta-blocker. Although use of vasoactive drugs and fluid infusion intraoperatively can be considered confounding factors, they can be seen as a measure of haemodynamic instability as well. Even so, in most studies they did not differ significantly.

Second, patients in the phenoxybenzamine group were treated years before the last patients in the doxazosin group. Because surgical techniques, anaesthesia and multidisciplinary collaboration have been improved over the years, we can assume that the most recently operated patients underwent surgery under better circumstances.[30] It is, however, difficult to translate these findings to a quantifiable effect on intraoperative haemodynamics. In Weingarten's study, patients were partially treated during the same period. Although treated in different hospitals, they still found similar results as the other studies, potentially diminishing the influence of surgery periods.

Third, the operative approach differed between studies. In the studies by Prys-Roberts and Kocak the last nine and six patients, respectively, were treated by laparoscopic surgery, whereas the rest were treated by open surgery. All patients in Yu Zhu's study were treated with conventional open surgery; in contrast, all operations in Weingarten's study were laparoscopic. Bruynzeel included patients whom underwent both types of surgery and concluded that there was no difference in intraoperative blood pressure fluctuations, as did Tiberio *et al.*[31] However, it has to be noted that laparoscopic surgery is performed on relatively small tumours with no suspicion of malignancy. In the case of studies only using laparoscopic surgery there could be selection bias, although not mentioned, because only laparoscopically operable tumours were included.
Fourth, there was no correction for tumour size or excretion profile. Although they share a linear relationship, tumour size and plasma catecholamine levels are both independent risk factors for intraoperative catecholamine release and thus haemodynamic instability.[29,32,33] Furthermore, the degree of norepinephrine production is associated with intraoperative hypertension.[13] Correction is, however, very difficult; using stratification on a small sample size diminishes the already low statistical power.

When considering the fact that effects might be influenced by study design, bias and sample size, it seems that the results represent some of the properties of the used compounds. The non-competitive block of phenoxybenzamine resulted in the seemingly better controlled systolic blood pressure, whereas the relatively short-acting doxazosin had a less pronounced postoperative hypotension, which could be hypothesised considering the pharmacological properties of both compounds. There does not seem to be any difference in the use of fluids and vasoactive drugs. Although analysed in a very small sample size, side effects occur significantly less often in the doxazosin group.
Currently there are no guidelines that prefer a certain type of alpha-blockade. On the basis of current evidence there is no reason to prefer either of the two compounds concerning haemodynamics, since clinically relevant differences are minimal. As the two drugs do not seem to differ much in effectiveness of haemodynamic control, more practical reasons can tip the balance in favour of one compound. For example, Kocak and Bruynzeel both switched from phenoxybenzamine to doxazosin, because they had trouble acquiring the phenoxybenzamine. Side effects seem to be more favourable in the doxazosin group as well. Moreover, in some cases it was possible to use only a single dose a day in the doxazosin group, instead of multiple doses of phenoxybenzamine.
On the basis of the current evidence, it is difficult to gain a solid conclusion about which drug is superior. To reach a definitive conclusion a randomised study is warranted. Investigators of the UMC Groningen, the Netherlands, are preparing such a randomised study. This is necessary for the fine tuning of current management and could solve this dilemma. However, whether using phenoxybenzamine or doxazosin, mortality is extremely low and severe complications as a consequence of excessive catecholamine release rarely occur. Patients who died did so because of metastasis or were more than 30 days post-surgery. Some people are even starting to doubt the use of preoperative alpha-blockade at all, claiming that intraoperative use of vasoactive agents is sufficient to control haemodynamics.[34] Shao *et al.* showed that 59 normotensive patients with a pheochromocytoma did not benefit from pretreatment with alpha-blockade (n=38) when compared with no pretreatment (n=21).[35] Haemodynamics in both groups were similar, but the use of vasoactive agents and fluids were significantly greater in the doxazosin group. Whether giving phenoxybenzamine, doxazosin or nothing, all three options should be analysed in further prospective studies.

CONCLUSION

The operative treatment of pheochromocytoma can be considered safe. On the basis of current evidence there is no evident superior alpha-blocker for the pretreatment of patients with pheochromocytoma. Perioperative haemodynamics seem to be slightly better controlled with phenoxybenzamine, at the cost of more pronounced postoperative hypotension. Side effects occurred less often in the doxazosin group. The use of vasoactive drugs and fluid administration do not differ significantly. More practical factors as availability and experience of the treating physician may tip the balance in favour of one of the two compounds. Randomised studies are required to solve this problem.

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ORIGINAL ARTICLE

Perioperative glycaemic control in insulin-treated type 2 diabetes patients undergoing gastric bypass surgery

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ABSTRACT

Background: Roux-and-Y gastric bypass (RYGB) rapidly reduces insulin requirements in patients with insulin-dependent type 2 diabetes mellitus (T2DMi). A too modest reduction in insulin dose may lead to hypoglycaemia in the early postoperative period.

Objective: To evaluate a regimen designed to maintain blood glucose levels between 5-15 mmol/l and to prevent hypoglycaemic events (blood glucose <3.5 mmol/l) after RYGB surgery.

Design: The effect of a 75% reduction in insulin dose was studied in 85 T2DMi patients during the first ten days after RYGB. Patients with severe β-cell failure (fasting C-peptide <0.3 nmol/l) were excluded. Primary outcome measures: percentage of patients exceeding the upper or lower blood glucose limits, and the number of hypoglycaemic events.

Results: The mean blood glucose level was 12.4±0.3 mmol/l (mean ± SE) on the day of surgery (day 0), 10.7±0.3 mmol/l on day 1, 10.0±0.5 mmol/l on day 2, and 8.3±0.3 on day 10. Of all measurements performed during this ten-day period, 12.4% were above the target range, and 2.6% were <5 mmol/l. There were no hypoglycaemic events during the stay in hospital. During the first week at home 2% of the measurements were <3.5 mmol/l.

Conclusion: A 75% reduction in insulin dose is safe in T2DMi patients without severe β-cell failure, and prevents hypoglycaemia in the early postoperative period of RYGB in most cases.

KEYWORDS

Diabetes mellitus, insulin, gastric bypass, glucose control

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) in patients with morbid obesity is about 20 -30%.[1] Roux-and-Y gastric bypass (RYGB) is very effective in improving glucose control in these patients.[2,3] Current guidelines state that T2DM patients with a BMI ≥35.0 kg/m^2 should be offered the option of bariatric surgery, with RYGB as the method of choice.[4] An improvement in glucose control can be observed within hours to a few days after surgery, before any significant weight loss has occurred.[5-7] The underlying physiological changes leading to this rapid improvement have not been fully elucidated yet.[8]

About one-third of the T2DM patients presenting for bariatric surgery are treated with combinations of oral glucose-lowering drugs and subcutaneous insulin (T2DMi). It is not uncommon that massive doses of insulin are needed preoperatively to achieve at least some degree of glucose control. These patients on insulin are at risk to develop severe hypoglycaemia after RYGB if the insulin dose is not adjusted appropriately.

The main aim of perioperative glucose control is safety and stability of patient conditions. Hypoglycaemia is a powerful stimulus for catecholamine release, and may elicit strong haemodynamic responses such as tachycardia and hypertension. These alarming symptoms should be avoided during surgery. Postoperative hypoglycaemia should also be prevented because of patient discomfort, and the need for medical personnel emergency responses. On the other hand, marked hyperglycaemia is also undesirable because it is associated with delayed wound healing and increasing infection rates.[9]

To date, the actual incidence of post-RYGB hypoglycaemia has not been documented yet, and validated guidelines for

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perioperative glucose control in T2DMi patients planned for RYGB are not available. We therefore decided to design a regimen for structured insulin dose reduction and to monitor its efficacy. The present study describes our experience in the first 85 patients.

MATERIAL AND METHODS

Patient selection

This is a single-centre observational study in T2DMi patients with a BMI ≥35.0 kg/m^2, scheduled for RYGB. Preoperatively, all patients were referred to the outpatient clinic of internal medicine to prepare for perioperative glucose control. Medical history and medication were recorded and a fasting blood sample was drawn between 08.00 and 10.00 hours to measure serum creatinine, glucose, and C-peptide levels. To minimise the risk of ketoacidosis in the perioperative period, only T2DMi patients with a fasting C-peptide level >0.3 nmol/l were included. Patients with a fasting C-peptide level <0.3 mmol/l were considered to have severe β-cell failure, and were not eligible for massive insulin dose reduction. Other exclusion criteria were not employed. The aim was to achieve blood glucose levels of 5-15 mmol/l in the early postoperative period, and to avoid hypoglycaemia (glucose <3.5 mmol/l). The upper limit of 15 mmol/l was chosen because rapidly progressive improvement in insulin action was anticipated in the days after surgery. Tuning of medication to induce tight glycaemic control during the brief in-hospital postoperative period would increase the risk of developing hypoglycaemia when returning home, in particular in patients resuming their normal daily physical activities.

Protocol

All patients were admitted to the hospital on the evening preceding surgery (day -1). In patients on bedtime long-acting (LA) insulin, the bedtime dose was reduced by 50% to minimise the risk of hypoglycaemia during the day of surgery. On the day of surgery (day 0), all oral antidiabetics were temporarily discontinued, and at 06.00 hours a saline-glucose infusion (NaCl 0.45% + glucose 2.5%) was started at a rate of 2 litres/24 hours, supplemented with potassium chloride 40 mmol/24 hours. Patients with a preoperative daily insulin dose <50 IU/day only received the saline-glucose infusion with potassium chloride during, whereas patients with a preoperative daily insulin dose >50 IU/day also started on continuous intravenous insulin by pump device at 06.00 hours. The insulin delivery rate was derived from the preoperative total daily insulin dose: Insulin delivery rate in IU/h = (0.25 x preoperative total daily dose)/24. During day 0 all patients remained in the fasting state, but from six hours postoperatively they were allowed to drink water. During the next ten days food intake was limited to thickened fluids and minced foods with an approximate caloric intake of 800 kcal/day. Thereafter, a more regular diet was started, consisting of six small meals a day.

On the first day postoperatively (day 1), saline-glucose infusion and intravenous insulin were discontinued at 07.00 hours, and all patients previously on intravenous insulin now started a regimen of short-acting (SA) insulin three times a day (insulin aspart, TID), injected subcutaneously just before a meal. This was combined with metformin in the same dose as used preoperatively. SA insulin was given in a dose that was 75% lower than the preoperative mealtime doses. Bedtime LA insulin was discontinued permanently in all patients and replaced by glimepiride, taken at 20.00 hours, to achieve night-time glucose control. In patients with fasting C-peptide levels >0.3 nmol/l it has been shown that suppression of nocturnal hepatic glucose output can be achieved by raising portal insulin concentration with glimepiride administered at 20.00 hours.[10] This approach was specifically chosen to avoid the effects of peripheral tissue overinsulinisation that is induced by LA insulin and is associated with inhibition of lipolysis and hindering of weight loss. In an uncontrolled study, the combination of SA insulin TID with glimepiride at 20.00 hours has been shown to provide long-term glycaemic control without weight gain, and we considered such a regimen preferable in the setting of morbid obesity.[10] The glimepiride starting dose was 2 mg, and further adjustment was based on the mean of three consecutive fasting glucose levels. The maximum daily dose of glimepiride was set at 8 mg.

Three examples may serve to illustrate how the most common preoperative regimes were converted into an adjusted postoperative schedule on day 1. First, patients on a four times a day schedule resumed SA insulin in doses that were 75% lower than their preoperative mealtime doses. Their bedtime LA insulin was discontinued and replaced by glimepiride 2 mg at 20.00 hours, irrespective of the magnitude of the LA insulin dose. Second, patients on twice daily premixed insulin (30/70) also changed to a schedule of SA insulin TID, combined with glimepiride 2 mg at 20.00 hours. The amount of SA insulin prescribed for breakfast and lunch was 75% lower than their preoperative premixed morning dose. The dinner SA insulin dose was 75% lower than their formerly premixed evening dose. Third, patients using only LA insulin preoperatively were also put on a schedule of SA insulin TID with glimepiride 2 mg at 20.00 hours. The three mealtime SA doses were reduced to 1/12 of the preoperative total daily dose of LA insulin.

Capillary blood glucose levels were measured at 8.00, 12.00, 17.00 and 22.00 hours (Accu-Check®, Roche Diagnostics, Almere, the Netherlands). On the day of surgery, fasting glucose levels were measured at 06.00 hours instead of 08.00 hours, i.e. before the start of intravenous insulin infusion. Additional ad hoc measurements were performed if hypoglycaemia or severe hyperglycaemia was suspected. Medication was adjusted if glucose levels were <5 mmol/l or >15 mmol/l, for two consecutive measurements. Additional SA insulin was given if daytime glucose levels were >15 mmol/l. Discharge was considered safe if blood glucose levels had remained between 5-15 mmol/l. All patients had telephone contact with the diabetes nurse one week after discharge to discuss the management of their blood glucose levels. In case of markedly abnormal glucose levels they were free to advance this call. Ten days after surgery the medication was adjusted to obtain blood glucose levels in the order of 8-10 mmol/l for the next four weeks.

Statistics

Results are shown as mean values ±standard error of the mean (SEM). Comparison of groups was done by unpaired t-test. A p-value <0.05 was considered to represent statistical significance.

RESULTS

Baseline characteristics

Eighty-five patients were included in the study. Baseline characteristics are summarised in *table 1*. Their mean age was 52.7±0.9 years, and they had a mean BMI of 42.8±0.6 kg/m². The interval between diagnosis of diabetes and the time of surgery was 11.3±0.7 years. Preoperative C-peptide levels ranged from 0.31-3.59 nmol/l. Seventy-two patients (85%) used metformin with a mean dose of 2024±79 mg/day. Seventy-one patients were on LA insulin (mean daily dose 75±5.4 IU/day) and in 59 patients this was combined with SA insulin (mean daily dose 89±5.5 IU). Eleven patients used premixed insulin preoperatively, with a mean daily dose of 81±9.8 IU/day. Three patients only used SA insulin TID. The mean preoperative total daily insulin dose in all patients taken together was 133±8.4 IU. Ten patients used less than 50 IU/day, 21 patients used 50-100 IU/day, 22 patients used 100-150 IU/day and 32 patients used more than 150 IU/day.

Table 1. *Baseline characteristics of patients*

Characteristics	Patients (N=85)
Age (years)	52.7±0.9
Male / female ratio	1 / 1.7
BMI (kg/m²)	42.8±0,6
Waist circumference (cm)	135.6±1.4
Oral glucose-lowering drugs	
Metformin	84.7%
Sulfonylureas	29.4%
Thiazolidinediones	2.4%
Insulin dose (IU/day)	136±8.5
Additional medication (%)	
Statins	70.6%
Diuretics	51.2%
ACE inhibitors	66.7%
β-blockers	30.6%
Calcium channel blockers	22.6%
Laboratory results	
Fasting glucose (mmol/l)	11.9±0.9
HbA1c (mmol/mol)	67.4±1.7
Fasting C-peptide (nmol/l)	1.1±0.1
Creatinine (µmol/l)	74.3±4.6
Microalbuminuria (mg/l)	109.3±28.9
HDL (mmol/l)	1.2±0.1
LDL (mmol/l)	2.3±0.1
Triglycerides (mmol/l)	2.4±0.3

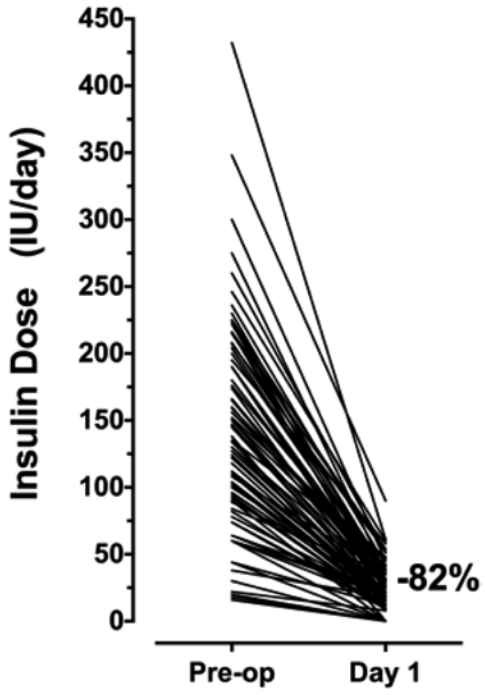
Day of surgery (day 0)

Fasting glucose levels at day 0, the result of a 50% dose reduction of LA bedtime insulin on the night before, ranged from 3.9-16.1 mmol/l with a mean of 9.7±0.4 mmol/l (*figure 2*, day 0). At 06.00 hours the continuous intravenous insulin pump was started in 75 patients, according to protocol, with a mean infusion rate of 1.2±0.1 IU/h, or 29 IU/day. This resulted in a mean 24-hour blood glucose level of 12.4±0.3 mmol/l. Twenty-six percent of all glucose measurements were >15 mmol/l, the highest level being 23.1 mmol/l (*figure 2*). Only two measurements (1%) were <5 mmol/l. No hypoglycaemic events were observed. As shown in *figure 3*, variability in glucose levels during insulin infusion was acceptable. There was a trend of progressively declining glucose levels, in particular during the night, but hypoglycaemia did not occur. The fasting glucose levels on day 1 varied from 6.1-23.1 mmol/l. Three of the four patients with a day-1 fasting glucose level >15.0 mmol/l were found to have a postoperative surgical complication.

Ten patients were not treated with insulin on the day of surgery because their preoperative insulin dose had been <50 IU/day. Their preoperative fasting glucose levels were comparable with those on high-dose insulin (9.7±1.2 mmol/l versus 12.2±1.0 mmol/l, p=0.13), but their preoperative C-peptide levels had been significantly higher (1.6±0.3 nmol/l versus 1.0±0.1 nmol/l, p<0.05). In this

subgroup not receiving insulin infusion during surgery, mean glucose levels varied from 8.8-15.5 mmol/l. Twenty percent of these measurements were >15 mmol/l and none were <5 mmol/l.

Figure 1. *Insulin dose reductions in individual patients with type 2 diabetes mellitus: preoperative daily dose versus daily dose on day 1*



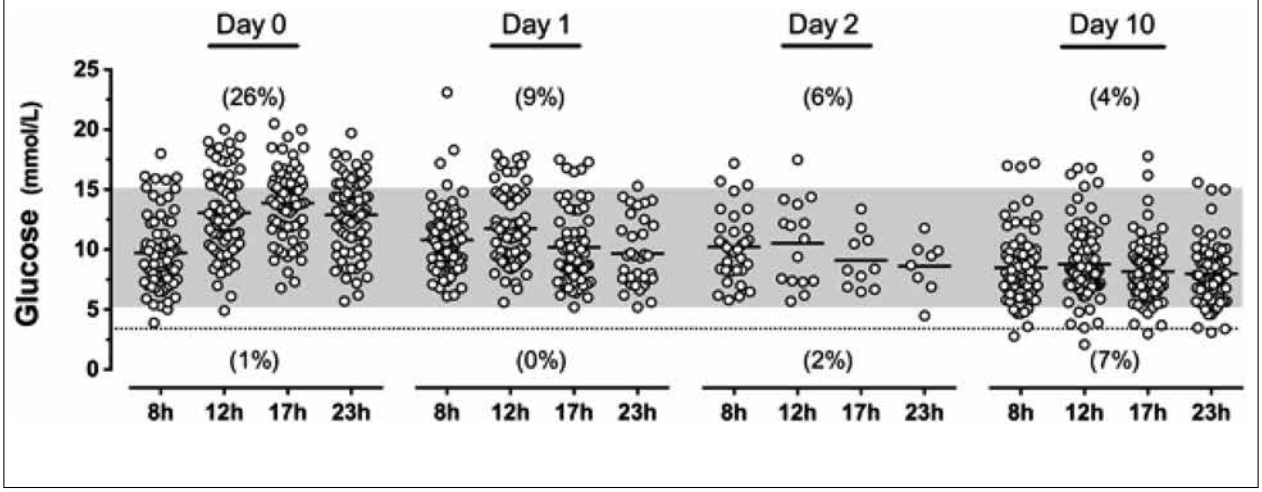
Day 1

The first day after surgery, all 75 patients using a preoperative insulin dose >50 IU/day started subcutaneous SA insulin TID, combined with glimepiride if indicated by protocol, and metformin in the same dose as used preoperatively. The mean total insulin dose was 24.4±1.9 IU/day, i.e. 82% lower than preoperatively (*figure 1*). Glimepiride was resumed in all 25 patients who had been using it preoperatively in a dose >2 mg/day. In 45 patients who had been on evening or bedtime LA insulin preoperatively, LA insulin was replaced by glimepiride 2 mg at 20.00 hours. This 2 mg dose replaced a mean dose of LA insulin of 75±5.4 IU. The regimen produced a mean glucose level of 10.7±0.3 mmol/l. Nine percent of measurements were >15 mmol/l, none were <5 mmol/l. Six patients had one glucose measurement >15 mmol/l, six patients had two measurements >15 mmol/l, and one patient had three glucose measurements >15 mmol/l. Seven percent of patients received an extra dose of subcutaneous insulin.

Day 2

On the morning of the second day after surgery (day 2), 70 of all 85 patients were discharged. Patients who remained in hospital either had a surgical complication or blood glucose levels outside the target range. Discharge reduced the total number of in-hospital glucose measurements on day 2 to 66. A complete 24-hour glucose profile was available in ten patients. The mean fasting glucose level was 10.3±0.5 mmol/l. The mean glucose level of all measurements performed at day 2 was 10.0±0.5 mmol/l.

Figure 2. *Glucose levels on the day of surgery (day 0) and 1, 2 and 10 days later. Grey area: target range, glucose levels of 5-15 mmol/l. Numbers in parentheses: percentage of glucose measurements >15 mmol/l or <5.0 mmol/l. Black interrupted line refers to a glucose level of 3.5 mmol/l*



Eight percent of all measured glucose levels were outside the target range, 6% because of a glucose level above 15 mmol/l. Hypoglycaemic events were not observed.

Surgical complications and blood glucose levels

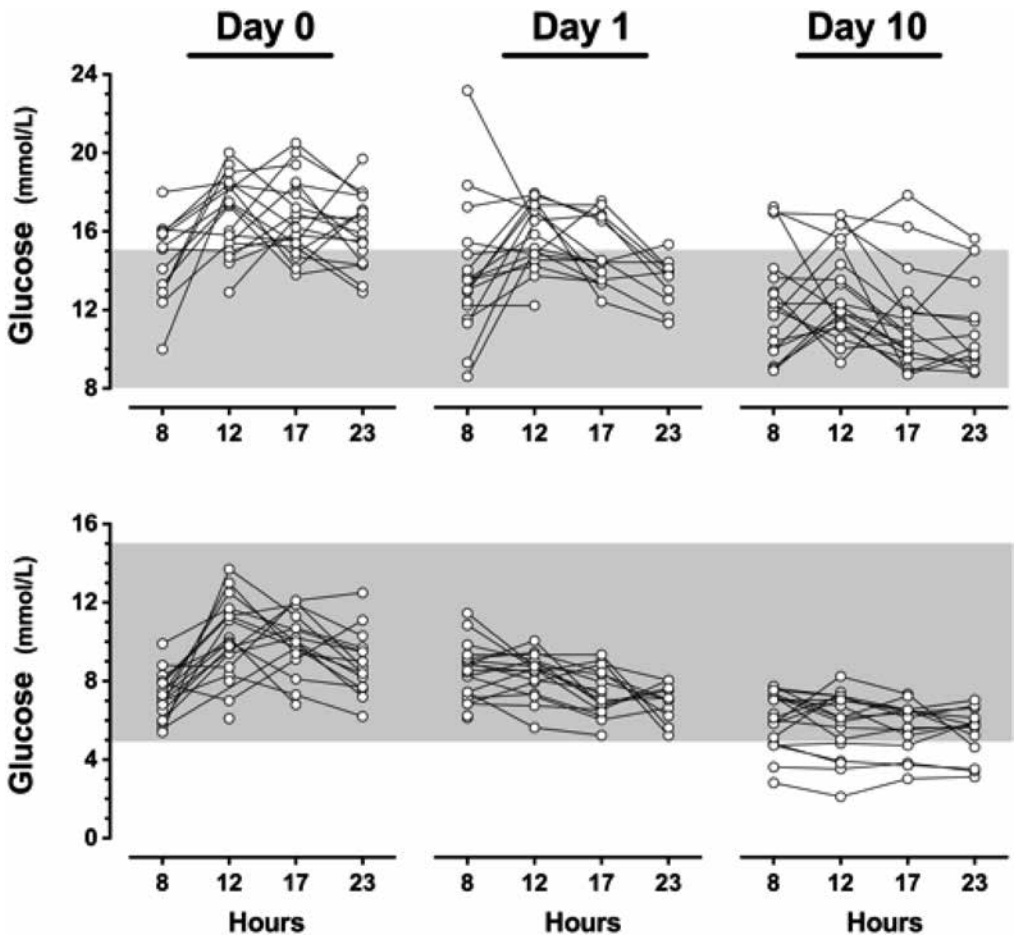
Seven patients (8.2%) had surgery-related complications requiring re-laparoscopy: four patients had a leaking anastomosis, and three patients had postoperative bleeding. Blood glucose levels in these patients were markedly higher than in the group without surgical complications. Forty-six percent of their glucose levels were >15 mmol/l on day 0, 35% on day 1 and 13% on day 2. Hypoglycaemic events were not observed. Preoperative glycaemic control was comparable in patients with and without surgical complications: HbA1c 64.3±3.4 versus 67.7±1.8 mmol/mol (p=0.70).

One week after discharge

Seven patients (8.2%) were lost to follow-up. In the remaining 78 patients, the fasting glucose level ranged from 2.8-17.5 mmol/l, and the mean daily glucose level was 8.3±0.3 mmol/l. Four percent of all measurements were >15 mmol/l, and 7% were <5 mmol/l. Blood glucose levels of patients with values in the lowest quartile were fairly stable throughout that day (*figure 3*). Glucose levels <3.5 mmol/l were observed on five occasions, and occurred in two patients (*figure 3*). Severe hypoglycaemia requiring the help of a third party was not reported. Seventy-six percent of patients were advised to continue glimepiride as before. The glimepiride dose was raised in ten patients (13%) because of a fasting blood glucose level >8 mmol/l. In four patients (5%) the dose of glimepiride was reduced because of a fasting glucose <4 mmol/l, and in three patients (4%) glimepiride was discontinued.

Forty patients (51%) were advised to continue the dose of insulin as prescribed at discharge, 23 patients (30%) were advised to lower their insulin dose by a mean of 6.0±1.1 IU/day, and 14 patients (18%) were advised to stop insulin treatment. In one patient, the insulin dose was raised by 6 IU/day.

Figure 3. *Variability in glucose levels in individual patients on the day of surgery (day 0), day 1, and day 10. Top figures: patients from the upper quartile of that day. Bottom figures: patients from the lowest quartile of that day*



Prediction of glucose levels at day 10

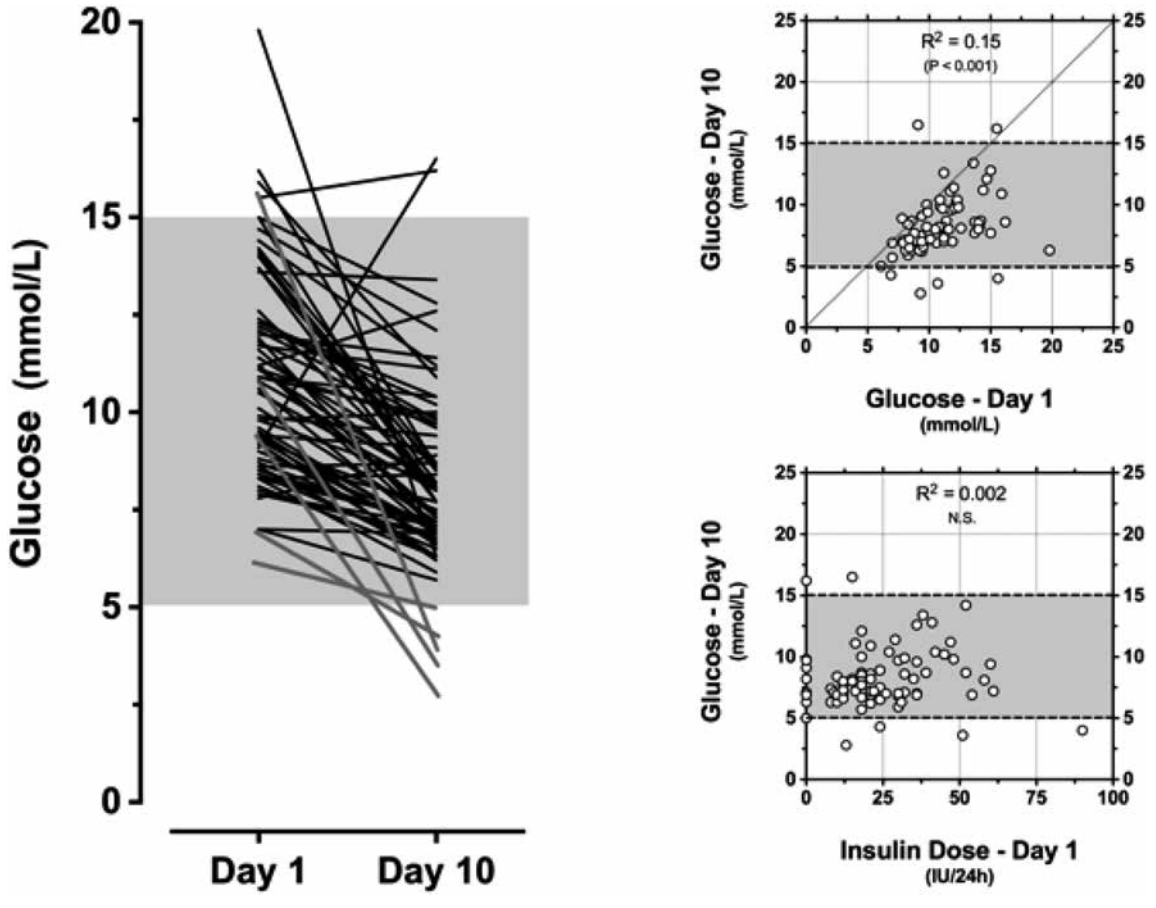
Ninety-one percent of patients demonstrated a decline in mean blood glucose levels between day 1 and day 10. The mean decrease was 3.0±0.3 mmol/l. Interindividual variability was large, with individual changes ranging from +7.4 to -13.5 mmol/l (*figure 4*). Mean 24-hour glucose levels at day 1 were weakly correlated with levels at day 10 (R^2=0.15, p<0.001). At day 10, five patients (6%) had developed a mean glucose level ≤5 mmol/l, this had occurred after declines in mean glucose levels between day 1 and 10 of 1.0-11.6 mmol/l (*figure 4*). The mean glucose levels at day 10 were not correlated with preoperative or postoperative insulin doses.

DISCUSSION

The results of this study indicate that a 75% lowering of the daily insulin dose is safe after RYGB in patients with T2DMi and proven residual β-cell function. This regimen was very effective in avoiding hypoglycaemia during the first ten days after surgery in the majority of patients. The study also illustrates that there is room for improvement. Extension of the in-hospital period to allow a full 48-hour monitoring on subcutaneous insulin may help to achieve a more stable blood glucose level at discharge and might improve the prediction of changes in blood glucose levels in the days after discharge. Secondly, patients with in-hospital postoperative blood glucose levels of 5-10 mmol/l are at increased risk to develop hypoglycaemia at home (*figure 3*), and their insulin doses should be reduced at discharge to avoid that. Finally, advancing the first telephone contact from the 7th to the 3rd day after discharge may help to detect patients with rapidly declining glucose levels at an earlier stage and further reduce the risk of hypoglycaemia.

The present study has investigated five aspects of perioperative glucose control in morbidly obese patients with T2DMi: 1) The effect of a 50% reduction of bedtime LA insulin on the evening before surgery, 2) The efficacy

Figure 4. *Changes in mean 24-hour glucose levels between day 1 and day 10 after surgery, and the correlation between mean glucose levels measured on day 10 and those on day 1. Grey lines: patients developing mean glucose levels <5 mmol/l on day 10*



of low-dose intravenous insulin pump delivery during the day of surgery in patients using a preoperative insulin dose >50 IU/day, 3) The glucose response to withholding perioperative intravenous insulin in patients using a preoperative insulin dose <50 IU/day, 4) The safety of a major reduction in postoperative subcutaneous insulin treatment, and 5) The efficacy of replacing LA insulin by glimepiride at 20.00 hours to obtain nocturnal glucose control.

The observation that fasting and daytime glucose levels on the day of surgery were never <3.5 mmol/l indicates that the preoperative 50% lowering of bedtime LA insulin was effective in avoiding hypoglycaemia. This dose adjustment also did not result in clinically significant hyperglycaemia, the highest fasting glucose level being 16.1 mmol/l (*figure 2*). It is therefore concluded that a 50% reduction on the night before surgery is appropriate in these patients.

Ten patients used insulin in a dose <50 IU/day. It was, prospectively but arbitrarily, decided that insulin treatment on the day of surgery was not likely to be necessary. The present data suggest that this appraisal was correct. The highest glucose level was 16.9 mmol/l, and glucose levels <5 mmol/l did not occur. Preoperative fasting C-peptide levels indicated that β-cell function was better in this subgroup. Apparently, their β-cell function was sufficient to maintain blood glucose levels with an acceptable range while fasting. However, the first day after surgery three of these patients required a restart of insulin at a dose of 8-18 IU/day.

Seventy-five patients were given intravenous insulin by pump device on the day of surgery. The dose was 78% lower than the subcutaneous dose used preoperatively. This major reduction in insulin prevented hypoglycaemia in all patients. However, 26% of the measurements were >15 mmol/l. The surgical complication rate was markedly higher in patients with glucose levels >15 mmol/l than in patients with glucose levels <15 mmol/l: 18.2% versus 6.4%. As preoperative glycaemic control was similar in patients with and without surgical complications, the high glucose levels are considered a consequence and not a cause of these complications.

The first day after surgery all patients on intravenous insulin were put on a regimen of insulin aspart TID, combined with glimepiride 2 mg at 20.00 hours, and metformin was resumed in the same dose as before surgery. Discontinuation of LA insulin is attractive in T2DM patients because it reduces the risk of hypoglycaemia and may be associated with better RYGB-induced weight loss because overinsulinisation with inhibition of lipolysis is avoided. As described previously, glimepiride was used for night-time glucose control with its dose titrated based on fasting glucose levels.[10] In view of glimepiride's plasma half-life of 5-8 hours, several days of use are required to reach a steady state. The fasting glucose levels at ten days after surgery are therefore a good indication of its efficacy. The results are promising: 89% of patients had fasting glucose levels within the desired range.

The present study has some limitations. First, it is a single-centre study and it lacks comparator arms. Future studies might consider inclusion of a treatment arm with continued use of bedtime LA insulin at an adjusted dose to examine the hypothesis that glimepiride at 20.00 hours is preferred over LA insulin because of its presumed lower risk of hypoglycaemia and less hindering of RYGB-induced weight loss. In addition, inclusion of a study arm with gliclazide instead of glimepiride might be useful to examine whether gliclazide is associated with a lower risk of hypoglycaemia than glimepiride in this particular setting.[11,12] Another limitation is the low number of in-hospital observations on day 2. A 48-hour postoperative in-hospital observation period on subcutaneous insulin may be required to ensure a higher degree of stability in glycaemic control and a better predictability of glucose levels during the first week at home. Future studies focusing on the results of treatment on day 1 and 2 and studying their correlation with glucose control during the first week out-of-hospital may reveal subcategories of patients who can be safely discharged on the morning of day 2, based on the glucose measurements of day 1. However, as long as this information is lacking, we advocate a postoperative in-hospital two-day observation period on subcutaneous insulin, for reasons of safety, particularly in those on high-dose insulin. Finally, the perioperative glucose upper target limit of 15 mmol/l used in this study is higher than the generally recommended upper limit of 11 mmol/l.[13] Although postoperative wound infections did not occur, the current number of patients is too small to exclude a negative impact on infection rates.[14] The issue of preoperative glycaemic control and its consequences for postoperative infection rates after gastric bypass is still under debate. Studies evaluating this aspect have produced conflicting results.[15,16]

In conclusion, a perioperative 75% reduction in daily insulin dose in T2DMi patients with residual β-cell function appears to be appropriate to avoid hypoglycaemia and marked hyperglycaemia after bariatric surgery. Confirmation of this observation in a controlled, multicentre study is recommended to increase the evidence of safety and efficacy and to allow comparison with other regimens.

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ORIGINAL ARTICLE

X-linked sideroblastic anaemia due to ALAS2 mutations in the Netherlands: a disease in disguise

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ABSTRACT

Background: X-linked sideroblastic anaemia (XLSA; OMIM#300751) is the most common inherited form of sideroblastic anaemia and is associated with several mutations in the erythroid specific 5-aminolevulinate synthase gene (*ALAS2*). This gene encodes for aminolevulinic acid synthase 2 (ALAS2), the catalytic enzyme involved in the first en rate-limiting step of haem biosynthesis.[1-3] The disorder is characterised by mostly mild hypochromic microcytic anaemia with bone marrow ring sideroblasts. Even untransfused patients with mild or no anaemia are at risk for severe systemic iron overload due to ineffective erythropoiesis. To date, 61 different *ALAS2* mutations have been reported in 120 families with XLSA. Descriptions of molecularly confirmed case series from the Netherlands, however, are lacking.

Methods: We reviewed age of presentation, clinical and biochemical features, ALAS-2 defects and treatment characteristics of 15 Dutch patients from 11 unrelated families diagnosed with XLSA.

Results and Conclusions: In one family a novel pathogenic c.1412G>A (p.Cys471Tyr) mutation was found. All other families shared the previously described c.1355G>A (p.Arg452His) mutation. Haplotype analysis in seven probands with the p.Arg452His mutation strongly suggests that six of them were ancestrally related. Nevertheless, their phenotype was very different. Our patients illustrate the phenotypical heterogeneity in the presentation of XLSA patients, the effectiveness of treatment regimens and the various pitfalls associated with the diagnosis, follow-up and treatment of the disease. A timely diagnosis avoids unnecessary investigations and allows adequate treatment that can prevent systemic iron load with subsequent severe life-threatening complications. Therefore, we suggest considering XLSA in both male and female patients with unexplained iron overload and/or (mild) microcytic anaemia, also at older age.

KEYWORDS

ALAS2, iron, sideroblastic anaemia

INTRODUCTION

X-linked sideroblastic anaemia (XLSA; OMIM #300751) is the most common inherited form of sideroblastic anaemia and is associated with several mutations in the erythroid specific 5-aminolevulinate synthase gene (*ALAS2*), which is the first and rate-limiting step of haem-biosynthesis. [1-3] The disorder is characterised by hypochromic microcytic anaemia with ring sideroblasts in the bone marrow in combination with systemic iron overload due to ineffective erythropoiesis. Phenotypic expression of XLSA is highly variable even in patients with identical mutations, but affected males generally present in the first decades of life with symptoms of anaemia or later with manifestations of parenchymal iron overload. Occasionally patients present later in life [4,5] As in most X-linked recessive disorders, the majority of female carriers of XLSA are spared from clinical manifestations. However, sporadically women with *ALAS2* mutations may be affected due to inactivation of the normal X-chromosome or age-related skewed X-inactivation in haematopoietic cells.[6-8] Standard treatment of XLSA consists of high-dose pyridoxine supplementation and iron-reducing strategies such as phlebotomies and iron chelation.[9] The effect of high-dose

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pyridoxine is based on the high prevalence of mutations in the pyridoxine-binding region of the *ALAS2* gene. The high dose enhances the half-life of *ALAS2*; however, this is not true for mutations outside this region.[10] Reduction of iron overload in XLSA improves erythropoiesis and prevents complications of chronic iron overload, especially liver cirrhosis and hepatocellular carcinoma.[11-13]

In this article we describe 14 male patients and one female patient from 11 unrelated families. All patients are of Dutch origin. These case series are illustrative for the biochemical and clinical presentation of XLSA patients, the effectiveness of treatment regimens and the various pitfalls associated with the (early) diagnosis, follow-up and treatment of the disease.

PATIENTS AND METHODS

Patients

We reviewed clinical and molecular data of 15 patients (14 male and one female) diagnosed with XLSA in the Netherlands in 2011 and 2012. The diagnosis of sideroblastic anaemia was made at the University Medical Centre Utrecht, Utrecht and the Radboud University Medical Centre, Nijmegen, the Netherlands. We reviewed age at presentation, biochemical and clinical features, treatment regimens and type of *ALAS2* mutations.

Genotyping

Genotyping was performed by PCR and DNA sequence analysis of the full coding part of the *ALAS2* gene. The pathogenicity of a mutation was assessed by review of the literature, association of the mutation with the phenotype in a family, and with bioinformatic tools, which were used to complement the genetic studies in case of a not previously reported mutation. SIFT (=Sorting Intolerant from Tolerant), PolyPhen (Polymorphism Phenotyping) and HOPE (Have (y)Our Protein Explained) provide an *in silico* prediction of the functional consequences of missense mutations.[14-17]

A search for a founder effect was done in seven of the ten families with the p.Arg452His mutation by genotyping the short tandem repeats (STRs) DXS1044, DXS8032, DXS991 and DXS1190 close to the *ALAS2* gene by PCR using fluorescent primers. PCR products were pooled and analysed on an ABI 3730 DNA sequencer.

RESULTS

Overall clinical and biochemical features and treatment strategies of Dutch XLSA patients

Fifteen XSLA patients from 11 unrelated families were included in the study; all were of Dutch and Caucasian origin (*table 1*). Age at the time of clinical and biochemical diagnosis in our patients ranged from 2-72 years. In the male patients, haemoglobin at diagnosis ranged from 3.9-7.8 mmol/l with the mean corpuscular volume (MCV) between 56-71 fl. Serum ferritin at diagnosis ranged from 99-5040 µg/l.

All patients were treated with high-dose pyridoxine (200 mg daily, except for patient 10 who received 150 mg daily), phlebotomies or chelation. Per phlebotomy, 500 ml blood was withdrawn, except in patient 2B who started on 200 ml per phlebotomy every two weeks for two months. Because of a stable and even increasing Hb, the phlebotomy volume was increased to 400 ml every two weeks until his ferritin became <100 µg/l (*figure 1*).

Also in the other patients, phlebotomies were well tolerated, even in a patient with more severe anaemia (patient 3). In general this treatment regimen resulted in a significant increase of Hb in six out of 15 patients and a decrease of ferritin levels in five out of 15 patients.

The only female proband, patient 1A, died at the age of 79 years due to the complications of diabetes mellitus and heart failure. Patient 2A died at the age of 71 years from a hepatocellular carcinoma (HCC). The other patients are still alive and in good clinical condition. None of them have developed severe complications of systemic iron overload, probably due to timely treatment.

Molecular features

Thirteen out of the 15 patients showed hemizygosity for the previously reported pathogenic c.1355G>A (p.Arg452His) mutation in exon 9 of the *ALAS2* gene. One female patient was heterozygous for the c.1355G>A (p.Arg452His) mutation (patient 1A). These 13 patients with a p.Arg452His mutation are from ten apparently unrelated families. Haplotype analysis of patients 3 and 6-11 showed that all patients, except for proband 9, carried the same length of the four STRs analysed, suggesting that the p.Arg452His mutation arose from one common ancestor in these probands. The lengths of all four STRs of the patients differed from those found for proband 9. The common haplotype of patients 3, 6-8, 10 and 11 is at least 2.473 kilobase in size.

In two patients (brothers 5A and 5B) a novel mutation was found in exon 9: c.1412G>A (p.Cys471Tyr). For this mutation bioinformatic tools were not consistent in their assessment, i.e. SIFT predicted the mutation as non-pathogenic, whereas PolyPhen predicted the mutation as 'probably damaging'. HOPE reports: 'the wild-type (cysteine) and mutant amino acids (tyrosine) differed in size. The wild-type residue was buried in the core of the protein; the mutant residue was bigger and probably not fitting. The hydrophobicity of the wild-type and mutant residue differed. The mutation probably caused loss of hydrophobic interactions in the core of the protein'. The

Table 1. *Haematological, biochemical and molecular data, and treatment characteristics of 15 patients from 11 unrelated families diagnosed with X-linked sideroblastic anaemia*

Patient characteristics				**Laboratory characteristics**					**Genotype**	**Treatment characteristics**		**Remarks**
ID[1]		Age (yrs)	Sex (m/f)	Hb (mmol/l	MCV (fl)	Ferritin (µg/l)	TS (%)	Bone marrow	*ALAS2* mutation[2]	Pyridoxine	Chelation/ phlebotomy	
1A	At presentation	72	F	6.0	76	ND	ND	ND	p.Arg452His	Yes	ND	Blood transfusion per 3-6 months; Diabetes mellitus II; Myocardial infarction; Hypercholesterolaemia
	Death	79		ND	ND	ND	ND					
1B Son	At presentation	25	M	5.3	65	117[3]	40[3]	Ring sideroblasts +++	p.Arg452His	Yes	Phlebotomy	
	With therapy	46		7.2	69	135	ND					
	With therapy	61		7.6	63	244	32					
2A[4,5]	At presentation	66	M	7.8	68	346	57	ND	p.Arg452His	Yes	Phlebotomy	Heterozygosity for P.Cys282Tyr in *HFE;* death at age 71 because of hepatocellular carcinoma
	With therapy	69		7.2	70	316	48					
2B Grandchild	At presentation	2	M	6.8	ND	180	94	Ring sideroblasts 30%	p.Arg452His	Yes	Phlebotomy	Homozygous for p.Cys282Tyr in *HFE* gene
	With therapy	16		7.4	70	454	97					
	With therapy			7.8	71	72	80					
3	At presentation	35	M	4.3	56	5040	86[6]	Ring sideroblasts +++	p.Arg452His[11*]	Yes	Chelation phlebotomy	
	With therapy	47		8.0	64	1162	ND					
	With therapy	62		8.3	65	516	67					
4	At presentation	25	M	7.1	69	220	48	ND	p.Arg452His	Yes	No	Nail clubbing
	With therapy	34		7.0	70	281	42					
	With therapy	40		7.2	71	526	24					
5A	At presentation	<21	M	3.9	59	158	35	ND	p.Cys471Tyr	Yes	ND	
	With therapy	54		7.8	71	260	47					
5B Brother	At presentation	23	M	6.2	59	1200	ND	ND	p.Cys471Tyr	Yes	Phlebotomy	
	With therapy	53		8.4	68	259	37					

6	At presentation	32	M	6.8	71	258	52	Ring sideroblasts 11%	p.Arg452His[11*]	Yes	No	
	With therapy	54		7.4	76	150	48					
7	At presentation	<28	M	7.2	70	193	43	ND	p.Arg452His[11*]	Yes	No	
	With therapy	51		6.6	66	275	42					
8	At presentation	<28	M	7.1	62	573	82[7]	ND	p.Arg452His[11*]	Yes	Chelation phlebotomy	Rheumatoid arthritis IgA deficiency
	With therapy[8]	32		7.1	62	546	82					
9A	At presentation	30	M	6.8	70	610	52	No ring sideroblasts	p.Arg452His[11]	Yes	EPO phlebotomy	Bone marrow biopsy: MDS type RCMD with iron loaded macrophages
	With therapy	32		7.4	70	436	48					
9B Grandfather	At presentation	ND	M	ND	ND	ND	ND	ND	ND	ND	ND	Hereditary primary sidero-achrestic anaemia[9]
	With therapy			ND	ND	ND	ND					
10	At presentation	13	M	6.8	68	99	34	ND	p.Arg452His[11*]	Yes	No	Intention tremor, no ataxia, defect in *ABCB7* gene excluded
	With therapy[10]	14		6.8	68	64	58					
11	At presentation	18	M	7.5	70	252	56	Ring sideroblasts	p.Arg452His[11*]	Yes	No	
	With therapy	18		7.6	76	191	30					

[1]Numbers stand for families (probands are mentioned) for families 1,2, 5, and 9, also a 2nd affected relative is included; [2]hemizygous for men and heterozygous for women; [3]At age 28 years; [4]patient 2 was originally diagnosed with iron overload at the age of 38 years which later, at age 57, was attributed to hereditary haemochromatosis due to heterozygosity for the p.Cys282Tyr mutation in the *HFE* gene. Treatment with phlebotomies was started. Because of low Hb levels and ferritin levels within the reference range, phlebotomies were stopped at the age 51; [5]Patient previously reported in Cuijpers *et al.*[18]; [6]At age 38, no earlier values available; [7]At age 32; [8]Results of 1 year treatment with pyridoxine (200 mg per day) and phlebotomy every 4-6 weeks. EPO was stopped after diagnosis at age 30 yrs; [9]Patient previously reported in thesis of Dr. Ploem[20]; [10]Low compliance; MDS type RCMD = myelodysplastic syndrome type refractory cytopenia with multilineage dysplasia; [11]Probands investigated by haplotype analysis, in subjects indicated by [11*] this analysis suggests a common ancestor; ND = not determined or data not available; TS = transferrin saturation; NASH = non-alcoholic steatohepatitis; EPO = erythropoietin.

fact that both brothers share the same mutation and have similar phenotypes suggested the mutation to be pathogenic.

Case descriptions

Table 1 shows haematological, biochemical, molecular data and treatment characteristics of the XLSA patients. We will describe some of these patients and relatives in more detail in order to illustrate the biochemical and clinical presentation of XLSA patients, the effectiveness of treatment regimens and the various pitfalls associated with the management of this disease.

Patient 1A illustrates that women may develop a phenotype of XLSA later in life. At the age of 78 years, sideroblastic anaemia was diagnosed after she presented with anaemia (Hb 6.0 mmol/l). Three years earlier, her Hb was 7.7 mmol/l. Post-mortem she was found to have the same *ALAS2* defect as her son (patient 1B).

Patient 2A was originally diagnosed with iron overload at the age of 38 years.[18] Treatment with phlebotomies was started. Because of low Hb levels and ferritin levels within the reference range, phlebotomies were stopped at age 51. After the discovery of the *HFE* gene in 1996, at age 57, the patient was tested for hereditary haemochromatosis (HH). A heterozygous p.Cys282Tyr mutation in the (haemochromatosis) *HFE* gene was found. Based on this finding, the patient's iron overload was attributed to HH. However, HH is an autosomal recessive inherited disorder and complications due to iron overload alone are extremely rare in individuals who are heterozygous for defects in the *HFE* gene.[19]

In the same period, a male grandchild (patient 2B) was diagnosed with sideroblastic anaemia. DNA analysis in this child revealed a p.Arg452His mutation in the *ALAS2* gene, responsible for XLSA. The same mutation was subsequently found in his grandfather. So, in retrospect, patient 2A suffered from XLSA with secondary systemic iron overload due to ineffective erythropoiesis. At age 70, liver biopsy revealed a hepatocellular carcinoma with substantial iron accumulation in the hepatocytes and some steatosis. The lesion was attributed to iron overload and was not resectable. At age 71, the patient died of this complication. The patient had no history of liver cirrhosis.[18]

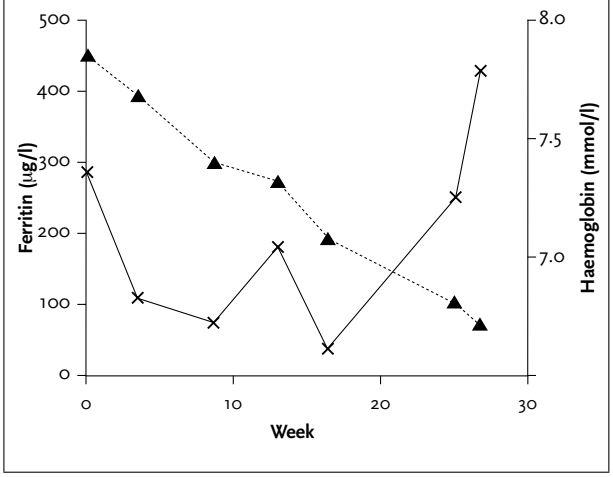
Because of the family history, mutation analysis of the *HFE* gene was also performed in his grandson, which revealed homozygosity for the p.Cys282Tyr mutation. Because of increasing ferritin levels at age 16, treatment with phlebotomies was started. Within a 30-week period, this resulted in a decrease in ferritin levels from 454 µg/l to 72 µg/l and an increase of Hb from 7.4 mmol/l to 7.8 mmol/l (*figure 1*).

Patient 3 presented with both severe anaemia (4.3 mmol/l) and very severe and systemic iron overload (ferritin of 5040 µg/l) at age 35. Despite his severe anaemia, phlebotomies were well tolerated and are likely to have contributed to normalisation of his iron stores and Hb in addition to treatment with pyridoxine and iron chelation.

In his teens, patient 5 presented with severe anaemia and ferritin within reference ranges. His younger brother was diagnosed with sideroblastic anaemia at the age of 23 years by family screening. He had no signs and symptoms of anaemia. However, serum ferritin was 1200 µg/l, suggesting severe iron overload. Treatment for sideroblastic anaemia and iron overload was started, consisting of pyridoxine and phlebotomies.

Patient 9 was initially diagnosed with myelodysplastic syndrome (MDS) at the age of 30 years, subtype refractory cytopenia with multilineage dysplasia (RCMD). Interestingly, no ring sideroblasts were seen in the bone marrow and the MCV was low, 70 fl. Since his grandfather had previously been described with 'hereditary primary sidero-achrestic anaemia' (patient 41 in the study by Bloem[20]) and since the index patient presented with a hypochromic microcytic anaemia in combination with iron overload, an *ALAS2* mutation was suggested and subsequently confirmed.

Figure 1. *A male patient (table 1, patient 2B) was diagnosed with sideroblastic anaemia and HFE-related haemochromatosis at the age of 2 years. At the age 16, treatment was started with phlebotomies because of increasing serum ferritin levels. The treatment consisted of a 200 ml phlebotomy every 2 weeks for 8 weeks, followed by 400 ml blood drawings every 2 weeks for another 22 weeks. Within a 30-week timeframe this treatment resulted in a significant decrease in ferritin levels and an increase in Hb. These data illustrate that reduction of systemic iron overload improves erythropoiesis in XLSA patients. X-axis indicates weeks after start of treatment with phlebotomies; X, Hb concentration; ▲, serum ferritin level*



DISCUSSION

Our Dutch case series is illustrative for the pathophysiology, the biochemical and clinical presentation of XLSA patients, the effectiveness of treatment regimens and the various pitfalls associated with the (early) diagnosis, follow-up and treatment of this disease. In this article we add a novel mutation to the previously described 61 different *ALAS2* mutations reported in 120 families with XLSA.[21-24]

All of our 15 XLSA patients had microcytic anaemia and all had a mutation in the exon 9 domain of the X-chromosome. In 10 out of 11 families (13 out of 15 patients) it concerned a p.Arg452His mutation, making this the most prevalent mutation in Dutch XLSA patients. A search for a founder effect by haplotype analysis in seven of the families with this mutation suggests that this mutation arose from a common ancestor in six of them. Worldwide the p.Arg452His is also the most frequent *ALAS2* defect in XLSA. In one patient a novel p.Cys471Tyr mutation was found. Bioinformatic analysis and family genotype-phenotype association study was highly suggestive for a pathogenic defect. Recently, we reported on a 12th Dutch family with XLSA due to a g.55054634G>C mutation in the GATA transcription factor binding site located in a transcriptional enhancer element in intron 1 of the *ALAS2* gene.[24]

Age at diagnosis, degree of anaemia and iron overload widely differed between these patients, illustrating heterogeneity in the clinical and biochemical penetrance of this congenital disease.

One of our patients (patient 3) illustrates that besides anaemia, severe systemic iron overload can occur at early age in transfusion-independent XLSA patients. Preclinical and clinical studies in β thalassaemia major and intermedia and other iron-loading anaemia suggest the ineffective erythropoiesis in these disorders may increase the production of humoral factors, which may include growth differentiation factor 15 (GDF 15), twisted gastrulation (TWSG1) and erythroferrone,[25-27] leading to decreased production of the iron-regulatory hepatic peptide hormone hepcidin, (reviewed by Kroot *et al.*,[28]). Hepcidin acts by inhibiting intestinal iron absorption and macrophage recycling of iron from senescent erythrocytes. Suppression of hepcidin production by these proteins has been suggested to cause inappropriately high intestinal iron absorption and iron release from the reticulo-endothelial system (RES), despite iron overload.[25-28]

We previously reported that patient 2A indeed had elevated serum GDF 15 levels which were associated with an inappropriately low serum hepcidin in relation to his iron stores, as reflected by a low hepcidin/ferritin ratio.[18] We did not measure serum GDF 15 and/or serum hepcidin in our other sideroblastic anaemia patients since the results have no therapeutic implications. As far as we know, no studies are available on the above-mentioned humoral factors or hepcidin in sideroblastic anaemia patients due to *ALAS2* defects.

In general, systemic iron overload develops in the third or fourth decade, also in patients without overt anaemia.[1,2] This emphasises the importance of early diagnosis, since the effects of systemic iron overload are potentially very serious, such as liver cirrhosis and HCC, especially in the presence of concurrent liver toxic conditions (alcohol abuse or non-alcoholic steatohepatitis). Moreover, we suggest that first-degree relatives should be screened for the relevant mutation, because they may develop severe iron overload without any signs and symptoms of anaemia.

This phenotype of iron overload with only mild anaemia may lead to a false diagnosis of hereditary haemochromatosis. We suggest that *ALAS2* mutations might be the underlying cause of patients (falsely) diagnosed with unexplained forms of HH. In these cases the low MCV should point the clinician to the presence of an iron-loading anaemia such as XLSA. To the best of our knowledge the prevalence of *ALAS2* defects among patients with genetically unexplained HH is unknown.

Other genes implicated in iron metabolism and HH may also affect the phenotype of XLSA. Anecdotal data support the suggestion that coinheritance of heterozygosity of the p.Cys282Tyr mutation in the *HFE* gene is likely increased in XLSA patients with moderate to severe phenotypes.[11,29,30] It is well possible that penetrance of HH due to homozygosity for the p.Cys282Tyr mutation might be modified by *ALAS2* mutations and vice versa, as the biochemical presentation of patient 2B suggests, i.e. he developed systemic iron overload already in his teens.

The majority of female carriers of XLSA are asymptomatic, as in most X-linked recessive disorders. However, as illustrated by patient 1A, they may be affected due to the predominant inactivation of the normal X-chromosome. Furthermore, physiological age-related skewed X-inactivation in haematopoietic cells may play a role in developing XLSA in female carriers with increasing age. So a combination of congenital and acquired skewing can result in the late onset of XLSA in women.[6-8] Because of the co-existence of normal and affected erythroblasts this anaemia may be normocytic with an increased red cell distribution width (RDW) or even two separate erythrocyte populations.[31] Patient 1A also shows that even in elderly patients who present with anaemia, a congenital disorder should be considered. Interestingly, Furuyma *et al.* describe a male patient with chronic renal failure who developed sideroblastic anaemia at the age of 81 years. This patient was found to have an *ALAS2* mutation which only became manifest by an acquired pyridoxine deficiency due to haemodialysis. [32]

Anecdotal data support the possibility of misdiagnosing XLSA for MDS-RARS (myelodysplastic syndrome-refractory anaemia with ringed sideroblasts) without MDS-specific cytogenetic and genetic abnormalities in elderly people. This may be attributed to the fact that the diagnosis of MDS is solely based on the morphological aspect of the bone marrow, which is often difficult.[33] Our patient 9 was also originally diagnosed with MDS (type RCMD) based on the morphological aspect of bone marrow biopsy, despite low MCH and MCV and a grandfather who was diagnosed with inherited primary sideroachrestic anaemia 50 years ago.[20] Even in retrospect, however, ring sideroblasts, characteristic for sideroblastic anaemia, were not seen in the bone marrow. We have no explanation for this phenotype. To the best of our knowledge, no studies are available on the prevalence of inherited *ALAS2* mutation among patients diagnosed with MDS with refractory anaemia (RARS, RA and RCMD). However, in a recent study among 137 cases of sideroblastic anaemia, XLSA patients had MCV levels below the reference range, whereas the MCV of patients with MDS-RARS and MDS-RCMD was within reference range.[34] This indicates that a reduced MCV is important to distinguish XLSA from MDS with refractory anaemia.

As illustrated by our case series, in many patients with XLSA the anaemia is to some extent, responsive to pyridoxine. Pyridoxine is metabolised to pyridoxal 5'phosphate, the cofactor for ALAS2. Pyridoxine responsive XLSA is generally based on missense mutations that reduce the affinity between ALAS2 and pyridoxal 5'phosphate, resulting in a shorter half-life of the enzyme. In these cases treatment with a high dose of the cofactor pyridoxine partly enhances the stability of ALAS2.[10] *ALAS2* mutations that alter the posttranslational processing resulting in diminished enzyme activity are mostly pyridoxine unresponsive.[10] Apart from the mutation, the iron status is also important for the pyridoxine responsiveness, because iron overload may compromise mitochondrial function and hence haem-biosynthesis. Therefore, XLSA patients should not be considered refractory to pyridoxine therapy until iron stores have normalised with serum ferritin and transferrin saturation in the normal range.[11] Because of this mechanism it is feasible to phlebotomise in XLSA, even in patients with severe anaemia. Hb typically increases, rather than decreases, after reversal of iron overload by blood removal, as shown by patient 2B and 3. In patients who develop anaemia, frequent withdrawal of a small volume is often feasible (our unpublished observations).

Although 13 out of 15 patients shared the same missense mutation, response to pyridoxine was highly variable. The reason for this remains unclear. Low compliance should be considered, as was the problem in patient 10. If patients are unresponsive to pyridoxine, it is recommended to discontinue it, since increased levels of pyridoxine are associated with peripheral neuropathy.[35,36] Peripheral neuropathy was not observed in our cases.

In conclusion, our case series describes the biochemical and clinical presentation of XLSA patients and the effectiveness of treatment regime, and it illustrates the various pitfalls associated with diagnosis, follow-up and treatment of the disease. We suspect *ALAS2* mutations to be more frequent, but not easy to diagnose. The combination of these data with previously published patient information led us to the following recommendations for the clinical management of patients with XLSA:

1. Diagnosis. Consider XLSA in:
   - Men with unexplained microcytic anaemia, even if the anaemia is mild, since missing the diagnosis might result in severe iron overload and associated morbidity and mortality.
   - Men of all ages presenting with the phenotype of MDS with refractory anaemia (RA), without MDS specific cytogenetic abnormalities, and microcytosis, because patients with MDS-RA have MCV levels within the reference range.
   - Women with unexplained microcytic or normocytic anaemia because of the possibility of late-onset XLSA due to a combination of congenital and acquired unbalanced lyonisation.
   - Patients with unexplained hereditary haemochromatosis and concomitant (mild) microcytic anaemia.
2. Treatment
   - Pyridoxine unresponsiveness in XLSA should not be diagnosed until iron overload has been treated adequately, as iron accumulation is known to reduce pyridoxine activity.
   - Phlebotomies should be considered even in patients with severe anaemia in order to reduce the toxic effects of iron overload and to improve erythropoiesis.
3. Family screening
   - All first-degree family members should be genetically and phenotypically (Hb, MCV, iron, transferrin and ferritin) screened. Even though XLSA is an X-linked disease, women can develop the disease.

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ORIGINAL ARTICLE

Outcome of patients with primary central nervous system lymphoma treated outside clinical trials

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ABSTRACT

Reports on the outcome of patients with primary central nervous system lymphoma (PCNSL) are mainly based on results obtained in the context of clinical trials. However, due to poor performance status and cognitive impairment, most patients are actually treated outside clinical studies. The aim of this retrospective study was to get more insight into the outcome of HIV-negative PCNSL patients, treated between 2000-2010 in two hospitals (one academic centre and one categorical cancer centre).

Fifty-two patients were identified. Eight patients were treated with corticosteroids only. Sixteen patients received high-dose methotrexate (MTX)-based chemotherapy, ten received radiotherapy and 18 patients were treated with a combination of MTX-based chemotherapy and radiotherapy. At a median follow-up of 63.1 months, the median overall survival for all patients was 24.4 months (95% CI: 11.5-39.8 months), with an event-free survival of 14 months (95% CI: 7.3-24.4 months). Causes of death were progressive PCNSL in 29 patients, MTX toxicity in four patients and epileptic seizures in one patient. These results are comparable with the outcome of prospective clinical trials in this disease, which still has a relatively poor prognosis.

KEYWORDS

High dose MTX, primary central nervous system lymphoma, radiotherapy, retrospective study, survival, toxicity

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an extranodal lymphoma that involves the brain parenchyma, spinal cord, eyes, cranial nerves and/or meninges. PCNSL accounts for approximately 4% of newly diagnosed central nervous system tumours. Ninety-five percent are diffuse large B-cell lymphomas (DLBCL).[1] The incidence of PCNSL is 4.7 cases per million person-years.[2] The only established risk factor for PCNSL is acquired or congenital immunodeficiency.[3] Treatment options for PCNSL include corticosteroids, chemotherapy and radiotherapy. Surgical therapy other than a diagnostic biopsy is not recommended.[4] Current knowledge and guidelines are mainly based on results obtained from small clinical trials. However, because of poor performance status and cognitive impairment, most patients are actually treated outside prospective studies.

We therefore performed a retrospective analysis of HIV-negative patients with a PCNSL treated outside clinical trials, to obtain more insight into the nature, clinical course and outcome of this disease in comparison to results obtained in the context of prospective clinical trials.

PATIENTS AND METHODS

This is a retrospective study of all HIV-negative patients ≥18 years with PCNSL diagnosed between 2000 and 2010 who were treated outside prospective clinical studies in the

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Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (a comprehensive cancer centre) and the Academic Medical Centre in Amsterdam. HIV-positive patients were excluded from this study because the course of their disease can differ from that of HIV-negative patients with PCNSL. The data were retrieved from the registries of both hospitals. The following items were collected: age, sex, World Health Organisation performance status (PS), comorbidities, presence of immune deficiencies other than HIV infection, presenting symptoms, pathology, treatment, response, duration of response, acute and late toxicities, recurrence-free survival, overall survival and event-free survival (RFS, OS, EFS) and cause of death. The PCNSL prognostic score at presentation was calculated based on the following parameters: age (≤60 vs. >60 years), PS (0 to 1 vs. 2 to 4), serum lactate dehydrogenase (LDH) level (normal vs. elevated), cerebrospinal fluid (CSF) protein concentration (normal vs. elevated) and involvement of the deep regions of the brain (no vs. yes).[5] RFS was only considered for patients with a response to chemotherapy and/or radiotherapy, and was defined as the time from diagnosis to date of recurrence or death, whichever occurred first. OS was defined as time from diagnosis to death (irrespective of cause) and EFS was defined as time from diagnosis to any disease failure for all patients. For patients still alive without disease failure at the time of analysis and for patients lost to follow-up, the date of last contact in the hospital was chosen to measure duration of response and the calculation of OS, RFS and EFS.

The date of histological confirmation was defined as the date of diagnosis. In the absence of pathology results, the date of diagnostic MRI or CT scan imaging was chosen as the date of diagnosis.

The study was approved by the Ethics Committees of both hospitals.

Table 1. *Patient characteristics*

Characteristics	Percentage, number of patients
Total	52
Male	52% (27)#
Age (years)	
Median	64.5
Range	43-83
40-49	7.5% (4)
50-59	27% (14)
60-69	37% (19)
70-79	21% (11)
80-83	7.5% (4)
Performance status	
0-1	44% (23)
2	19% (10)
3	29% (15)
4	7.5% (4)
PCNSL Prognostic score	
Complete	48% (25)
0-2	19% (10)
≥3	29% (15)
Incomplete*	52% (27)
0-2	33% (17)
≥3	19% (10)

***No cerebrospinal fluid data: n=25; serum LDH level unknown: n=2; #absolute numbers between brackets.**

RESULTS

Patient characteristics

The main baseline characteristics are summarised in *table 1*. Fifty-two patients were identified with a median age of 64.5 years. Thirty-two patients had comorbidities which, however, did not influence the treatment choice. Two patients were considered to be immune compromised, one patient due to chronic use of prednisolone for 15 years for arteriitis temporalis, the other patient because of treatment with mycophenolate mofetil for several years following a liver transplantation for cryptogenic cirrhosis of the liver.

In eight patients neither histological nor cytological confirmation of the PCNSL diagnosis could be obtained. In those patients the diagnosis was based on clinical presentation and MRI imaging of the brain. In five patients the diagnosis was based on the combination of the presence of a monoclonal B-cell population in the CSF and MRI imaging. One patient died before a histological diagnosis could be made, but the presence of PCNSL was confirmed by autopsy. The reasons for failure to obtain histological confirmation of the PCNSL lesions were: poor PS, risk of severe neurological deficit by biopsy, no lumbar puncture performed because of the risk of cerebral herniation. All patients with histological verification had a diffuse large B-cell lymphoma.

In *table 2* presenting symptoms are summarised. The main focal neurological deficits were: hemiparesis, gait abnormalities, motor and sensory aphasia, dysphasia and hemianopsia. Cognitive dysfunction included, but was not limited to: memory impairment, disorientation, confusion, bradyphrenia and mutism.

The sites of tumour localisation are summarised in *table 3*. The most likely reasons for not participating in a clinical trial were: no histological confirmation in 14 patients, poor performance status and cognitive impairment in 24 patients, no ongoing clinical trial available at the time of diagnosis in 14 patients.

PCNSL prognostic score

The PCNSL prognostic score of the patients is summarised in *table 1*. In 27 patients (52%), no complete PCNSL

Table 2. *Presenting symptoms*

Presenting symptoms	Percentage of patients
Total	52
Focal neurological deficit	77% (40)#
Cognitive dysfunction	50% (26)
Decreased consciousness	36.5% (19)
Epilepsy	32.5% (17)
Headache	29% (15)
Behavioural changes	27% (14)
Gait abnormalities	23% (12)
Nausea/vomitus	21% (11)

#: absolute numbers between brackets.

Table 3. *Location of tumour*

Location	Percentage of patients
Total	52
Number of sites involved	
Single	56% (29)#
Multiple	44% (23)
Location	
Supratentorial	85% (43)
Infratentorial	4% (2)
Both supra- and infratentorial	11.5% (6)
Leptomeningeal involvement	11.5% (6)
Ocular involvement	2% (1)

#: absolute numbers between brackets.

prognostic score could be calculated mainly due to lack of CSF data (25 patients). In two patients the serum LDH level was unknown.

Median time between symptoms and other parameters

The median time between the first neurological symptoms and diagnosis was 1.5 months (range 0-34 months). Treatment was started within a median time of two weeks (range 0-20 weeks) from diagnosis. The median time from diagnosis to death for patients receiving any kind of treatment was 7.0 months (range 0.25-78 months). The median time between diagnosis and relapse was 11.5 months (range 0.5-76 months) for responding patients.

Treatment and response

All patients were treated with corticosteroids (dexamethasone or prednisolone) in variable doses and during variable time periods. Thirty-two patients (62%) had a clinical response to corticosteroids. Seven patients (13%) received no further chemotherapy or radiotherapy due to poor PS and rapid deterioration despite treatment with corticosteroids. The median time to death for those patients was 26 days (range 0-35 days). One patient who achieved a complete remission (CR) after treatment with dexamethasone for 97 days (starting dose 4.5 mg twice daily) received no further treatment and is still alive 126 months after diagnosis. In this patient, the diagnosis was based on the presence of a monoclonal B cell population in the CSF in combination with MRI imaging showing tumour involvement of the right frontotemporal region, basal ganglia, thalamus and mesencephalon.

Thirty-four patients (65%) received high-dose MTX-based chemotherapy. Fourteen patients (27%) were treated according to the schedule of the EORTC 26952 study (MTX, CCNU, procarbazine and prednisolone, for the complete schedule see Hoang-Xuan *et al.*[6]), nine patients (17%) according to the MBVP (MTX, BCNU, teniposide=Vumon®, prednisolone) schedule of the EORTC 20962 study (for the complete schedule see Poortmans *et al.*[7]), seven patients (13%) according to the Berlin protocol[4] with monotherapy high-dose MTX (≥1 g/m^2 per cycle) and four patients were treated according to the standard arm of the HOVON 105 study (two MBVP cycles, followed by one cycle of high-dose cytarabine (8 g/m^2 in total). High-dose MTX was given as a three-hour infusion. The treatment choice was based on previous experience with the above-mentioned studies and the hospital site.

Fifteen patients received high-dose MTX-based chemotherapy alone. Five of these patients achieved a CR, two a partial remission (PR), four had progressive disease (PD) and four patients were not evaluable for response because of lethal MTX toxicity. The median duration of response was 20 months (range 1-86 months).

Nineteen patients received radiotherapy after MTX (median radiation dose 34 Gy, range 8-50.4 Gy). In 13 patients radiotherapy was given as consolidation therapy according to the EORTC 20962 and HOVON 105 protocol. Eleven patients achieved a CR and two patients a PR. The median duration of response was 13 months (range 1-114 months). One patient developed an intraocular lymphoma localisation after one month. He received intraocular treatment with MTX. This patient is still in continuous complete remission (CCR) three years after treatment.

In six patients radiotherapy was given because of progressive disease shortly after or during chemotherapy. Two patients achieved a CR, one patient a PR and three patients had PD. The median duration of response was two months (range 1-28 months).

Ten patients received radiotherapy only, with a median dose of 34.5 Gy (range 20-50 Gy). Four patients achieved a CR, four a PR, one had PD and one patient was not evaluable because of loss to follow-up. The median duration of response was 20 months (range 1-31 months).

Five patients received cranial irradiation for recurrence, with a median time interval of 14 months after the last cycle of chemotherapy (range 4-27 months). The median survival after irradiation was eight months (range 2-22 months).

Acute toxicities

We used the Common Terminology Criteria for Adverse Events (CTCAE) version 4 to classify side effects of the different treatments.[8] The toxicities are likely to have been recorded incompletely due to the retrospective nature of the study.

One patient suffered from CTCAE grade 3 side effects due to treatment with corticosteroids: osteoporosis with thoracic vertebral fracture and avascular femoral head necrosis. One patient suffered from aggravation of a schizophrenic disorder while using corticosteroids.

Seven patients who received chemotherapy suffered from toxicities grade ≥3: anaphylactic reaction to teniposide with hypotension and fever (1), deep vein thrombosis (1), pneumonia with respiratory failure (1), aspiration pneumonia resulting in death (2), pneumonitis probably due to MTX resulting in death (1), pulmonary embolism and pneumonia with sepsis resulting in death (1).

None of the patients suffered from any acute toxicity grade ≥3 following cranial irradiation.

Late toxicities and chronic symptoms

Late toxicities defined as occurring beyond 90 days after the end of therapy were not systematically recorded in the patient charts. Cognitive impairment, gait disturbances, fatigue and focal neurological deficits were spontaneously reported as chronic symptoms in 13 patients (median age 56 years, range 44-82 years), of whom one was treated with cranial irradiation only, nine were treated with chemotherapy and radiotherapy and three received chemotherapy only. The median time to follow-up (after treatment) of these patients was 54 months.

Survival

With a median follow-up of 63.1 months, 34 patients have died: 29 due to PCNSL (15 at initial diagnosis and 14 at relapse). As noted above, four patients died of treatment-related toxicity. One patient died due to an epileptic seizure while in CR. Four patients were lost to follow-up at 4, 18, 21 and 22 months after diagnosis. The patient in whom the diagnosis was confirmed by autopsy was excluded from the survival analyses.

The median RFS for the 32 responding patients was 23.8 months (95% CI: 15.9% - not applicable). The two-year RFS was 47.9% (95% CI: 32.3-71.0%) and the five-year RFS was 34.3 (95% CI: 19.8-59.4%). The median OS for all patients was 24.4 months (95% CI: 11.5-39.8 months), with a two-year OS of 53.7% (95% CI: 41.3-69.7%) and a five-year OS of 28.7% (95% CI: 17.4-47.1%). The median EFS for all patients was 14 months (95% CI: 7.3-24.4%). The two-year EFS was 34.0% (95% CI: 22.7-51.0%) and the five-year EFS was 23.0% (95% CI: 13.2-40.3%) (*figure 1a-c*).

Figure 1a. *Overall survival*

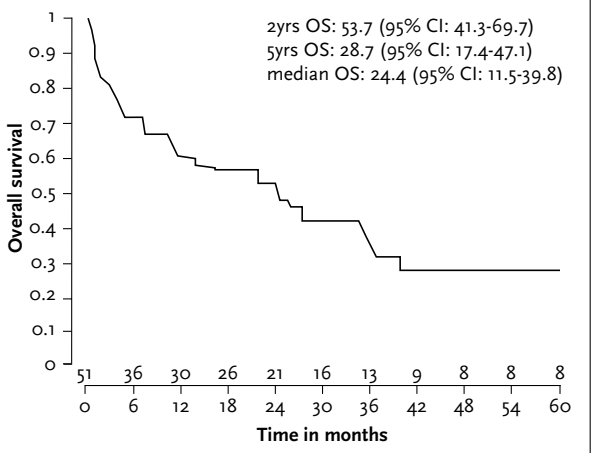


Figure 1b. *Event-free survival*

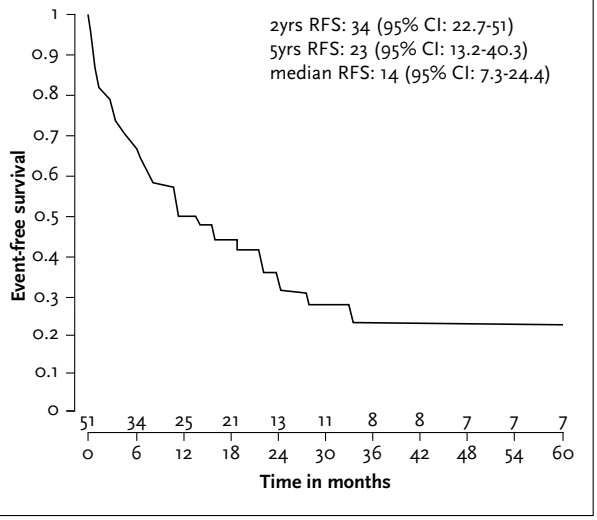
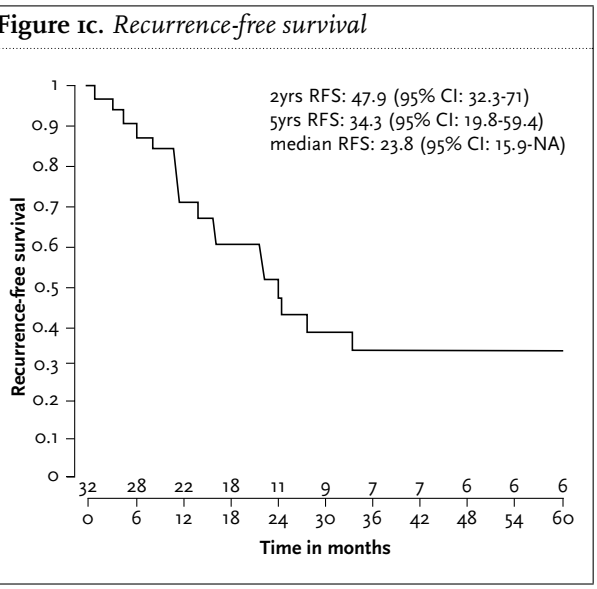


Figure 1c. *Recurrence-free survival*



DISCUSSION

Important issues regarding the treatment of PCNSL include the selection of therapy for each specific patient, the optimal dosage and schedule of (often MTX based) chemotherapy, the role of (consolidation) radiotherapy and the role of rituximab. These questions will hopefully be resolved by prospective trials, but many patients are actually treated outside clinical studies. The majority of the patients (73%) in this retrospective series could not enter a prospective clinical trial, either because of cognitive impairment, poor performance status and/or inability to obtain histological confirmation of the PCNSL diagnosis. In 27% of the cases no trials were available at the time of diagnosis.

The pretreatment characteristics of the patients included in our analysis are in line with those published in prospective series.[4,6,7,9,10] The median overall survival of our patients (65% >60 years) was 24.4 months (95% CI: 11.5-39.8 months). Especially elderly patients with PCNSL have a poor prognosis: the median overall survival as published in the EORTC 26952 study including 50 patients older than 60 years was only 14.3 months.[6] This was confirmed in a German PCNSL study, with a median survival of only 12.5 months in patients aged 70 years or more.[11] The best median overall survival for patients with PCNSL reported thus far (46 months) was found in the EORTC 20962 study.[7] In this trial, however, 42 of the 52 patients included were younger than 60 years, the majority had a good performance status, and most patients were able to receive both chemotherapy and radiotherapy as first-line treatment, which may explain their better overall survival. Of the 14 patients in our series who are currently still alive without disease, 11 patients had a PCNSL prognostic score of ≤2.[2] This confirms the experience that PCNSL patients in good clinical condition at the start of treatment have the best chance of being cured with MTX-based chemotherapy, which is considered to be the cornerstone of the treatment for PCNSL.[2]

Both dose and infusion rate are important when using MTX. A dose of ≥3 g/m^2 given as a short-lasting infusion as done in our series can reach tumouricidal levels in the CSF[12] whereas doses up to 8 g/m^2 delivered in a 24-hour continuous infusion do not.[13] MTX can be used either as monotherapy or in combination with other cytostatic drugs, such as high-dose cytarabine.[2]

Four of the 34 patients treated with MTX in our series, however, died due to treatment-related complications. All four patients had a PCNSL score of >2. Also in the EORTC 20962 study, the treatment-related mortality was 10%.[7] Therefore, high-dose MTX should be used in selected patients and under carefully controlled circumstances. Five of the 15 patients who were treated with MTX-based chemotherapy alone achieved a CR, three of whom relapsed within two years. In the study by Birnbaum *et al.* 31% of the patients achieving a CR after MTX-based chemotherapy suffered from an early relapse.[14] These patients have a dismal prognosis and the question is whether consolidation RT after MTX-based therapy can improve these results.

The study by Thiel *et al.*, in which complete responders were randomised between radiotherapy or no further treatment and the partial responders to radiotherapy or high-dose cytarabine, showed that the administration of radiotherapy had no impact on overall survival but a tendency to improve progression-free survival at the expense of more neurotoxicity in the irradiated patients.[4]

In our study, radiotherapy only was chosen in ten patients who were not able to tolerate high-dose MTX according to the opinion of the treating physician. Despite the fact that treatment with radiotherapy alone can cause long-lasting remissions, it seldom induces cure.[2] Radiotherapy, given as salvage therapy in chemotherapy refractory or relapsing patients, is a good palliative treatment but responses are not long lasting as also demonstrated in our series. The results of second-line chemotherapy are also disappointing.[15,16]

Corticosteroids given as monotherapy can induce transient responses in 70% of patients.[17] In our series, one cytologically confirmed PCNSL patient receiving monotherapy with corticosteroids is still alive without disease at 126 months after diagnosis. As corticosteroids can cause reduction or disappearance of the lesions within days to weeks, it can delay histological confirmation of the diagnosis and further treatment.[17,18] The disappearance of cerebral lesions following treatment with corticosteroids cannot, however, be used as confirmation of the PCNSL diagnosis, since 50% of patients responding to steroids have an alternative diagnosis.[18]

The inability to obtain CSF in 25 out of our 52 patients indicates that protein content of the CSF is a less usable prognostic factor, which corresponds to the results obtained by Ferreri *et al.*[5] In this study, a complete PCNSL score could be obtained in only 105 of the 378 patients. The Memorial Sloan Kettering prognostic score based on age (<50 years) and performance score (Karnofsky index >70%) can be applied to all PCNSL patients,[9] but the value is questionable since most patients are in fact >50 years of age.[2]

In the majority of the patients, recurrence of PCNSL usually develops within two years after the end of first-line treatment.[19,20] Late recurrences (>5 years after diagnosis) occur in 3-8% of the patients.[19,20] In our study one patient developed a late relapse 76 months after diagnosis.

The present study has several limitations which are inherent to a retrospective analysis. For instance, several patients are lost to follow-up and (late) toxicities were not consistently reported. In most studies, including

ours, a systematic evaluation of cognitive functions was not performed at the start of treatment or thereafter. This makes it difficult to discern whether the impaired neurological status often reported after the treatment for PCNSL is caused by the PCNSL itself, by pre-existing cognitive function impairment not related to PCNSL, or by the treatment.

In conclusion, the treatment and management of patients with PCNSL clearly requires improvement, especially for elderly patients and for those presenting with a PCNSL prognostic score >2, who have a poor prognosis due to lower response rates to treatment as well as higher toxicity following treatment with high-dose MTX. Also salvage therapy is less effective and less well tolerated in this patient population.[2,11,15,16] Prospective clinical trials and a centrally based registry including histological data on PCNSL patients might enhance our knowledge about this rare disease. Despite the fact that the majority of our patients could not enter a trial because they did not meet all inclusion criteria, their outcome is similar to patients treated in prospective trials. Less strict inclusion criteria could enhance the participation of more patients in trials which can lead to a more accurate estimation of the value of a given treatment in the whole patient population. Currently, the role of rituximab, radiotherapy and the value of high-dose chemotherapy followed by autologous stem cell transplantation in the treatment of PCNSL are being investigated in several clinical trials.[10,21-23] In addition, more targeted treatment targeting deregulated signalling pathways in this type of disease is being explored.[2]

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CASE REPORT

A 28-year-old pregnant woman with a very rare cause of jugular vein thrombosis

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ABSTRACT

During pregnancy, venous thrombosis of the distal extremities is not uncommon. However, thrombosis in the upper part of the body, such as jugular vein thrombosis, is rare. If underlying causes such as ovarian hyperstimulation syndrome (OHSS) or septic thrombophlebitis (Lemierre's syndrome) are excluded, a serous borderline ovary tumour (BOT) must be considered and MR imaging of the abdomen could be performed to find a primary tumour mass.

KEYWORDS

Cervical lymphadenopathy, jugular vein thrombosis, pregnancy, serous borderline ovarian tumour

What was known on this topic?
Jugular vein thrombosis in pregnancy is rare. It is described as a result of ovarian hyperstimulation syndrome (OHSS) in pregnancies achieved with artificial reproductive technologies (ART) or as a result of Lemierre's syndrome. Jugular vein thrombosis can also be the first symptom of a serous borderline ovary tumour (BOT) due to local lymphadenopathy related to implants, but this is extremely rare.

What does this case add?
This case is the first description of a jugular vein thrombosis as first symptom of a serous BOT in a pregnant woman. If pregnancy is achieved without ART and no underlying pathology is found, serous BOT should be considered and abdominal MR imaging could be performed to confirm the diagnosis.

INTRODUCTION

The risk of developing deep venous thrombosis is higher in pregnant women as compared with non-pregnant women of childbearing age.[1-3] In the vast majority of cases, thrombosis develops in the lower extremities.[4,5] Thrombosis in the upper extremities or in the internal jugular vein in pregnancy is a very rare complication and warrants further diagnostic work-up.[6] Here we report a very unusual cause of jugular vein thrombosis in a 28-year-old pregnant woman who presented at our clinic.

CASE REPORT

A 32-week pregnant 28-year-old woman was referred to our hospital by her general practitioner. She was not using any medication and the current pregnancy had been unremarkable except for intrauterine growth restriction of the foetus since the first trimester. Physical examination revealed a fixed elastic ill-defined mass in the right neck with several enlarged lymphatic nodes. Lymphadenopathy was not found at any other locations. An ultrasound of the mass revealed a right internal jugular vein thrombosis. As a possible underlying cause, Lemierre's syndrome was considered, as well as ovarian hyperstimulation syndrome (OHSS) and pregnancy-related thrombophilia.[7,8] Since an indwelling catheter was not present, this common cause of upper extremity thrombosis could be excluded.[9] Our patient was referred to the otolaryngologist. No local pathology, such as a peritonsillar abscess, was found. Pregnancy was achieved naturally and no artificial reproductive techniques (ART) were used. Laboratory findings for thrombophilia were unremarkable. Furthermore, lupus anticoagulant tests and tests for antiphospholipid syndrome were normal.

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Tinzaparine 0.9 ml once daily was started. MRI of the neck showed jugular vein thrombosis with infiltration of the surrounding fat and multiple small lymphatic nodules (*figure 1*). A fine needle biopsy was performed showing reactive lymphocytes and an otherwise non-classifiable atypical cell, but no specific diagnosis could be made. Because of foetal growth restriction, she was admitted for daily cardiotocography (CTG) monitoring. A caesarean section was performed 17 days after first presentation because of the foetal growth restriction. During the operation a tumour of the left ovary and Fallopian tube was seen. Biopsy was performed and pathological findings showed a serous borderline ovarian tumour (BOT) (*figure 2*). After three days of recovery our patient was discharged from hospital. After admission to the neonatal intensive care and subsequent paediatric ward, her baby could also be discharged and is developing well. Three months after the caesarean section a laparoscopic adnectomy was performed. The pathological findings confirmed the diagnosis of serous BOT and no further treatment was indicated.

Figure 1. *MRI showing jugular vein thrombosis with fat infiltration and multiple small lymphatic nodules*

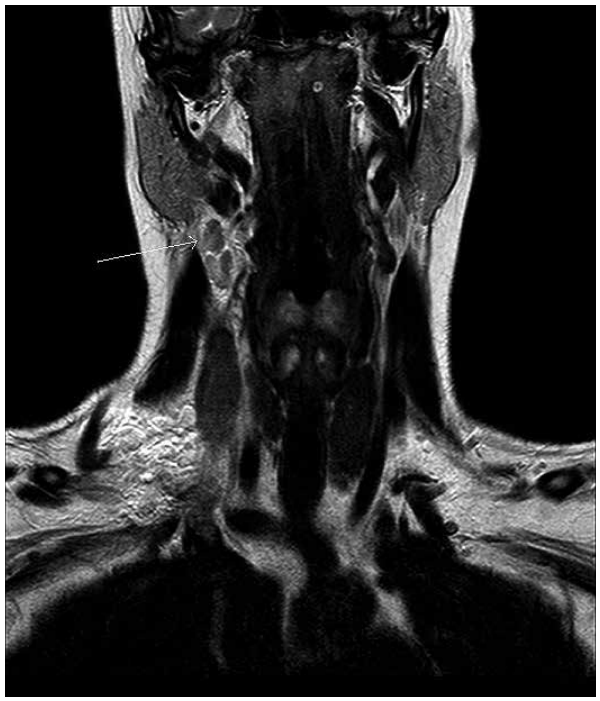
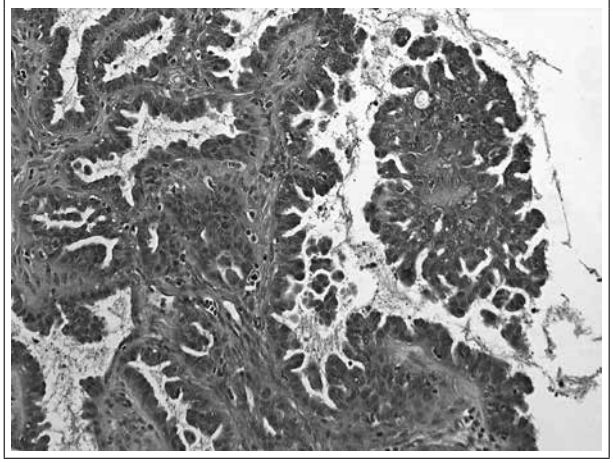


Figure 2. *Biopsy of the left ovary showing serous borderline tumour of the ovary (H&E staining, 400x)*



DISCUSSION

In this report we present a unique case of a pregnant woman with a jugular vein thrombosis which appeared to be the first symptom of a serous BOT. To our knowledge, this combination has never been described in literature before. A literature search using the terms "jugular vein thrombosis or upper extremity thrombosis AND pregnancy" showed that jugular vein thrombosis during pregnancy is linked to either OHSS or Lemierre's syndrome. In our patient, both were excluded shortly after initial presentation. Other causes of thrombosis such as the antiphospholipid syndrome or thrombophilia were also excluded. Thus, initially no explanation for this rare manifestation of thrombosis during pregnancy was found and the finding of a tumour mass of the left ovary during the caesarean section was essential for the diagnosis.

The relationship between serous BOT and upper extremity deep vein thrombosis has been described once before by Verbruggen *et al.* in 2006. They described three cases of non-pregnant women with cervical lymphadenopathy caused by lymph node localisation of a serous BOT.[10] These so-called implants cause lymphadenopathy and subsequently blood vessel compression and thrombosis. Immunohistochemical staining of the lymphatic material and the ovarian tumour mass confirmed the association.

In our patient it was not possible to confirm this association on the available cytological material. A subsequent lymph node biopsy was not performed since removal of the BOT will result in regression of lymphadenopathy, as shown by Verbruggen. In 2002, Camatte *et al.* analysed the effect of lymphadenectomy due to implants on the overall survival in patients with serous BOT. No significant difference was found between BOT patients with and without lymph node implants. Therefore no lymphadenectomy was performed in our patient.[11]

In our case, vaginal delivery would have obscured the primary tumour mass and the diagnosis could have been missed. To overcome this problem we recommend to perform an MRI of the abdomen in the case of unexplained jugular vein thrombosis in pregnancy. Based on the findings of the MRI further therapeutic options could be considered.[12] If MRI findings show an unusual mass an

explanation for the thrombosis is found. Next one should assess whether acute intervention is needed (malignancy is expected) or a wait-and-see policy can be followed (benignancy is expected). Because this situation is so unique each case should be evaluated separately.

We conclude that if jugular vein thrombosis in a pregnant woman is not explained by its usual causes a serous BOT should be considered and we suggest to perform abdominal MR imaging.

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PHOTO QUIZ

Blurred vision and elevated ESR, look beyond giant-cell arteritis

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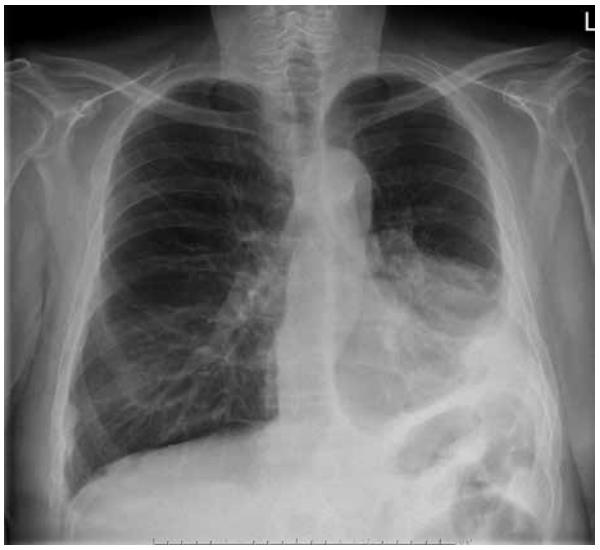
CASE REPORT

A 64-year-old male with a medical history of chronic obstructive pulmonary disease was referred by the ophthalmologist to the rheumatology department under suspicion of giant-cell arteritis (GCA). The patient presented with acute blurred vision related to bilateral retinal artery occlusions (RAO). Apart from an unintentional 25 kg weight loss, there were no other related symptoms such as headache, jaw claudication, fever, morning stiffness, nor pain and stiffness of the shoulder and pelvic girdle. At physical examination no abnormalities were discovered and pulsations of the temporal artery were normal with absence of tenderness. Laboratory tests revealed a raised erythrocyte sedimentation rate of 108 mm/hour, C-reactive protein of 122 mg/l and anaemia (haemoglobin 6.2 mmol/l). An electrocardiogram showed sinus rhythm. Because of the preliminary diagnosis of GCA and potential risk of permanent blindness, the patient was immediately treated with a high dose of prednisolone. However, a temporal artery biopsy did not confirm this diagnosis. The chest X-ray showed a central mass of the left lung with pleural effusion (*figure 1*). Computed tomography (CT) was performed.

Figure 1. *Chest X-ray suspicious for a central tumour with secondary pleural effusion and atelectasis on the left side*



WHAT IS YOUR DIAGNOSIS?

See page 231 for the answer to this photo quiz.

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PHOTO QUIZ

Is there free air in the abdomen?

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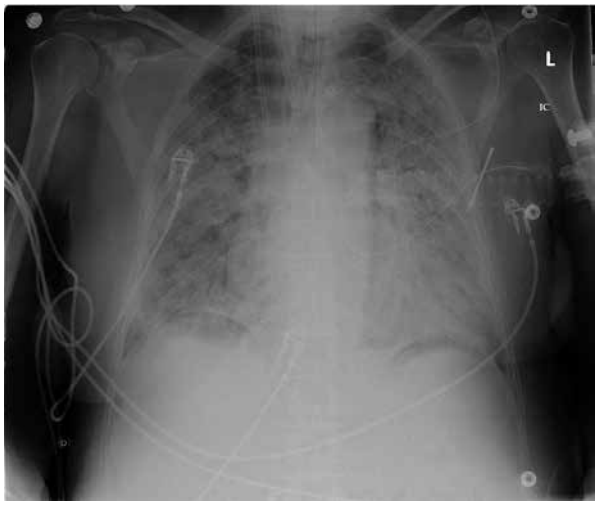
CASE REPORT

A 67-year-old woman was admitted to our ICU because of respiratory insufficiency. Her medical history revealed a microscopic polyangiitis with mild renal dysfunction, for which she was treated with prednisolone (30 mg once daily) and cyclosphosphamide (100 mg once daily).

The chest X-ray (CXR) on admission showed bilateral consolidation. Mechanical ventilation was started and because of her immunocompromised state a bronchoalveolar lavage was performed. *Pneumocystis jirovecii* pneumonia (PJP) was diagnosed for which she was treated with trimethoprim-sulfamethoxazole and corticosteroids. Cyclophosphamide was discontinued.

Despite treatment, the bilateral consolidation persisted. Acute respiratory distress syndrome (ARDS) and congestion were considered and she was treated with continuous venovenous haemofiltration with rigorous fluid removal and high-dose methylprednisolone. However, the consolidation still persisted (*figure 1*).

Figure 1. *Chest X-ray*



WHAT IS YOUR DIAGNOSIS?

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Jaw enlargement in a haemodialysis patient

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A 38-year-old woman presented to our district hospital in Suriname (South America) because she was unable to close her mouth. Physical examination demonstrated severe facial deformity with bony protrusion of both the maxilla and mandible (*figure 1A*). Oral inspection showed mandibular and palatal exophytic swelling and displacement of teeth. The patient's medical history was significant for end-stage renal disease of unknown origin and 11 years of adequately dosed haemodialysis treatment. She also had secondary hyperparathyroidism complicated by pelvic and hip deformations. Her laboratory tests revealed mild hypocalcaemia (2.20 mmol/l, normal value 2.10-2.55 mmol/l), hyperphosphataemia (1.76 mmol/l, normal value 0.8-1.4 mmol/l) and an extremely high parathyroid hormone value (336 pmol/l, normal value 2-7 pmol/l). Facial radiography confirmed bony enlargement of the jaws (*figure 1B*; arrows indicate boundaries).

Figure 1. *Enlarged maxilla and mandible with inability to close mouth, due to bony hyperplasia of the jaws*

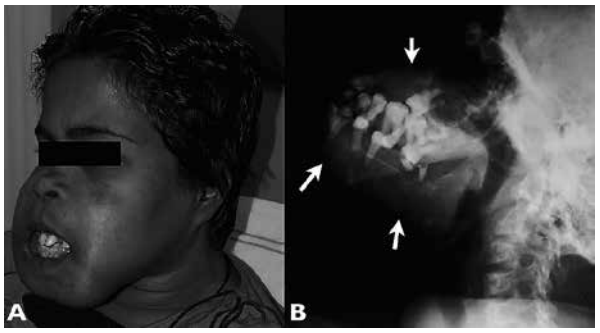

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PHOTO QUIZ

A sudden rash and blisters on the left leg in Bali

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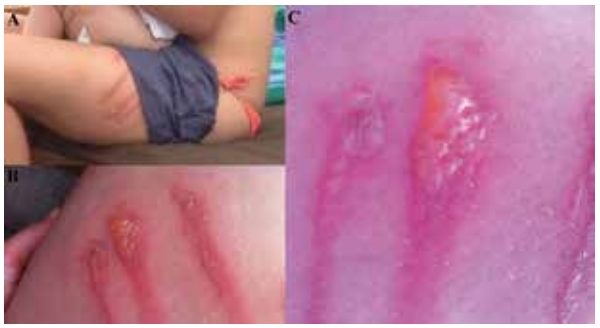
CASE REPORT

A 23-year-old previously healthy Dutch woman developed an erythematous, non-itching rash in a handprint pattern at the lateral side of her left thigh on the fourth day of a beach holiday in Bali. Apart from her stay on the beach and an enjoyable nightlife, her further exposure and travel history was unremarkable. In the following 24 hours, the rash became extremely painful with development of blisters at the sites of the erythema. Physical examination (*figure 1A*) revealed a tender skin with coalescing vesicles and bullae (*figure 1B* and *1C*) atop streaky erythematous plaques on her left thigh (*figure 1A*). The patient was afebrile and the rest of the physical examination was unremarkable.

Figure 1. *Physical examination revealed a tender skin (A) with coalescing vesicles and bullae (B and C) atop streaky erythematous plaques on her left thigh (A)*



WHAT IS YOUR DIAGNOSIS?

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ANSWER TO PHOTO QUIZ (PAGE 227)

BLURRED VISION AND ELEVATED ESR, LOOK BEYOND GIANT-CELL ARTERITIS

DIAGNOSIS

A CT scan showed a tumour of the left upper lobe invading the left pulmonary vein and atrium, slightly enlarged adrenal glands and a large (tumour) thrombus in the left atrium (*figure 2*). The latter was confirmed by transthoracic ultrasonography. Oncological work-up led to the diagnosis of a stage IV squamous cell lung carcinoma.

The retinal artery occlusions (RAO) were caused by embolism from the left atrial (tumour) thrombus. Prednisolone was discontinued and low-molecular-weight heparin (LMWH) was initiated. This led to a serious haemoptysis and because of the high risk of a fatal bleeding LMWH had to be discontinued. Salvage surgery was not an option due to the extension of the tumour into the mediastinum and the radiotherapist was afraid of massive bleeding complications when applying radiotherapy. The patient refused palliative chemotherapy and died several months later.

The differential diagnosis of RAO is extensive, including serious systemic disease.[1-3] RAO affects 10-13% of those with visual loss in GCA.[4] GCA is only the cause in 1-4.5% of the cases of central RAO.[3,5] The combination with elevated inflammatory parameters makes GCA more likely, although this does not exclude other causes, such as the one in the above-mentioned patient. A cardiac tumour related embolism as cause of RAO is rare and mainly related to myxomas.[6] A few cases have been reported regarding spontaneous systemic tumour embolism secondary to lung cancer with invasion of the left atrium and pulmonary vein, but these patients presented with ischaemic stroke.[7] We are not aware of a case with bilateral RAO as presenting symptom.

RAO in the presence of elevated inflammatory parameters should raise the suspicion of GCA. However, other causes, such as a cardiac origin of a (tumour) embolism, should always be considered. In the absence of contraindications, treatment with corticosteroids is warranted to prevent ongoing ocular damage. Waiting for a definite diagnosis of GCA before initiating therapy might result in permanent vision loss. Furthermore, this case taught us that an obvious diagnosis should always be confirmed by a proper clinical investigation.

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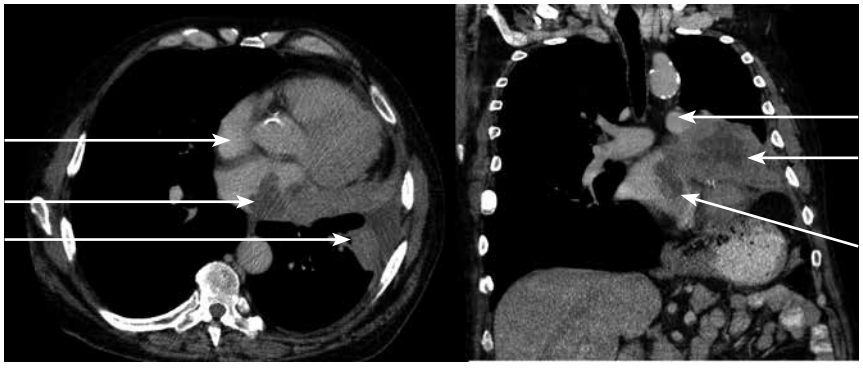
Figure 2. *Computed tomography showing a large tumour of the left upper lobe invading the left pulmonary vein and atrium and a large (tumour) thrombus in the left atrium*



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ANSWER TO PHOTO QUIZ (PAGE 228)

IS THERE FREE AIR IN THE ABDOMEN?

DIAGNOSIS

A false impression of a pneumoperitoneum.

The CXR seems to show free air below the diaphragm. A pneumoperitoneum due to an intestinal perforation masked by high-dose corticosteroids or pneumothorax with pneumoretroperitoneum and break through to the peritoneum was suspected and a computed tomography (CT) scan of the chest and abdomen was performed. This ruled out free intraperitoneal air (*figure 2*) and pneumothorax (not shown), but showed that the lung tissue just adjacent to the diaphragm was much less affected by the ARDS than the rest of the lower lobes, which gave the false impression of pneumoperitoneum on the conventional image.

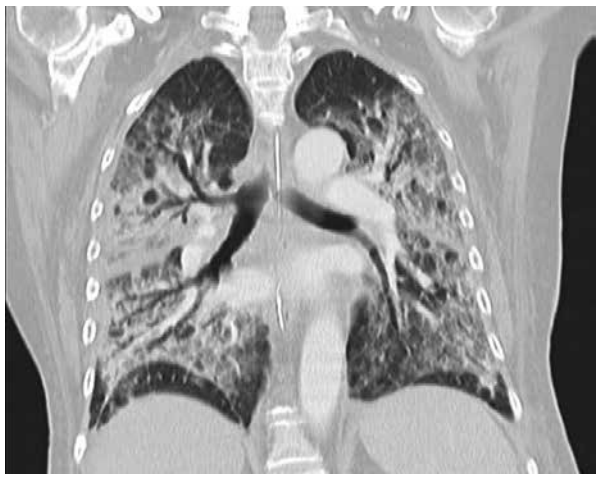
DISCUSSION

Plain radiographs can be misleading in diagnosing free intraperitoneal air.

Although plain radiographs can be helpful in diagnosing a bowel perforation by showing the presence of free intraperitoneal air on an upright CXR, it cannot be relied upon to exclude it.[1,2] Free air is missed on an upright posteroanterior CXR in 20-62% of cases.[3,4] However, in most cases plain radiography is sufficient. Incorporation of a left lateral decubitus abdominal radiography showed to improve the sensitivity to detect pneumoperitoneum.[5]

Ultrasonography (US) is an alternative diagnostic modality and showed to be superior to plain radiography in the diagnosis of pneumoperitoneum and when both upright CXR and US are combined, sensitivity can further be increased.[6,7]

Figure 2. *CT scan showing diffuse consolidations of both lungs with relatively normal lung tissue in the lower areas of both lungs*



CT has demonstrated to be the most sensitive imaging test for detection of pneumoperitoneum (sensitivity 83-100%), but it would not be cost-effective or justified if all patients with suspected hollow-organ perforation were to undergo CT examinations, since most free air can be detected by plain radiography.[4,8,9] CT can be reserved for patients with suspected hollow organ perforation where plain radiography and US still fail to make the diagnosis. Surgery is still the 'gold standard' for the diagnosis of pneumoperitoneum.

In retrospect, an US might have been helpful in this patient to rule out pneumothorax, although the actual diagnosis would still be missed.

In this case, the lung tissue just adjacent to the diaphragm was much less affected by the ARDS than the rest of the lower lobes, which gave the false impression of pneumoperitoneum on the conventional image. The distribution of affected areas in ARDS may follow different patterns according to the nature of the underlying disease. The ARDS in this patient was thought to be pneumonia-induced (PJP) or vasculitis induced. Pneumonia-induced ARDS roughly corresponds to the initial infected area, and since PJP often affects the perihilar areas, this might be why the lower areas of the lungs in our patient were relatively free of consolidations.

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ANSWER TO PHOTO QUIZ (PAGE 229)

JAW ENLARGEMENT IN A HAEMODIALYSIS PATIENT

DIAGNOSIS

A diagnosis was made of severe bony deformation with hypertrophia of the jaws caused by uncontrolled secondary hyperparathyroidism.

Secondary hyperparathyroidism is a common complication in chronic renal failure. It is caused by disruption of the calcium and phosphorus homeostasis. The rise of parathyroid hormone results in renal osteodystrophy with different clinical manifestations such as osteitis fibrosa or osteomalacia. Mixed bone disease often develops, characterised by increased number and activity of osteoblasts with marked bone turn-over, in conjunction with proliferation and differentiation of osteoclasts leading to superimposed mineralisation defects. Thus, fractures and bone deformities develop as late consequences.[1]

Treatment consists of reduction of dietary phosphorus intake, oral phosphate binders, vitamin D derivatives, calcimimetics or parathyroidectomy. The last two treatments are, however, not widely available in middle-income countries such as Suriname due to high costs and limited expertise in neck surgery, respectively. Although better access to dialysis in middle-income countries significantly improves survival for renal insufficiency, adequate management of dialysis-associated hyperparathyroidism remains cumbersome due to lack of resources.

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ANSWER TO PHOTO QUIZ (PAGE 230)

A SUDDEN RASH AND BLISTERS ON THE LEFT LEG IN BALI

DIAGNOSIS

The patient was diagnosed with 'Lime disease' or phytophotodermatitis as a result of exposure of lime juice to her left leg. Before the onset of the eruption, the patient had manually squeezed limes daily. Phytophotodermatitis is a phototoxic dermatological reaction that occurs when skin is exposed to lime or certain plants, or their extracts, containing furocoumarin (photosensitising agent), in combination with sunlight. Unlike photoallergic reactions, phototoxic reactions occur independently of the host's immune system. Exposure to long-wavelength ultraviolet radiation (UVA) can activate furocoumarin by absorption of photons, leading to type I reactions,[1] which are independent of oxygen and can cause cellular damage by forming aberrant cross-links in cellular DNA, resulting in inhibition of DNA synthesis. In type II reactions, psoralen and oxygen form free radicals, resulting in epidermal, dermal, and endothelial cell membrane damage that manifests as oedema, erythema, and bullae.[1]

The erythema develops 12-24 hours after exposure, with vesiculation occurring after 72 hours.[2] The lesions do not follow any dermatomes. Exfoliation and dyspigmentation follow, with resolution over 6-12 months, usually without scarring. The overall incidence of phytophotodermatitis is unknown and there appears to be no predeliction for race. The differential diagnosis may include cellulitis, impetigo, erythema migrans, herpes virus infection, allergic contact dermatitis and jellyfish envenomation.[3,4] Phytophotodermatitis in children may be misdiagnosed as child abuse, especially when the lesions have the appearance of a hand mark and fingerprints.

Here we report a case of lime-induced phytophotodermatitis. Careful history taking results in prompt recognition of this unique phototoxic reaction and an understanding of its cause will help physicians counsel patients to end this extremely painful skin reaction by avoidance of exposure and to prevent repeated episodes. In our patient, the eruptions resolved without specific treatment and the skin remained hyperpigmented for several months.

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SPECIAL REPORT

Access to expensive cancer drugs in Dutch daily practice: Should we be concerned?

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ABSTRACT

Background: To investigate whether equal access to bortezomib has been achieved under the Dutch policy regulations that guarantee equal access to expensive inpatient drugs.

Methods: We investigated accessibility to bortezomib treatment at national and regional levels by (i) conducting interviews with stakeholders in the Dutch healthcare system to explore prescription barriers and (ii) tabulating sales data from 2004-2009 and trial participation rates.

Results: Interviews revealed awareness of the high treatment costs, although prescription barriers were not encountered. National use of bortezomib increased slowly (treating 2% of patients in 2004 to 17% in 2009), indicating a long adjustment period. Furthermore, use remains below the rate estimated by the professional association of haematologists (27%). Regional differences were found for both daily practice use (e.g. ranging from 13-27% in 2009) and clinical trial participation (e.g. ranging from 1-12% in 2006).

Conclusion: Our results were somewhat conflicting: interviews did not reveal any prescription barriers, but quantitative methods showed regional differences, signs of underutilisation, and access inequality. Investigating use and accessibility, based on data triangulation, provides valuable feedback which can enhance evidence-based decision making for both physicians and policymakers. This could improve appropriate and efficient use and ensure equal access to expensive drugs.

KEYWORDS

Cancer drugs, accessibility, regional differences, policy regulations, bortezomib, daily practice utilisation

INTRODUCTION

Increasing healthcare expenditures may result in limited and unequal access, particularly with regard to new and innovative cancer drugs with high acquisition costs. Policymakers have to make reimbursement decisions considering both rapid and equal accessibility to promising drugs as well as the scarcity of resources. Usually, guaranteeing rapid access means making decisions while available evidence on clinical- and cost-effectiveness is limited.[1] One way of dealing with the need for rapid access and limited evidence is the 'coverage with evidence development' policy; reimbursement under the condition that additional research will be conducted.[1,2]

Such policies have been implemented in several countries for surgical procedures, medical devices and pharmaceuticals.[2] Over the last decade, a coverage with evidence development policy was also initiated in the Netherlands, partly triggered by signs of underutilisation and 'zip code prescribing' of trastuzumab.[3] Early access to expensive inpatient drugs is linked with the obligation to gather data on appropriate drug use and cost-effectiveness in daily practice.[4] Drugs meeting the criteria of added therapeutic value and expected budget impact of at least 2.5 million were temporarily included in the policy of 2006-2012. Four years after inclusion, a reassessment will determine whether or not additional financing should continue to exist. At the time we conducted our study, hospitals received 80% of its acquisition costs if a drug was included.[5]

Currently more than 30, mostly cancer, drugs are included in this policy. One of these drugs is bortezomib, used for treating multiple myeloma (MM). MM is the second most common haematological cancer. The five-year prevalence in Western Europe is 31,056 while the annual age-standardised incidence rate is 3.2 per

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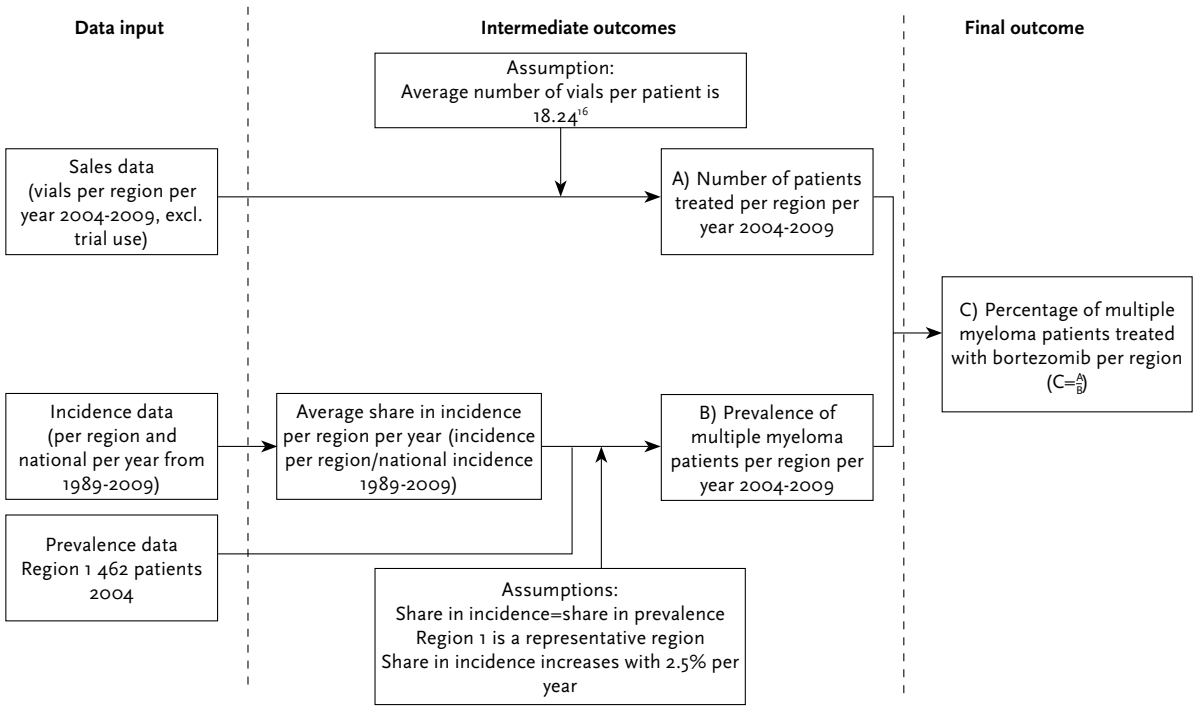
100,000 (IARC GLOBOCAN 2008). Bortezomib obtained European Medicines Agency (EMA) approval in 2004 by demonstrating superior efficacy compared with chemotherapy for the treatment of advanced MM;[6-8] it was included on the Dutch expensive drug list in 2006. Advances in MM treatment in the past decade significantly increased overall survival (44.8 vs 29.9 months[9]), which was largely due to the introduction of autologous stem cell transplantation and new therapeutic agents including thalidomide, lenalidomide, and bortezomib.[9,10] While thalidomide is relatively inexpensive, bortezomib and lenalidomide are expensive drugs. Both are incorporated in professional guidelines.[11] However, the orphan status granted to lenalidomide results in 100% reimbursement for lenalidomide compared with an 80% of reimbursement for bortezomib during our study period. Consequently, accessibility might be an issue, especially for bortezomib.
Previous research studied accessibility and use of expensive drugs in the Netherlands;[12,13] however, it remains unclear whether the Dutch policy actually guarantees equal access to expensive inpatient drugs. We investigated whether equal access to bortezomib has been achieved in the Netherlands. We analysed bortezomib use patterns by means of aggregate sales data and conducted interviews to shed light on perceived or real prescription barriers.

MATERIALS AND METHODS

We took a two-pronged approach. First, seven in-depth interviews were conducted to qualitatively investigate the existence of accessibility issues and prescription barriers. Interviewees were representatives of stakeholders in the Dutch healthcare system: (i) a representative of the Dutch Healthcare Authority (NZa), (ii) a representative of the Healthcare Inspectorate (IGZ), (iii) a hospital director of finance, (iv) four haematologists from hospitals varying in size and country location (the North-West, East, South-West, and South). Respondents were selected based on their involvement and knowledge of expensive inpatient drug regulations (NZa and IGZ) or geographical location and type of hospital (haematologists and director of finance). All semi-structured interviews were recorded and analysed according to the steps of Creswell,[14] including transcription, coding, interpretation, and description.
Second, we quantitatively investigated the use of bortezomib in daily practice. Because data on bortezomib use at the individual patient level are not available, we combined Dutch sales data (excluding use in clinical trials) from 2004-2009 from the manufacturer, Janssen Pharmaceutical Companies of Johnson & Johnson, with incidence and prevalence data from the Netherlands Cancer Registry.[15] *Figure 1* provides the flowchart of data used, intermediate and final outcomes and the underlying assumptions.

To estimate the number of treated patients ((A) in *figure 1),* the number of vials sold was divided by the average number of vials used per patient. The average number of vials per patient (18.24) was based on a Dutch observational study of 72 bortezomib patients treated in daily practice from 2004-2008.[16]
To investigate bortezomib use across regions, we used the regional division of the nationwide Netherlands Cancer Registry distinguishing eight Comprehensive Cancer Centres.[15] Since these regions differ in size, prescription rates were expressed relative to the number of patients per region. We assumed that equal accessibility to bortezomib would be achieved if the proportion of vials used per region was similar to their proportion of national incidence or prevalence. Regional shares in incidence were calculated over the years 1989-2009. For example, the share in incidence in 2009 for Comprehensive Cancer Centre Amsterdam (IKA) was 18.8%. We calculated this percentage by dividing the incidence of IKA (201) by the national incidence (1069).
Because prevalence numbers were only available for IKA (462 patients in 2004) for one year, we estimated other regional prevalence (B) from their relative shares in incidence. Hereby we assumed (i) IKA to be representative for the other regions and (ii) the share in incidence per region is equal to the share in prevalence (e.g. if IKA has 19% of the incidence it will also have 19% of the prevalence), and (iii) an annually increasing prevalence of 2.5% (average annual increase over the years 1989-2009[15]) per year because of rises in incidence.[10] Detailed additional information about incidence and prevalence estimates per year is available from the authors upon request.
To obtain a regionally comparable percentage of treated patients (C), we divided the estimated number of treated patients (A) by the estimated prevalence (B). To put regional percentages in perspective, we compared our computed use with the expected percentage of MM patients eligible for bortezomib treatment as estimated by the Dutch professional association of haematologists (the Dutch-Belgian Cooperative Trial Group for Haematology and Oncology (HOVON)). HOVON estimated that about 1600 patients would be eligible for MM treatment per year. Of these patients, one-third would not qualify for treatment with either bortezomib or lenalidomide due to age, the patient's condition or preferences. As result, 1070 patients are eligible for advanced therapy each year.[5] Since patients treated with bortezomib might also be eligible for treatment with lenalidomide and vice versa, HOVON assumed that the number of patients treated with each drug would be similar (50%). To compare the HOVON estimation with the proportion of patients treated with bortezomib per region, we divided the 535 eligible patients (i.e. 1070 divided by 2) by HOVON's estimated prevalence (i.e. 2000 patients), resulting in an estimation of 27% patients.

Figure 1. *Flowchart of data input, intermediate and final outcomes*



Furthermore, since bortezomib was a novel treatment, clinical trials were conducted during our years of investigation. Because MM patients are often included in clinical trials, relatively high or low trial participation could distort our computed daily practice use and identified regional differences. Therefore, we selected the two largest clinical studies including bortezomib during our investigated time period and studied trial participation at the regional level. Calculation methods were similar: we divided the number of patients included in trials by regional prevalence to obtain regional trial participation rates for the years 2005-2009. We then combined trial participation with regional daily practice use to compare similarities and differences across regions.

RESULTS

Interview results

Interviewees of the NZa and IGZ did not reveal any accessibility issues for expensive drugs. The IGZ representative, however, admitted that the body had no active role in investigating such issues.

Hospitals regulate financial management in various ways. As a result, it may differ per hospital who is responsible for the budget and who is making the financial decisions. According to the interviewed physicians, their financial department divided the total hospital budget by department, whereas physicians organised the division and implementation of the budget within departments. These assumptions were verified and confirmed by the hospital financial manager. Based on these results, we concluded that in the studied hospitals financial management, of both treatment decisions and organisation of care, was the physicians' responsibility.

Generally, all physicians agreed that access to bortezomib is guaranteed in the Netherlands for patients in need. The existence of strict quantitative restrictions was explicitly denied. Physicians adhered to professional guidelines as far as treatment is concerned, which were frequently mentioned as important. Consultation with colleagues and patient characteristics also seemed to be important factors in the decision (how) to treat. Apart from some variation immediately after the introduction of bortezomib, respondents believed that all eligible patients had equal access.

The Dutch policy of 2006-2012 aimed to facilitate prescription and guarantee access while maintaining incentive for efficiency. According to haematologists, the effects of this policy were two-sided. An additional budget of 80% facilitated prescription but the remaining 20%, financed from the general hospital budget, could hinder prescription. The policy was therefore perceived as ambiguous: while the government relieved the high financial burden, the remainder still had to be financed from the general hospital budget. The situation stimulated local initiatives to manage access to expensive drugs, resulting in a local expensive drug committee to judge

appropriate use and structures for consultations with more experienced physicians. Although expensive drugs were perceived as a high financial burden, according to the respondents, budget played no role in treatment choices.

Data results

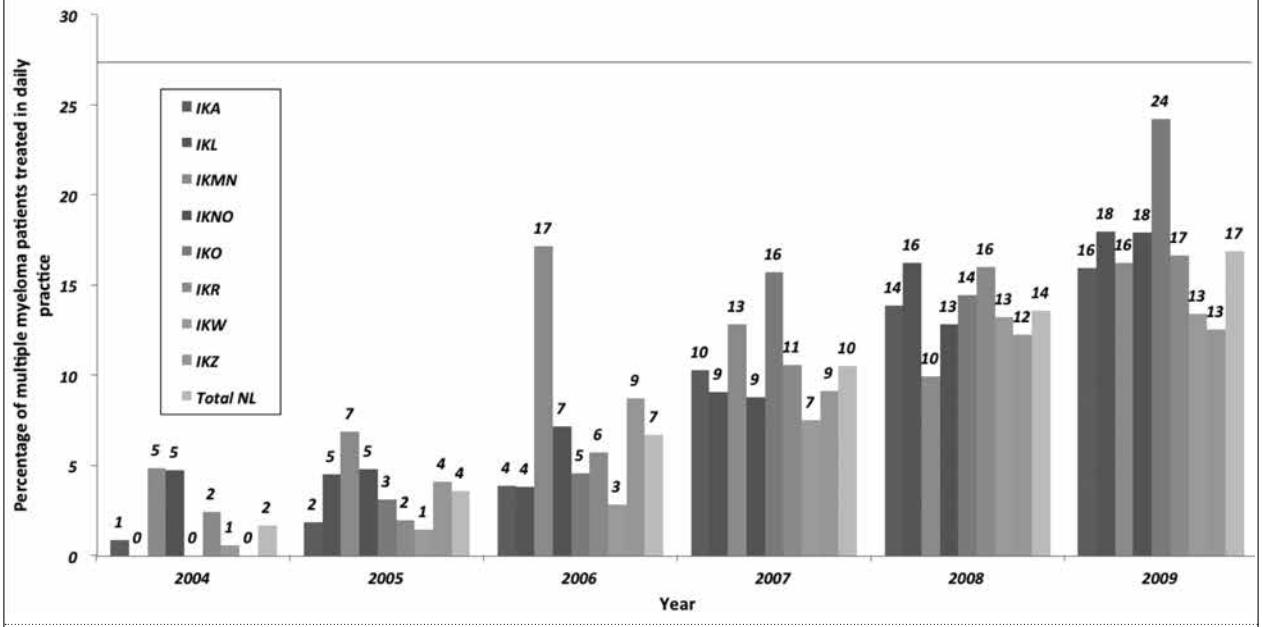
Daily practice use. *Figure 2* presents the percentage of patients treated with bortezomib from 2004-2009 irrespective of treatment line. As mentioned in the method section, HOVON estimated that 27% of MM patients are eligible for bortezomib treatment in daily practice. This is presented as a horizontal line in *figure 2*. *Figure 2* reveals relatively low use in 2004 and 2005 for all regions, which was expected since bortezomib was then an innovative treatment and not included on the expensive drug list until 2006. Three regions did not use bortezomib in 2004; all regions used it in 2005. Differences across regions exist in all years with no stable pattern; sometimes regions switched from a high prescription rank in 2005 and 2006 to a low one in 2008. In 2008, two years after inclusion on the expensive drug list, differences between the regions decreased. In 2009, Comprehensive Cancer Centre East (IKO) was the highest prescribing region and Comprehensive Cancer Centre South (IKZ) the lowest, revealing that in one region 24% of patients received bortezomib while in another only 13% received bortezomib. In all regions the prescription rate was below the 27% of eligible patients as estimated by HOVON.

Use in trials. *Figure 3* shows the participation in the HOVON 65[17] (phase I/II study) and HOVON 86[18] study (Phase III randomised controlled trial) per region in the 2005-2009 period. We observed different trial participation rates and, as *figure 3* illustrates, trial participation increased from 2005-2007, and decreased in 2008 to almost no participation in 2009. A comparison of *figures 2* and *3* reveals that the percentage of patients treated in trials is lower than daily practice use of bortezomib.
Finally, *figure 4* presents the regional percentages of treated patients aggregated over the years 2005-2009. Comprehensive Cancer Centre Netherlands Central (IKMN) had the highest daily practice use and trial participation (19% were either treated with bortezomib or included in one of the larger trials); IKZ had the lowest (10%). *Figure 4* also shows that although differences remain, the fluctuation reduced over time. In general, regions with above average daily practice use also had above average trial participation rates.

DISCUSSION

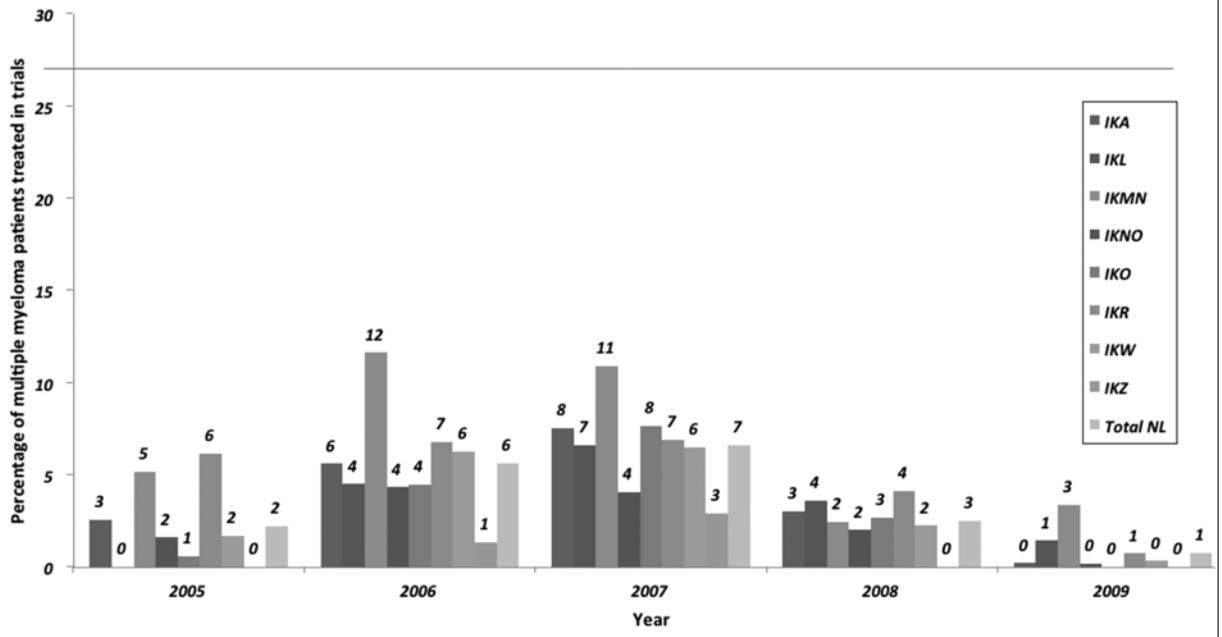
The aim of our study was to investigate whether bortezomib treatment conformed to policy regulations that were designed to guarantee equal access to expensive inpatient drugs in the Netherlands. Interviews revealed that physicians feel some financial pressure but do not

Figure 2. *Percentage of multiple myeloma patients treated in daily practice (not in a clinical trial) with bortezomib per region from 2004-2009*



IKA = Comprehensive Cancer Centre Amsterdam; IKL = Comprehensive Cancer Centre Limburg; IKMN = Comprehensive Cancer Centre Netherlands Central; IKNO = Comprehensive Cancer Centre North East; IKO = Comprehensive Cancer Centre East; IKR = Comprehensive Cancer Centre Rotterdam; IKW = Comprehensive Cancer Centre West; IKZ = Comprehensive Cancer Centre South.

Figure 3. *Percentage of multiple myeloma patients treated in clinical trials (HOVON 65 and HOVON 86) per region from 2005-2009*



IKA = Comprehensive Cancer Centre Amsterdam; IKL = Comprehensive Cancer Centre Limburg; IKMN = Comprehensive Cancer Centre Netherlands Central; IKNO = Comprehensive Cancer Centre North East; IKO = Comprehensive Cancer Centre East; IKR = Comprehensive Cancer Centre Rotterdam; IKW = Comprehensive Cancer Centre West; IKZ = Comprehensive Cancer Centre South.

experience prescription barriers and believe that access to expensive cancer drugs is guaranteed. In addition, at that time there were no signs of accessibility issues among IGZ and NZa. Our results, however, also showed that (i) after the introduction of bortezomib, it took one to two years before the drug was prescribed regularly in all regions; (ii) the percentage of patients treated is below the expected 27% of eligible patients; and (iii) there are unexplained regional differences.

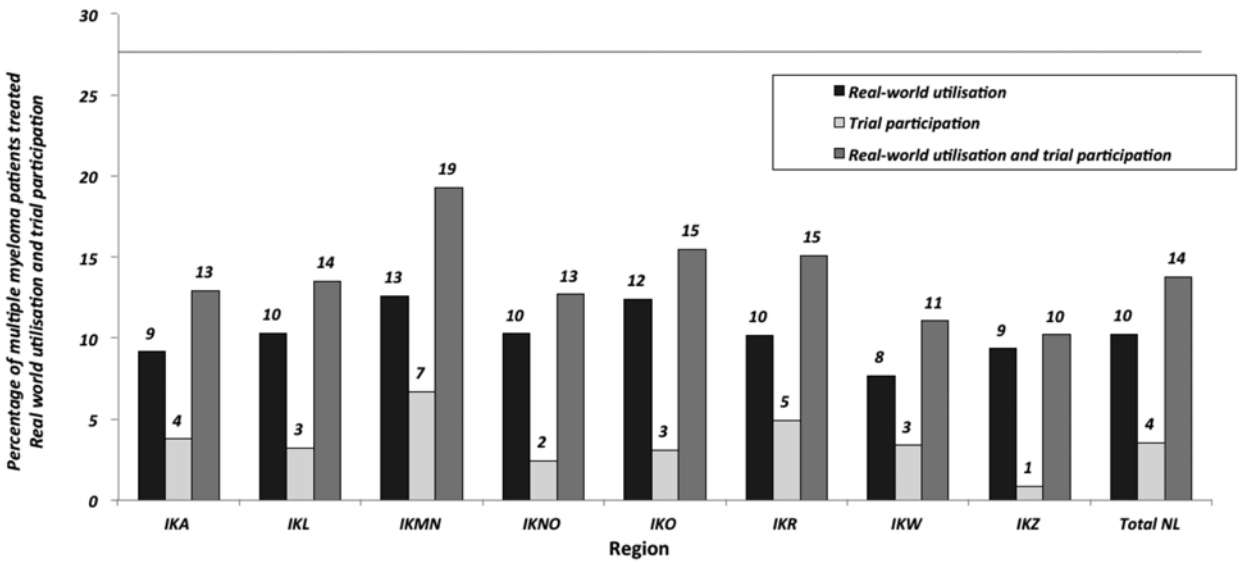
In order to investigate accessibility issues and compare regional use levels we had to make several assumptions, especially to calculate the percentage of MM patients treated with bortezomib. While the regions defined by the Dutch cancer registry vary in size, population and available hospital facilities, we expect the baseline patient characteristics to be comparable across regions. Since accurate prevalence numbers were unavailable, we assumed prevalence could be obtained from the distribution of incidence after verifying that the regional distribution of incidence was stable over a long period with a maximum deviation of only 3%. Some uncertainty surrounding total prevalence, however, remains.

Although these assumptions influence the percentage of patients treated, we believe our conclusion of low prescription rates will not be effected. Levels of use would only be closer to HOVON's expected use of 27% if the prevalence of multiple myeloma was much lower (i.e. less than 1700 patients). Considering incidence is 1100 patients per year, prevalence of less than 1700 seems highly unlikely.

Nevertheless, the share in incidence per region was remarkably stable, confirming a stable division between the regions over time. If prescription rates per region were similar, we expected the regions to be accountable for a similar share in bortezomib as their share in incidence. Therefore, regional variation was definitely established, although violations of our assumptions could enlarge or reduce the differences.

Observed regional variation, in both daily practice and trial use, indicates either differences in prescription behaviour or referral of patients to, for example, more experienced hospitals. Because we used sales data aggregated per hospital, we cannot distinguish between patients living in the region and patients referred to the region. Both causes – prescription behaviour and patient referral – limit accessibility. IKZ may have been especially sensitive to regional border crossing because it is the only region without an academic hospital. In this region, use and trial participation is low while relatively high numbers are observed in its neighbouring region (i.e. IKMN). Bortezomib administration, however, does not require specialised skills or hospital facilities, implying that expertise may have been a valid reason for referral immediately after the introduction in 2004, but should be of minor importance in subsequent years.

Figure 4. *Percentage of multiple myeloma patients treated in daily practice and clinical trials 2005-2009*



IKA = Comprehensive Cancer Centre Amsterdam; IKL = Comprehensive Cancer Centre Limburg; IKMN = Comprehensive Cancer Centre Netherlands Central; IKNO = Comprehensive Cancer Centre North East; IKO = Comprehensive Cancer Centre East; IKR = Comprehensive Cancer Centre Rotterdam; IKW = Comprehensive Cancer Centre West; IKZ = Comprehensive Cancer Centre South.

We studied treatment patterns at an aggregated level, hence neglected other treatment options such as thalidomide and lenalidomide. Because thalidomide is relatively inexpensive in the Netherlands, accessibility should not be an issue. Lenalidomide was accepted for reimbursement at the end of 2007 in Dutch daily practice, creating a competitive alternative treatment option for the years 2008 and 2009 in our analyses. However, lenalidomide does not compensate the low levels of bortezomib prescription. In 2007, 75 patients were treated with lenalidomide and this number increased to 452 and 671 in 2008 and 2009, respectively.[5,19]

Regional differences and under-provision have been previously reported in the Netherlands. Large regional differences and under-provision of trastuzumab in the Netherlands were, according to the Dutch Breast Cancer Association,[3] mainly due to cost. After the accessibility issues of trastuzumab, the Dutch policy for expensive drugs was revised in 2006. Although bortezomib has been on the market since 2004, it was not until it was admitted to the expensive drug list in 2006 that its use in daily practice doubled compared with the previous year. The increase might indicate that the implemented policy facilitated prescription. Other developments occurred simultaneously, however, including changes in professional guidelines that recommended bortezomib in earlier treatment phases. The relatively low use in the first years might have been caused by a long adjustment period of physicians who needed to be familiarised with a new drug.[20,21] Bortezomib was, apart from the re-introduction of thalidomide, the first new innovative treatment option for multiple myeloma patients in four decades. It is important that physicians and policymakers are aware of such lags in the regular use of a new innovative and effective drug. Their implementation should receive more attention to accelerate diffusion by, for example, providing feedback about daily practice use. Groot *et al.*[12] showed that the use of bortezomib in 2005 was almost three times higher in Sweden and France compared with the Netherlands. Furthermore, Dutch use in 2007 was a little less than 35 mg per 100,000 inhabitants while the European average (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and the UK) was above 50 mg per 100,000 inhabitants.[13] Our results also showed that use was below HOVON's expected rate. Despite financial assistance, use and accessibility issues might thus still exist.

It remains subject to further research whether observed regional differences are due to physician prescription behaviour or referral to more experienced or wealthier hospitals. Differences seem to have decreased compared with previous outcomes of the trastuzumab study in 2005, which might be a result of the changes in the policy regulations. However, we should note that the trastuzumab study analysed patients with breast cancer, whose prevalence is much higher than multiple myeloma. Wagelaar *et al.* studied accessibility of two expensive drugs in the Netherlands, bortezomib and trastuzumab, mainly by investigating whether prescription was in accordance with guidelines at the individual patient

level.[22] Medical files were examined and interviews were conducted with physicians, members of hospital boards of directors, and patients. They concluded that guidelines were strictly followed and that recommendations by the professional association and patient characteristics determined treatment decisions. Although the budget of 80% was insufficient according to their respondents, accessibility was not an issue. Interestingly, while their results align with our interview results, they are in contrast with our quantitative findings and our research shows that differences in accessibility might not be revealed by using a qualitative research method only.

In 2012, changes in the regulations increased the additional earmarked budget to full coverage of the 'add-on' diagnoses-related group (i.e. 100% reimbursement of expensive drugs but hospitals and insurers negotiate on the price of the 'add-on'). Although hospital resources remain scarce, this might improve access and reduce remaining regional differences. It will be interesting to closely follow the consequences of this new policy.

We investigated equality in access to bortezomib in the context of Dutch policy regulations for expensive drugs. Use of bortezomib has increased over time although regional differences are still present. We obtained different conclusions using two methods. While interviews did not reveal absolute prescription barriers, regional differences and possibly underutilisation were observed by comparing sales data with incidence and prevalence data. It seems that appropriate drug use and thus also accessibility depends on various factors, regulatory and organisational characteristics of a healthcare system being two important ones. An evaluation of health policies should therefore be based on mixed methods and data triangulation. Such an evaluation provides insight and valuable feedback that can enhance evidence-based decision making for both healthcare providers and policymakers. This could improve appropriate drug use and ensure equal access to healthcare. In the end, efficient and equitable use of scarce resources increases society's benefits from a healthcare system.

Previous presentation

An abstract of the preliminary results was presented at the International Society for Pharmacoeconomics and Outcomes Research 2010, Value in Health Vol. 13, Issue 7, Page A471.

Conflict of interest statement

M. van Agthoven is employed at Janssen-Cilag, pharmaceutical companies of Johnson & Johnson. Janssen-Cilag had no role in the design of the study or interpretation of results. The remaining authors have nothing to disclose.

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SPECIAL REPORT

Venous thromboembolism in overt hyperthyroidism – a direct association with clinical implications?

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ABSTRACT

Hyperthyroidism is associated with procoagulant changes in the haemostatic system. At present, it is uncertain whether this leads to an increased risk of venous and/or arterial thrombosis. Only a few small studies have investigated this association but due to methodological limitations it is not possible to draw any definitive conclusions at this stage. Here we report two patients with severe venous thromboembolism (VTE) and concomitant hyperthyroidism without any risk factors for VTE. Hereby, we emphasise a possible association as supported by a number of previous studies. In a planned prospective multicentre cohort study we will examine the association between hyperthyroidism and VTE and determine its clinical relevance.

KEYWORDS

Hyperthyroidism, venous thromboembolism, pulmonary embolism, sinus thrombosis

INTRODUCTION

Hyperthyroidism is associated with potential procoagulant changes in the haemostatic system.[1-3] It is uncertain whether this also leads to an increased risk of venous and/or arterial thromboembolism. A gradual rise in venous thromboembolism (VTE) risk with increasing levels of free thyroxine within the reference range has been reported,[4] but thus far only four small studies have directly investigated the association between overt hyperthyroidism and VTE.[5-8] The contradictory results of these studies may – at least in part – be due to methodological differences and limitations. In a retrospective study, 5 out of 587 patients with hyperthyroidism experienced a VTE during the study period of nine months, resulting in an incidence rate of 8.7 per 1000 person-years, which is higher than in the general population.[5] Another retrospective study identified a similar incidence rate[6] and Lin *et al*. found a 2.3-fold risk of pulmonary embolism (PE) during a five-year follow-up period in patients with hyperthyroidism compared with a comparison cohort.[7] By contrast, another study could not detect an increased risk of VTE in hyperthyroidism.[8]
Here, we report two patients with severe hyperthyroidism who suffered from venous thrombosis. One had cerebral venous thrombosis of the left transverse sinus, while the other patient was diagnosed with multiple pulmonary embolisms in the upper and lower lobe of the right lung.

CASES

A 50-year-old woman with an unremarkable medical history was admitted with severe hyperthyroidism. She was confused, which was initially attributed to the hyperthyroidism, and suffered from vomiting and headache. Physical examination revealed a diffuse goitre. On neurological examination, she had a normal consciousness, was aphasic, had a right-sided hemianopia, and a mild paresis of the right arm. Laboratory tests showed severe thyrotoxicosis (TSH <0.01 mE/l and FT4 >100 pmol/l; reference range TSH 0.25-4.0 mU/l and FT4 11.0-22.0 pmol/l) due to Graves' disease (T.B.I.I. 29.9 E/l and anti-TPO >3000 kU/l). ECG showed a sinus rhythm. A CT scan of the brain revealed a large left-sided temporo-parietal haemorrhagic infarct with mass effect and a midline shift of approximately 5 mm (*figure 1*). MRI/MRV showed absence

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of flow in the left transverse and sigmoid sinus, consistent with a diagnosis of cerebral venous thrombosis (*figure 2*). Low-molecular-weight heparin was started in a therapeutic dose. During admission she suffered from focal epileptic seizures, which were treated with clonazepam and valproic acid. The hyperthyroidism was treated with potassium iodide drops 1.6 ml 3 times a day, propranolol 40 mg 4 times a day and propylthiouracil 200 mg 6 times a day. Her clinical situation improved, obviating the need for neurosurgical intervention. The heparin was switched to a vitamin K antagonist which she used for a total of 18 months. Three weeks after admission she was discharged on valproic acid, hydrocortisone, propranolol and propylthiouracil. After discharge her aphasia improved but she repeatedly suffered from epileptic seizures which were successfully treated with phenytoin, lamotrigine and clobazam.

The second case was a 46-year-old woman who presented with a fever, productive cough, haemoptysis and painful breathing during the last couple of days. In the previous weeks she had noticed swelling and redness of her left leg which had spontaneously resolved. She had a history of Graves' disease treated with thiamazole 30 mg once a day and levothyroxine 100 µg once a day for the last year. She had been on amoxicillin for four days. No risk factors for venous thrombosis were present. On physical examination she had a breathing frequency of 30 per minute, a temperature of 38.6 °C and a pulse rate of 115 beats per minute. CT scanning showed multiple segmental pulmonary emboli in the right upper and lower lobe with infarctions of the right lung. The patient was treated with low-molecular-weight heparin and a vitamin K antagonist was started. Laboratory tests three days prior to presentation showed a TSH of 0.01 mE/l and FT4 of >70 pmol/l (reference range TSH 0.05 -5.00 mE/l and FT4 10.0-23.0 pmol/l). It appeared that she had not used her block-and-replacement therapy.

DISCUSSION

By presenting these two cases, our aim is to emphasise the possibility that hyperthyroidism is a risk factor for VTE, as indicated previously by a small number of retrospective studies. Neither of these patients had any identifiable risk factors for VTE and both were relatively young. Until now, four small retrospective studies have investigated the association between hyperthyroidism and VTE[5-8] but due to methodological limitations we cannot draw any firm conclusions at this stage. So at present, the available literature does not provide us with answers to our main questions: is the risk of VTE during hyperthyroidism high enough to classify such VTE as provoked, thereby diminishing the need for prolonged anticoagulant therapy? And, does VTE in hyperthyroid patients mainly occur prior to the start of antithyroid agents? If this is true, VTE should be considered a possible first presentation of hyperthyroidism and thromboprophylaxis in patients with hyperthyroidism may not be very effective.

In order to gain more insight into the relationship between hyperthyroidism and VTE, we intend to carry out a prospective multicentre cohort study among 4000 patients with newly diagnosed overt hyperthyroidism. Our aim is to quantify the incidence rate of VTE, myocardial infarction, ischaemic stroke and atrial fibrillation during overt hyperthyroidism and compare this with the rate in a control population.

In summary, we emphasise the possibility that hyperthyroidism is a risk factor for VTE as suggested by a number of previous studies. We address this issue by

Figure 1. *Axial CT of the brain showing a large parieto-temporal haemorrhagic infarct on the left side*

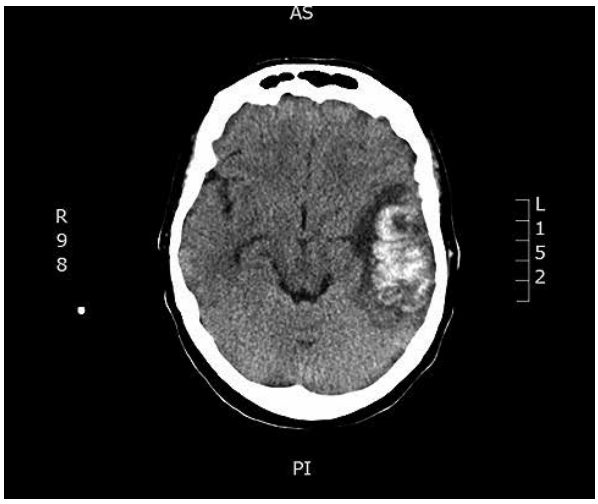
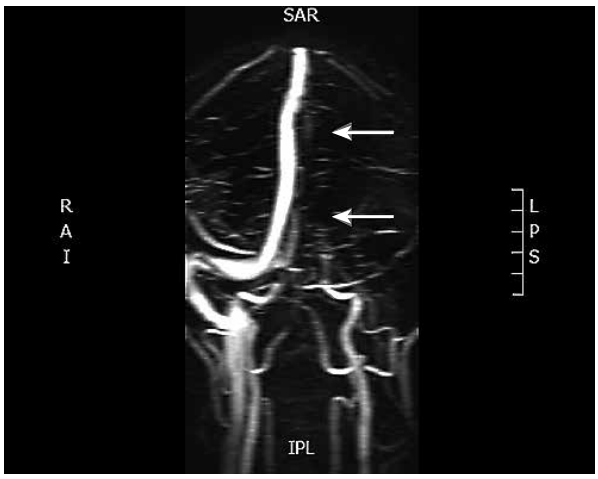


Figure 2. *Magnetic resonance venography of the cerebral sinuses showing absence of flow in the left transverse and sigmoid sinuses and the internal jugular vein*



reporting two patients with severe VTE and concomitant severe hyperthyroidism without any risk factors for VTE. In a planned prospective multicentre cohort study we will examine the association between hyperthyroidism and VTE and determine its clinical relevance.

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DISCLOSURES

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A case of acute generalised pustulosis due to amoxicillin/clavulanic acid

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To the Editor,

Penicillins are very useful antibiotics with a long history. They are still widely used. Unfortunately, they are a common cause of adverse skin reactions. In daily practice, two types of skin reactions are seen.

Type I (acute, IgE-mediated) reactions mostly cause a general itching, erythema and urticaria. Anaphylaxis (dyspnoea, gastrointestinal symptoms, hypotension and even shock) can occur. Laboratory testing will reveal specific IgE for penicillins.[1] In contrast, type IV reactions (delayed type, T-cell mediated) primarily cause skin reactions due to high levels of T cells in the skin. This kind of allergy can be tested via patch testing.[1]

We will present a case of an uncommon type IV hypersensitivity reaction after administration of amoxicillin.

CASE REPORT

A 41-year-old Caucasian male presented himself with an acute erythematous itching rash over his entire body. The day before presentation, he started on amoxicillin with clavulanic acid for treatment of a urinary tract infection. After the second antibiotic tablet, the rash arose suddenly starting in the groin. Physical examination showed a diffuse erythematous rash on arms, legs, trunk and anogenital region, with generalised pinpoint (1-2 mm) pustules. In addition localised purpura on the ankles and blisters were seen (*figure 1*). The patient had a low-grade fever (38.4 °C) and general malaise. Laboratory tests showed a leukocytosis of 20.6 x 10^9/ml with a marked neutrophilia of 19.6 x 10^9/l, and an elevated C-reactive protein of 190 mg/l. There were no signs of renal failure or elevation of liver enzymes. Urinary and blood cultures were negative. Specific IgEs to penicillins (penicilloyl G, penicilloyl V and amoxicilloyl) were not detectable in the serum. Unfortunately, no patch tests were performed. Based on the clinical presentation and blood neutrophilia, our working diagnosis was an acute generalised exanthemous pustulosis (AGEP). The differential diagnosis, taking into account the fever and night sweats, included a (viral) infection, a systemic autoimmune disease with vasculitis and a B-cell malignancy with paraneoplastic phenomena. He was admitted to hospital and treated with 60 mg oral prednisone once daily, 2 mg clemastine thrice daily and 0.5 mg/g fluticasone topically twice daily. The antibiotics were stopped. Skin biopsies of the upper leg and upper arm were taken. In the papillary dermis a mixed perivascular infiltrate of histiocytes, lymphocytes, neutrophils and eosinophils was seen, with oedema. The epidermis showed locally dense infiltrates of neutrophils, confirming the diagnosis of AGEP (*figure 2*). Initially, the itching and rash worsened, but two days after admission the rash and itching faded and the patient was discharged in good health.

DISCUSSION

AGEP is characterised by an acute erythematous eruption together with sterile pustules. As with our patient, this

Figure 1. *Close-up of inguinal region, showing generalized erythematous rash superimposed with sterile pustules*

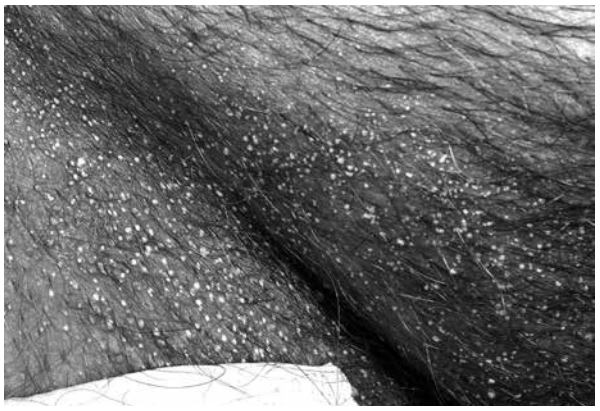

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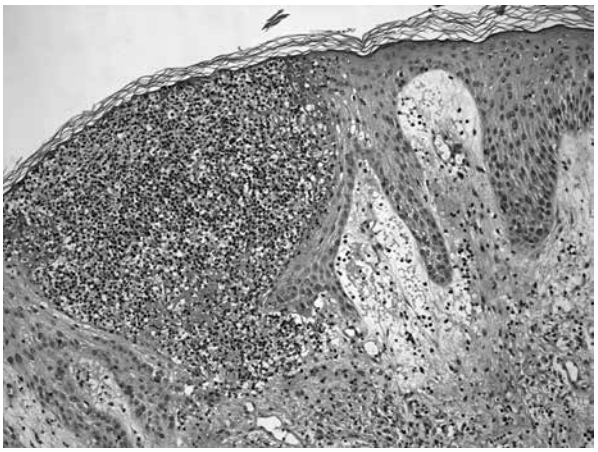
Figure 2. *Skin biopsy of upper arm: in papillary dermis edema and perivascular mixed infiltrate of histiocytes/ lymphocytes and neutrophils plus some eosinophils. Epidermis shows locally dense infiltrates of neutrophils*



usually starts in the intertriginous areas.[2] Additionally, there can be blisters, vesicles and purpura, especially on the legs. A low-grade fever and marked neutrophilia are other hallmarks of the disease.[3] It is primarily considered an adverse drug reaction, but can also be caused by viral infections. The incidence is 1-5 cases per million per year. Treatment consists of discontinuing the culprit drug, after which recovery takes 4-14 days.[2,4] Although clinical evidence for the use of systemic immunosuppressive therapy is lacking, in common practice this is often given. A midway advice might be to administer topical steroids.[5]

Diagnosis is based on the clinical presentation, supported by patch testing (sensitivity 50%) and histology. Histology shows subcorneal pustules, sometimes with necrosis of the keratinocytes, oedema in the papillary dermis and a perivascular infiltrate of neutrophils and possibly eosinophils.[3,4] Although the eruption resembles that of pustular psoriasis, psoriasiform changes such as papillomatosis and acanthosis do not appear.[2]

The drugs mostly associated with AGEP are antibiotics. The EuroSCAR study revealed that 18% of cases were due to aminopenicillins.[3,6] An important difference between AGEP caused by antibiotics and AGEP due to by other 'highly suspected' medications such as diltiazem and hydrochloroquine is the time to onset of the eruption: in the case of antibiotics this is one day or less, with other drugs a median of 11 days. This may suggest different pathogenetic mechanisms.[6]

Studies explain that AGEP is a T-cell mediated immune reaction. Patients show proliferation of drug-specific polyclonal T cells.[7] Skin biopsies and T-cell stimulation tests of AGEP patients show a high production of IL-8, higher than in patients with other drug reactions.[8,9] IL-8 is known for attracting neutrophils and prolonging their survival. This leads to neutrophilic infiltration in the skin and the eruption of sterile pustules.[10] Due to the involvement of both T cells and neutrophils, a classification as a type IVd hypersensitivity reaction has been suggested.[1]

In summary, we present a patient who developed an adverse reaction to a very commonly used antibiotic. Although it is a very rare complication, it is important to keep in mind that such acute adverse reactions can also occur when the patient previously had never been exposed to the culprit drug.

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3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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