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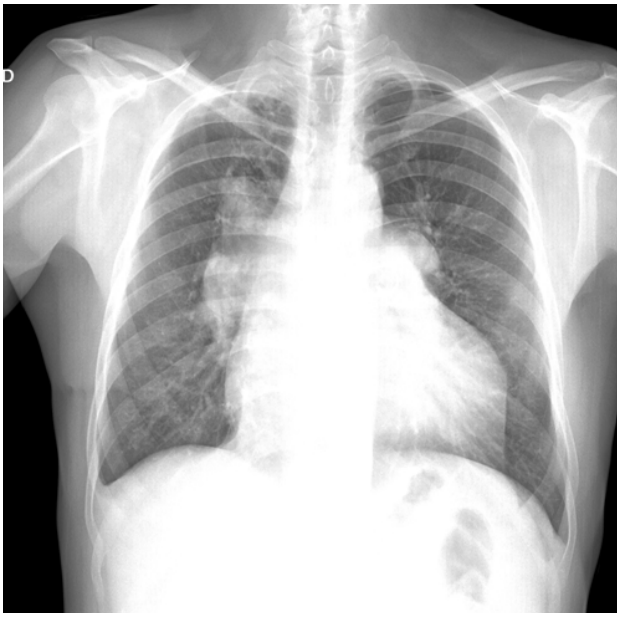

A patient with angina; what is the cause?

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EDITORIAL

Is there a need for dietary consultation in elderly non-European migrants?

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Ethnic minority populations in the Netherlands visit their general practitioner more often than the indigenous population.[1] But does that mean that they are less healthy? Mackenbach et al. showed that despite the fact that most migrants originate from countries with a substantially higher mortality rate than the Netherlands, most groups had similar or more favourable total mortality rates than native Dutch people. Apparently, they are healthier.[2]

Yet, Brederveld et al., in the current issue of the journal, suggest that health in this elderly migrant group can be further improved.[3] In a case-control design they investigated the difference in prevalence of low serum ferritin and of iron deficiency anaemia between a first-generation Turkish and Moroccan geriatric migrant population on the one hand and an equal number of Dutch controls on the other. Both low ferritin level and iron deficiency anaemia were significantly more prevalent among migrants. Unfortunately, due to small numbers they were not able to establish the reason for this difference. Differences in dietary intake were mentioned as a possible explanation.

Apart from the lower iron levels in migrants there were two other striking differences between the two populations; migrants were significantly more often overweight and there was a significantly lower mean vitamin B12 level. Whether they also had a higher prevalence of overt vitamin B12 deficiency was not mentioned. Not mentioned in the article either, but already well established, is that non-European migrants also have lower levels of vitamin D. This is probably due to other factors besides diet.[4] The combination of a high BMI, low ferritin and lower vitamin B12 in my opinion suggests that there is indeed an alimentary issue.

Supplementation is an effective way to correct low levels of iron, vitamin D and vitamin B12 but obviously has no effect on obesity. Dietary consultation, providing information on healthy food, is probably the most effective way to tackle both nutrient deficiencies and weight problems combined. Biesbroek et al. showed that adhering to the WHO and Dutch dietary guidelines will lower the risk of all-cause mortality.[5] Whether this will also lead to better survival in this elderly population is a matter of debate but at least worth investigating.

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REVIEW

Thyrotoxic periodic paralysis: an unusual presentation of hyperthyroidism

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ABSTRACT

Thyrotoxic periodic paralysis (TPP) is a complication of hyperthyroidism among Asians, characterised by sudden onset of hypokalaemia and muscle paralysis. Several factors may contribute to a delay in diagnosis, including the subtlety of hyperthyroidism, the transient nature of the events and the rarity of this disease in the West. As life-threatening arrhythmias may occur during an attack, awareness among physicians is necessary for early recognition and treatment. Advances have been made in understanding the pathophysiological mechanism leading to hypokalaemia, which include recently identified mutations of the inwardly rectifying potassium channel Kir2.6. Treatment includes the supplementation of potassium, a nonselective beta-blocker, and ultimately treatment of the underlying hyperthyroidism. Here we report three cases of TPP in the Netherlands, and review the literature on clinical features, pathophysiological hypothesis and treatment.

KEYWORDS

TPP, hypokalaemia, periodic paralysis

INTRODUCTION

Periodic paralysis is an intriguing medical emergency, with otherwise healthy young individuals presenting with acute painless muscle weakness due to potassium shifts. Two subtypes of hypokalaemic periodic paralysis can be distinguished: a hereditary and an acquired form.[1] In Western countries, autosomal dominant hypokalaemic periodic paralysis (HPP) is common, with a prevalence of 1 in 100,000.[2] This is caused by mutations of voltage-dependent calcium, sodium or potassium channels of the skeletal muscle membranes, with symptoms typically beginning in the first or second decade of life. Although clinical features of sporadic hypokalaemic paralysis are similar to HPP, de novo mutations were identified in a minority of patients.[3]

In Asia, the acquired form is common although, to our knowledge, its exact prevalence has not been reported. Due to its association with hyperthyroidism, this form is called thyrotoxic periodic paralysis (TPP), and it usually occurs after the second decade of life. TPP has an incidence of 1.8% among patients with hyperthyroidism in Asia, whereas rates are estimated to be around 0.1% in the West and usually include patients of Asian background.[4-6] Only few cases of Caucasians with TPP have been described in the literature.[7,8] In contrast to primary autoimmune hyperthyroidism occurring predominantly in females, TPP mostly affects males (male-to-female ratio 26:1).[9,10] The average age of onset is around 30 years which, unsurprisingly, coincides with the average age of onset of Graves' disease.[9-15]

Because this condition is rare, it may be frequently overlooked and misdiagnosed, while recognition and therapy could prevent deleterious outcomes. Mortality rates are unknown, but TPP may explain a portion of sudden cardiac deaths among young Asians.[16] With increasing migration it is likely to be seen more frequently in Western countries. Here, we briefly report three cases of TPP patients in the Netherlands, and review the literature.

HISTORY

The combination of muscle weakness and hyperthyroidism was first described in 1902.[17] In 1931, four cases of

hyperthyroidism and attacks of muscle weakness were described in the English literature.[18] Treatment of the hyperthyroidism resulted in resolution of the periodic paralysis, but this recurred in one case during a relapse of hyperthyroidism.[18] Subsequently, the decrease in serum potassium levels was found to be proportional to the severity of the paralysis.[4]

GENETICS AND PATHOPHYSIOLOGY

Genetic predisposition only combined with hyperthyroidism is thought to induce TPP (*figures 1 and 2*).[19] Observations indicating a genetic predisposition include a higher prevalence among Asians, and the association of paralysis with recurrence of hyperthyroidism. Because of the clinical similarity between TPP and HPP, candidate genes that cause HPP were initially evaluated. These included genes that encode for channels needed for membrane potential stability or excitability, including the voltage-gated skeletal sodium channel $Na_v1.4$ (*SCN4A*), calcium channel $Ca_v1.1$ (*CACNA1S*) and less frequently the inward rectifier potassium channel Kir2.1 (*KCNJ2*).[20-24] Despite clinical resemblance, no mutations of these genes have been identified in patients with TPP.[25,26] However, single-nucleotide polymorphisms (SNP) in the CACNA1S region (encoding for $Ca_v1.1$) have been discovered. Expression of this calcium channel may alter thyroid hormone action.[26]

Ryan and colleagues identified a mutation of *KCNJ18*, which encodes for the potassium channel Kir2.6.[27] Kir2.6 associates with other Kir2.x subunits, such as Kir2.1, forming a homotetrameric complex and, thereby, alters inward potassium trafficking.[28] Potassium fluxes are required for stabilising the resting membrane potential. Interestingly, Kir2.6 contains a thyroid responsive element that may regulate gene transcription (*figure 1*). Decreased inward currents of potassium predispose the sarcolemma to paradoxical depolarisation, which in turn may lead to muscle paralysis.[27,29] Very recently one c-terminus mutation of Kir2.6 (D252N) was shown to decrease potassium currents by 34%.[30] However, the *KCNJ18* mutation is only present in 25-33% of TPP patients from France, United States, Brazil and Singapore, and it was absent in Chinese and Thai subjects.[27] Therefore, the majority of TPP patients have as yet unidentified disease-causing mutations. Genome-wide association studies identified the genetic variant *rs312729*, which is located downstream and may affect Kir2.1 expression, as a new susceptible locus for TPP in Thai patients.[31] This association, but also other variants such as *rs312691*, were further confirmed in Chinese and Korean TPP patients.[32-34] In Chinese patients, Song and colleagues identified the genetic variant *rs312736*, which mapped to *CTD-2379E21.1* that encodes for a noncoding RNA and regulates KCNJ2 expression, to be associated with TPP.[35] With these recent findings, it seems the inward rectifier potassium channels play a pivotal role in the predisposition of TPP.

These findings, however, do not explain why TPP patients have attacks of hypokalaemia during hyperthyroidism. Further evidence indicates that increased activity of the Na+/K+-ATPase may be the link (*figure 1*). Indeed, Na+/K+-ATPase abundance and activity is exaggerated in TPP as compared with healthy control subjects, but also as compared with non-TTP patients with primary hyperthyroidism.[36] This is attributed to a direct effect of hyperthyroidism, but also through an increased expression of β2-adrenergic receptors.[37] In addition, insulin, adrenergic stimulation, androgens or exercise further increase Na+/K+-ATPase activity.[38-40] This explains why these factors may predispose to an attack in TTP patients.[9,10,12,41] Impaired potassium efflux caused by mutations of the inward rectifier potassium channels, combined with increased Na+/K+-ATPase activity may lead to paradoxical depolarisation with muscle inexcitability and eventually paralysis (*figure 1*).[42]

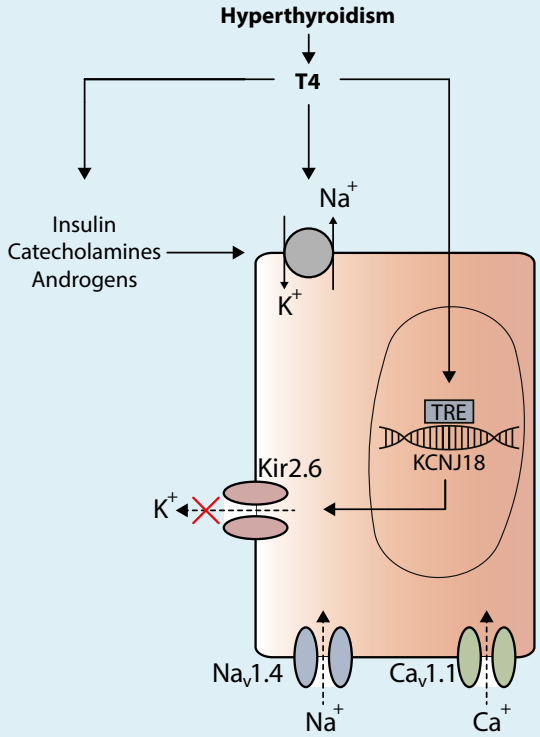
CLINICAL FEATURES

Hypokalaemic paralytic attacks only occur during hyperthyroidism (*figure 2*). Prodromes include muscle aches, stiffness, weakness or cramps 1 hour to 3 days before paralysis.[4,12] Before presentation, most patients have experienced less severe muscle weakness that resolved spontaneously. Attacks usually begin with weakness of the proximal muscles of the lower extremities, and may progress to tetraplegia, with the degree of muscle weakness corresponding to serum potassium levels.[15] No correlations with serum T3 or T4 levels have been found. Bowel and bladder function, facial expression, swallowing and respiration are usually unaffected.[12,15] A precipitating factor for an attack could be identified in 34% of patients.[9] Precipitating factors include high carbohydrate ingestion, alcohol, infection (mainly respiratory or urinary tract infections have been described), excessive exercise and use of β2-adrenergic bronchodilators (*figure 2*).[9,10,12,41] Furthermore, an attack was inducible by glucose loading in a minority of patients.[9] Patients usually experience attacks in the early mornings, and during warm seasons.[4,10]

Laboratory findings

At presentation, laboratory findings include very low levels of serum potassium (on average 2.0 mmol/l), without acid-base disturbances.[9,10,12-15] Renal excretion of potassium is also low, excluding renal potassium wasting. Some reports also mention low serum phosphate and magnesium levels, which also tend to resolve

Figure 1. *A single myocyte is depicted with channels relevant to the membrane potential. In thyrotoxic periodic paralysis (TTP), increases in thyroxin (T4) stimulate the sodium-potassium channel directly and indirectly through exaggerated insulin and catecholamine responses. Also, a thyroid-responsive element (TRE) adjacent to the KCNJ18 gene is thought to alter gene expression of the mutated Kir2.6 channel. Both increased[27] and decreased[30] gene expression have been found in the hyperthyroid state. With the decrease in potassium excretion by Kir2.6, membrane potential increases resulting in a state of cell in-excitability*



spontaneously.[12-14] A high urinary calcium-to-phosphate ratio has been proposed to distinguish TPP patients from those with HPP.[13]

Furthermore, suppressed serum thyroid-stimulating hormone (TSH) with high T4 and T3 levels are pathognomonic for TPP, and distinguish TPP from HPP patients. Free T4 levels are similar to those in non-TTP patients with primary hyperthyroidism.[10,12-14] Graves' disease is diagnosed in the majority of TPP patients, which is also unsurprisingly the main cause of hyperthyroidism in general. However, other causes such as toxic adenoma, toxic multinodular goitre, thyroiditis, and TSH-producing pituitary tumours have been reported in patients with TPP.[9,12,43-45] Notably, 17-85% of TPP patients have mild signs of hyperthyroidism at the time of diagnosis,[9,10,12] and TPP is the first presentation of hyperthyroidism in about 80% of the cases.[46]

Electrocardiogram

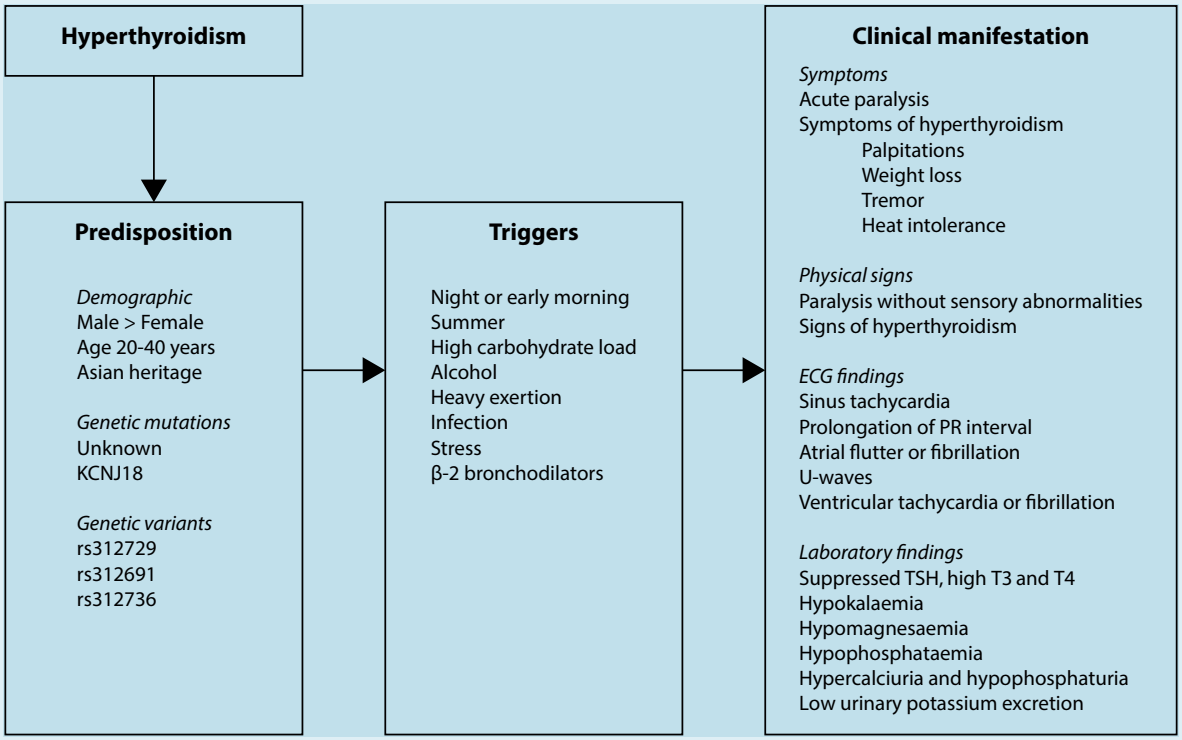
In TPP, both hyperthyroidism and hypokalaemia may cause cardiac arrhythmias that will be apparent on the electrocardiogram (ECG). Sinus tachycardia, and also atrial fibrillation or flutter, are common findings in hyperthyroidism.[47] During an attack, hypokalaemia slows repolarisation, prolongs the refractory period and thereby predisposes to arrhythmias. This is exacerbated as ventricular repolarisation is also lengthened in hyperthyroidism;[48] the ECG may show supraventricular or ventricular ectopic beats, prolonged PR interval, and U waves.[14] Because the risk of serious ventricular arrhythmias is high, including life-threatening ventricular tachycardia or fibrillation,[16] cardiac monitoring is necessary until hypokalaemia is corrected.

TREATMENT

To prevent major complications, such as cardiac arrhythmias, the initial therapy of TTP should be directed to the correction of the hypokalaemia. Some report a shortened recovery time of the paralysis by potassium supplementation,[49] while others do not.[12] Because total body potassium levels are normal, aggressive treatment may result in rebound hyperkalaemia, which occurs in approximately 40-60% of TPP.[12,14] Therefore, low-dose potassium supplementation (10-20 mmol/h) is recommended, unless there are serious cardiovascular complications.[49,50] Propranolol (a nonselective beta-blocker) has been reported to normalise serum potassium within two hours without rebound hyperkalaemia. The mechanism of action of this drug is the reversal of the adrenergic stimulation of the Na^+/K^+-ATPase and reduction of the conversion of T4 to T3 in the liver resulting in lower circulating T3 levels.[51,52] Propranolol may be continued until a euthyroid state is achieved. However, awaiting correct diagnosis, potassium supplementation should also be initiated, with frequent monitoring of serum potassium levels. Meanwhile, patients should be advised to avoid precipitating factors, such as alcohol, high carbohydrate ingestion and excessive exercise.

Initially, thyrotoxicosis should be treated with antithyroid drugs. Block and replace therapy is recommended because of better control of thyroid hormone levels compared with a titration strategy.[53] Next, definitive treatment of the hyperthyroidism is required to prevent relapse of paralytic attacks, which may occur in 62% of patients in the first three months after diagnosis.[10] Antithyroid drug treatment was associated with relapse of TPP, mostly during withdrawal or tapering of medication.[46] Radioactive

Figure 2. *Predisposition requires a multitude of triggers, of which hyperthyroidism is a necessity, to develop thyrotoxic periodic paralysis (TTP)*



iodine or surgical treatment is the most definitive treatment, thereby avoiding the risk of recurrence of TPP. When thyroid hormone replacement is initiated because of iatrogenic hypothyroidism, utmost care in dosing is essential, as even slight overtreatment can lead to TPP relapse.[4]

ILLUSTRATIVE CASE REPORTS

Table 1 shows the characteristics and main clinical findings of three patients with TPP who presented to the medical emergency department. All three patients were male, of Asian descent and presented with complaints of muscle weakness. One patient had experienced muscle weakness previously but this had resolved spontaneously. Possible triggers were high carbohydrate and alcohol consumption. Physical examination revealed paresis of the extremities in all three cases, while sensation was intact. In two cases, severe tetraparesis was present. Serum potassium levels were low to extremely low (1.4 to 2.4 mEq/l), without metabolic abnormalities. With low urinary potassium excretion, renal causes of hypokalaemia were excluded. All cases had abnormal ECG findings, corresponding with hypokalaemia. Interestingly, there were no prodromes indicating hyperthyroidism in all three cases. Serum TSH was only measured after correction of serum potassium, as causes of low potassium and paralysis were evaluated. Therefore, none were treated with propranolol at admission, and two patients had rebound hyperkalaemia after potassium supplementation. Graves' disease was diagnosed in all three cases based on high anti-TSH receptor antibody levels and diffuse thyroid uptake of radioactive iodine in combination with suppressed serum TSH and elevated serum free T4 levels. In all three cases the paralysis disappeared within hours of treatment, and patients were subsequently also treated for their primary hyperthyroidism. One patient (case 3) required thyroidectomy because of a recurrence of the paralysis shortly after initiation of treatment, which was likely triggered by alcohol consumption. Definitive treatment was advised to the other two patients, but case 1 declined and case 2 was lost to follow-up.

CONCLUSION

Sudden onset of paralysis with hypokalaemia, especially in Asian males, should trigger clinicians to consider acquired periodic paralysis. In many cases, TPP may

Table 1. *Characteristics of three cases of patients with thyrotoxic periodic paralysis (TTP)*

	Case 1	Case 2	Case 3
Age, years	26	31	20
Gender	Male	Male	Male
Race, background	Asian, Taiwan	Asian, Taiwan	Asian, Indonesian
History	Unremarkable	Unspecified arrhythmia	Unremarkable
Presenting symptoms	Tetraparesis, mostly upper extremities	Tetraparesis	Paresis of lower extremities
Previous muscle weakness	Yes	No	No
Possible trigger	High carb diet	None	Alcohol
ECG findings	Tachycardia, prolonged PR time, U-waves, frequent premature ventricular complexes	Prolonged PR time, U-waves, right bundle branch block pattern	Intraventricular conduction delay, U-waves
Potassium, mEq/l (ref 3.5-5.5)	1.5	1.4	2.4
pH and bicarbonate levels	Normal	Normal	Normal
Urine potassium, mmol/l	11	12	13
Clinical signs of hyperthyroidism*	No	No	No
Free T4, pmol/l (ref < 24)	53.8	36.3	80.0
Anti-TSH receptor antibody, IU/l (ref < 1)	13.6	14.6	12.7
Thyroid disease	Graves' disease	Graves' disease	Graves' disease
Treatment	Propranolol, thiamazole	Propranolol, thiamazole	Propranolol, thiamazole and later thyroidectomy
Relapse hyperkalaemia	No	Yes	Yes
Recurrence	No	No	Yes, once

*Including anxiety, tremor, palpitations, heat intolerance or weight loss.

be the first presentation of hyperthyroidism. If left untreated, recurrence of hypokalaemia is likely, and this may cause life-threatening arrhythmias. Treatment relies on supplementation of potassium chloride, nonselective beta-blockers and ultimately treatment of the underlying hyperthyroidism. Because total body levels of potassium are normal, frequent measurements of serum potassium levels and adjustment of the supplementation rate are needed to avoid rebound hyperkalaemia. With globalisation, clinicians in the Western world are more likely to encounter patients with TPP.

DISCLOSURES

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REVIEW

Ending the epidemic: Critical role of primary HIV infection

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ABSTRACT

Early identification and immediate treatment of individuals newly infected with HIV is important for two reasons: it benefits the long-term health of the infected patient, and it reduces onward HIV transmission. Primary HIV infection (PHI) reflects the period following HIV acquisition during which viraemia bursts until the establishment of a stable plasma HIV-RNA level approximately six months post infection. During this period, patients are particularly contagious and are often unaware of the infection. As a consequence, PHI disproportionally affects onward transmission. During PHI the immune system is irreparably damaged and persistent viral reservoirs are formed. Initiating antiretroviral therapy (ART) during PHI could potentially lead to a functional cure through early and prolonged viral suppression. Unfortunately, symptoms of PHI are nonspecific and the diagnosis is frequently missed. This impedes timely diagnosis and prompt initiation of ART. To increase awareness and underscore the importance of immediate ART initiation, we describe here the pathogenesis, clinical presentation, and impact of treating PHI.

KEYWORDS

Acute retroviral syndrome, functional cure, HIV reservoir, HIV transmission, post-treatment control, primary HIV

INTRODUCTION

Human immunodeficiency virus-1 (HIV) acquisition often elicits a severe inflammatory response and leads to irreparable damage to the immune system. The initial phase that follows HIV infection is known as primary HIV infection (PHI) and can be defined as the interval from the detection of the virus (HIV-RNA) in the plasma until the establishment of a stable plasma HIV-RNA level (viral set point) in the presence of evolving anti-HIV antibody reactivity.[1] Initiating antiretroviral therapy (ART) during the acute phase of HIV infection reduces the inflammatory response, lowers the viral set point[2,3] and can lead to a more rapid and robust immunological recovery compared with a later start. Early in the infection, a viral reservoir of memory CD4+ T cells with viral DNA integrated into the host DNA is formed. Viral transcription in these cells is nearly absent, which hinders immunological recognition and elimination. Starting ART immediately during the early phase of infection can reduce the size of this reservoir.[4-6] Moreover, since patients are most contagious during PHI due to high viraemia,[7,8] prompt treatment initiation reduces viraemia and thereby interrupts onward transmission. For these reasons, immediate initiation of treatment upon a positive HIV test is now recommended by the current international guidelines.[1] Unfortunately, PHI remains a diagnosis that is frequently missed and patients are often unaware of having PHI at a time when they are particularly infectious. Awareness among at-risk patients as well as clinicians of the possibility of PHI is therefore of vital importance. Here we describe the pathogenesis, clinical presentation, and impact of treatment of PHI on individual and public health.

PATHOGENESIS OF PHI

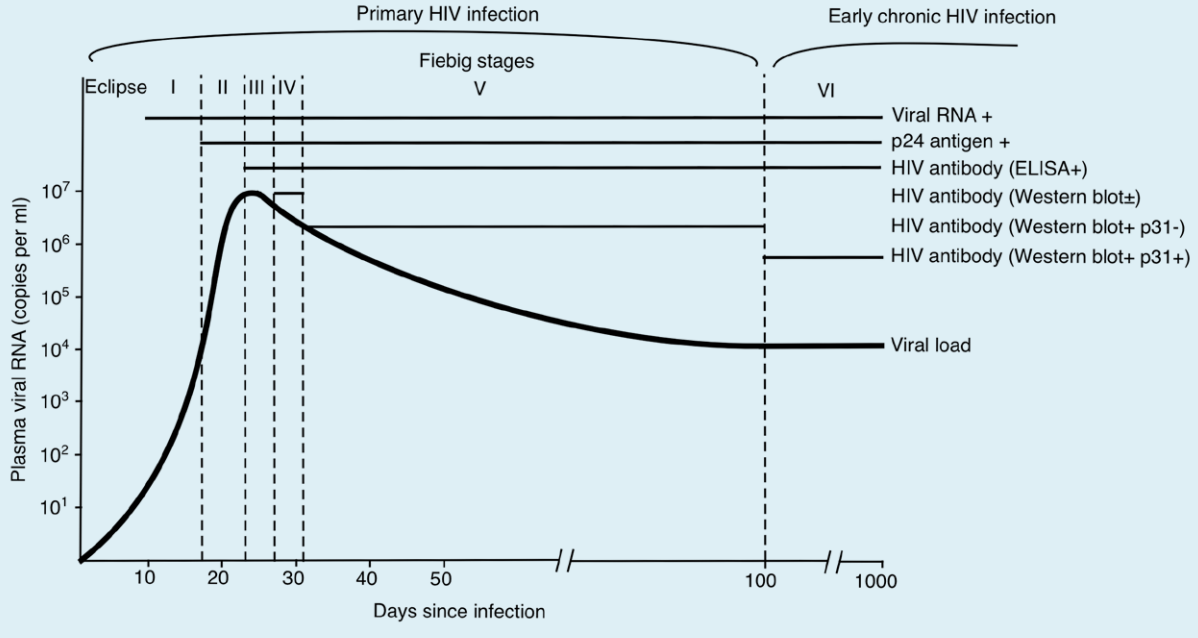
To this day, the viral reservoir remains one of the major barriers to curing HIV. After entering the body, HIV reaches the draining lymph nodes where it rapidly replicates in CD4+ T cells and subsequently spreads

throughout the body.[9] Already during this phase, HIV integrates in the genome of long-lived CD4+ T cells forming a stable latently infected reservoir.[10] CD4+ T cells in the gut-associated lymphoid tissue are particularly affected and their rapid depletion results in chronic damage to the gut mucosa.[10,11] HIV replicates in the lymphoid tissues and plasma viraemia increases exponentially while the adaptive immune system is still mounting a response. This ramp-up viraemia coincides with a large burst of pro-inflammatory cytokines produced by innate immune cells, including natural killer (NK) cells. NK cells help control viral replication through recognition of infected cells via specific types of receptors.[12] Although generally the NK cell response against HIV is insufficient, marked differences in anti-HIV effects can be appreciated based on their maturation status.[13] The NK cell compartment in any individual consists of more or less matured populations, resulting in a unique profile. A more mature NK profile improves several virological and immunological markers in patients with PHI. These patients have lower viral load set points and show a better early virological response to ART initiated during PHI.[14] During the adaptive immune response, B cells produce antibodies and CD8+ T cells mount a HIV-specific cytotoxic T cell (CTL) response. CD4+ helper T cells regulate the CTL response, but are also infected by HIV. As a consequence, they are killed by CTL or prone to virus-induced pyroptosis.[15] These combined effects result in a steep initial drop in CD4+ T cells during the first stages of PHI. This is only partly reversed through limited control over viraemia in later stages. Despite its magnitude, the immune response during PHI is unable to clear these reservoir cells. Interventions during PHI before a long-lived reservoir is established present an opportunity to achieve sustained control over the virus, and may even lead to a cure.

CLASSIFICATION OF THE STAGES OF PHI

Figure 1 provides an overview of the consecutive clinical stages following initial HIV transmission. The stages as classified by Fiebig are defined by a stepwise detectability of HIV antigens and HIV-specific antibodies using different diagnostic assays.[10,16] Successful HIV transmission marks the start of the eclipse phase. During this phase, the infection is established but viral markers in the blood are not yet detectable by routine diagnostics. At the end of the

Figure 1. *Overview of the different stages following HIV infection. The time between infection and the first detection of HIV-RNA (viral load) in plasma is referred to as the eclipse phase. Plasma HIV-RNA levels increase exponentially and peak around day 21-28. Patients can be categorised into Fiebig stages I-VI based on the sequential appearance in plasma of HIV-RNA, HIV-p24 antigen and HIV antibodies as detected by enzyme-linked immunosorbent assay (ELISA), and antibodies directed against several structural viral proteins, including p31 as detected by Western blot. Progression to Fiebig VI marks the onset of the early chronic stage during which the plasma HIV-RNA stabilises and a viral set point is established. A plus sign indicates the presence, a minus the absence of a marker, and a plus-minus sign a borderline-positive result. Adapted from McMichael et al.[10] and Cohen et al.[56]*



eclipse phase, the emergence of plasma HIV-RNA above the level of detection (approximately 11 days post infection) marks the start of Fiebig stage I. The detection of p24 antigen one week later marks Fiebig stage II. The plasma HIV-RNA increases exponentially and peaks between day 21 and 28 post infection, after which a slower decrease in plasma viral RNA follows. Fiebig stages III to V are based on the sequential detection of HIV-specific antibodies by enzyme-linked immunosorbent assay (ELISA) or Western blot. Progression to Fiebig VI marks the onset of the early chronic stage during which the plasma HIV-RNA stabilises and a viral set point is established.

CLINICAL PRESENTATION

Around two weeks after HIV acquisition, patients commonly experience symptoms that suggest a mononucleosis-like illness known as acute retroviral syndrome.[17-21] The acute illness may last from a few days to more than 10 weeks, but generally the duration is less than 14 days.[22,23] The estimated proportion of patients who seek professional medical care for their PHI-associated symptoms ranges from 53% to 87%.[17,20,24,25] One study estimated the prevalence of PHI among patients seeking care for fever or rash to be 0.5-0.7%.[26] Unfortunately, when patients present at healthcare facilities, PHI is hard to recognise due to the brevity of the symptomatic phase and nonspecific symptoms. In addition, in spite of current guidelines recommending pro-active testing,[27] the frequency of routine HIV testing of high-risk individuals by both primary and secondary care clinicians is low.[28-30] In Kenya, Sanders and colleagues identified seven characteristics that are independent risk factors of PHI: a younger age (18-29 years), fever, fatigue, body pains, diarrhoea, sore throat, and genital ulcer disease.[31] Based on those findings, they proposed and tested a targeted risk score algorithm to detect PHI.[31,32] In the Netherlands, a similar PHI testing strategy was developed as part of the H-team, an initiative originally launched by the late Professor Joep Lange.[33] This strategy includes a risk score algorithm aimed at men who have sex with men and involves standard of care HIV testing as well as a novel point of care (POC) RNA rapid test at the Amsterdam Public Health Service. Of 206 eligible men who presented for testing between August 2015 and January 2017, 17 men were newly diagnosed with HIV, 2 of whom were diagnosed as Fiebig I (RNA POC positive, p24 negative, antibody negative), 8 as Fiebig II (RNA POC positive, p24 positive, antibody negative), and 7 as Fiebig III-V (RNA POC positive, p24 positive and antibody positive).[34] Although these findings show that effective screening strategies can lead to diagnosis of patients in the early Fiebig stages, various studies in both resource-rich and low-resource settings indicate that regardless of clinical criteria, identification of PHI remains difficult.[19,21,22] *Table 1* presents a list of commonly considered differential diagnoses mimicking PHI in potential risk groups, including diagnostic tests that can help to differentiate. Given the wide range of symptoms associated with PHI, clinicians should have a low threshold to consider HIV testing. Moreover, awareness among clinicians of PHI in high-risk groups such as men who have sex with men, heterosexual individuals with multiple sexual partners, and migrants from areas with a high HIV prevalence is critical. When such high-risk patients present with signs and symptoms of syphilis, other STDs, or mononucleosis-like symptoms, clinicians must consider PHI as a possible co-infection or even the main cause of the clinical presentation. Finally, when known high-risk patients present with new symptoms associated with PHI clinicians should repeat HIV testing even if a very recent negative HIV test is available, because the diagnostic window of PHI is so narrow.[35]

IMPACT ON PUBLIC HEALTH

In 2011, Cohen and colleagues highlighted the potential impact of treatment of HIV on public health by showing that initiating ART immediately after diagnosis almost eliminated the risk of HIV transmission to an uninfected person in heterosexual serodiscordant couples.[36] Since PHI accounts for approximately half of onward HIV transmission in resource-rich settings,[37] treatment of PHI presents an effective tool to prevent onward transmission. Indeed, modelling studies indicate that early detection of PHI and an immediate start of ART provide an important opportunity for prevention of transmission, potentially even for HIV elimination.[38-40] Obviously, early ART initiation should not preclude patient support and risk reduction counselling, or other modifications of sexual risk behaviours.[41] In the Netherlands, general practitioners, community health services and STI clinics diagnose the majority of HIV infections (approximately 60%).[42] Unfortunately, observational studies found that PHI represents only 3.4% of all new HIV diagnoses.[43] Even in low prevalence areas where repeated HIV testing will predominantly yield negative test results, identification of only a few additional cases of PHI due to increased screening and pro-active testing of high-risk populations is modelled to be cost-effective.[44,45] Failure to identify PHI may compromise HIV prevention efforts and hinder the potential population-wide benefits. Therefore, continuous pro-active HIV testing of high-risk patients by healthcare professionals from all disciplines, and expanding coverage by including strategies such as HIV self-testing, are needed.[46]

Table 1. *Common differential diagnoses, possible differentiating diagnostics, and risk factors in patients presenting to the internal medicine department with PHI-associated symptoms*

Signs and symptoms[19,21,31]	Differential diagnosis and differentiating diagnostic assays	Sociodemographic and behavioural factors[27,31]
<u>Reported symptoms:</u>	Recent EBV infection	HIV endemic area[3,4]
Fever[1]	- Serology: EBV VCA-IgM, EBV VCA-IgG, EBV NA-IgG, EBV EA-IgG; PCR	
Headache[1]		STI endemic area[3,5]
Diarrhoea[1]	Recent CMV infection	
Fatigue[1]	- Serology: CMV IgM and IgG, CMV IgG avidity; PCR	MSM
Body ache (arthralgia, myalgia)[1]	Influenza infection	Prostitutes and their visitors
Swollen lymph nodes[1]	- Culture or PCR on throat swab, or bronchial wash, nasal or endotracheal aspirate, sputum	
Night sweats[1]		
Rash[1]		IV drug users
Weight loss[1]	Acute viral hepatitis A/B/C/E	
Sore throat	- Serology: HAV IgM/IgG, HBV (HBsAg, anti-HBc), HCV IgG, HEV IgG; liver function tests; PCR HAV-RNA, HBV-DNA, HCV-RNA, HEV-RNA	(Ex) prisoners
Coughing		
Malaise		Those with a sexual partner from the above groups
Nausea	TBC infection[2]	
Vomiting	- Auramine stain, culture or PCR on sputum, urine, lymph nodes, pleural effusion, or CSF	
Loss of appetite		
Genital lesions or discharge	Primary or secondary syphilis[2]	Age (18-29 years)
	- Non-treponemal test (VDRL or RPR); treponemal test (TPHA/TPPA, FTA-ABS); dark field microscopy, PCR on syphilitic lesions	>1 sex partner in the past 2 months
<u>Physical exam signs:</u>		
Rash[1]	Chlamydia/LGV, Gonorrhoea urethritis, pharyngitis or proctitis[2]	
Extra inguinal lymphadenopathy >2 sites[1]	- Gram stain; PCR on swab from rectum, anus, vagina, ulcer, oropharynx or conjunctiva, or on urine	
Pharyngitis[1]	Other (suspected SLE, ITP, IBD, gastro enteritis, meningitis/encephalitis, primary immunodeficiencies, travel-related pathogens)	
Oral ulcers[1]		
Genital ulcers[1]	- Depending on the specific differential, for example ANA, anti-dsDNA, biopsy; complete blood count, peripheral blood smear, DAT; colonoscopy, biopsy, stool culture, triple faecal test, immunoglobulins	
Oral thrush		
Genital warts		
Vaginal candidiasis		
Proctitis		

[1]Commonly reported signs and symptoms[21]
[2]In case of TBC, or syphilis, chlamydia, gonorrhoea, or any other STI, always consider HIV as a possible co-infection
[3]First and second generation immigrants
[4]HIV endemic area: Sub Sahara Africa, Caribbean[57]
[5]STI endemic area: Surinam, former Netherlands Antilles, Turkey, Morocco, Africa, South America, Asia, Eastern Europe[58]
EBV = Epstein-Barr virus, IgM = immunoglobulin M, VCA = viral capsid antigen, IgG = Immunoglobulin G, NA = nuclear antigen, PCR = polymerase chain reaction, CMV = cytomegalovirus, HCV = hepatitis C virus, HBV = hepatitis B virus, HBsAg = hepatitis B surface antigen, anti-HBc = anti-hepatitis B core antigen, HAV = hepatitis A virus, HEV = hepatitis E virus, TBC = tuberculosis, CSF = cerebrospinal fluid, VDRL = venereal disease research laboratory, RPR = rapid plasma reagin, TPHA = treponema pallidum hemagglutination assay, TPPA = treponema pallidum particle agglutination assay, FTA-ABS = fluorescent treponemal antibody absorbed, LGV = lymphogranuloma venereum, SLE = systemic lupus erythematosus, ITP = idiopathic thrombocytopenic purpura, IBD = inflammatory bowel disease, ANA = antinuclear antibody, anti-dsDNA = anti-double stranded DNA, DAT = direct antiglobulin Test, HIV = human immunodeficiency virus, STI = sexually transmitted infection, MSM = men who have sex with men, IV = intravenous

IMPACT ON INDIVIDUAL HEALTH

The best practice for clinical management of PHI is a subject of ongoing research. Ananworanich and colleagues found that T cell depletion and HIV reservoir seeding begins in the earliest days after HIV infection, and that commencing ART during this crucial period limits CD4+ T cell destruction and the HIV reservoir size.[47] These findings suggest a promising scenario where intervention with ART during PHI leads to favourable long-term viral and immunological outcomes compared with a deferred start of therapy. In recent years, three prospective, randomised controlled multicentre studies have shown individual health benefits of ART initiated during PHI.[2,3,48] The Short Pulse Anti-Retroviral Therapy at Seroconversion (SPARTAC) trial is the largest multicentre randomised controlled trial to date involving 366 PHI patients.[3] In this study, a 48-week course of ART during PHI resulted in significant CD4+ T cell improvement and a lower plasma viral set point after treatment interruption. The Dutch Primo-SHM trial involving 115 PHI patients showed a similar trend.[2] The Setpoint study (ACTG-A5217) included 130 PHI patients and was in fact prematurely terminated due to better outcomes in the group receiving immediate treatment.[48] Importantly, although these studies indicate that starting and then stopping treatment is a beneficial and potential therapeutic strategy, a large, long-term randomised controlled trial of patients with chronic HIV infection found treatment interruption to have harmful effects,[49] and consequently current guidelines recommend uninterrupted treatment.[1] Moreover, precisely which combination of antiretroviral medication presents the optimal treatment of PHI, and whether intensification of ART can yield greater benefits in reducing markers for HIV reservoir size and immune activation, is presently unclear. A small randomised controlled trial by Ananworanich et al. in which drugs that can block viral cellular entry (maraviroc), and integration (raltegravir) were added to a standard regimen with nucleoside reverse-transcriptase inhibitors (tenofovir and emtricitabine) and a non-nucleoside reverse-transcriptase inhibitor (efavirenz) did not show an additional effect in reducing the viral burden and HIV reservoir seeding in Thai individuals.[50] Furthermore, while early intervention seems favourable, data on definite clinical endpoints such as mortality are still unavailable. Nonetheless, these findings support the rationale of ART initiation during PHI at the earliest stage possible, before the immune system suffers irreparable damage and the reservoir size is established.

POTENTIAL FOR CURE

Initiating ART during PHI offers the potential for what is known as a functional cure. A patient is considered functionally cured, or a post-treatment controller, when ART can be interrupted without subsequent rebound plasma viraemia or progressive loss of cellular immunity. The potential for achieving a functional cure when treatment is started during PHI is reflected by a number of studies. The case of the Mississippi infant is illustrative. Since the baby was born to an HIV-infected mother who had received no prenatal care, it began receiving full ART 30 hours after birth. ART was interrupted and the baby was withdrawn from care by the mother after 18 months of continuous ART, but surprisingly, this infant sustained an undetectable plasma viral load at the age of three years when re-entering medical care.[51] Unfortunately, two months before reaching the age of 4 years viral rebound occurred and the girl had to be started on ART again. Similar observations were derived from the RV254/SEARCH 010 study, an ongoing prospective, longitudinal cohort of PHI patients in Thailand that was initiated in 2009. The authors of this study were the first to imply immediate treatment of PHI as a promising strategy to reduce reservoir formation to eventually achieve sustained drug-free viral remission.[47] A landmark study on post-treatment controllers is the Viro-Immunological Sustained CONtrol after Treatment Interruption (VISCONTI) cohort.[5] In this study, 14 post-treatment controllers were identified out of a much larger cohort of PHI patients who started ART during PHI and who subsequently interrupted ART after a median of three years. These 14 patients remained aviraemic for several years after ART interruption.[5] The small viral reservoir and altered CD4+ T cell subsets in these individuals have been hypothesised to be contributing factors. In line with this assumption, post-treatment controllers are far less frequently observed when ART is started in the chronic stage of HIV infection. Other treatment interruption studies have identified similar patients.[52] Furthermore, longer exposure to ART is associated with a greater chance of post-treatment control in patients with PHI,[53] and previous evidence points towards uninterrupted treatment.[49] Therefore, stopping ART in the context of a cure study should be carefully planned, HIV-RNA guided, and closely monitored. Unfortunately, clear markers to predict sustained virus control after treatment of PHI have yet to be elucidated. Clearly, post-treatment controllers hold an important clue with regard to future curative efforts, but for the majority of individuals including those with PHI, treatment interruption results in viral rebound and continuous ART remains a necessity.

CURRENT AND FUTURE PROSPECTS

In line with current guidelines, patients should be informed about the benefit of starting ART following

PHI diagnosis, and be counselled about the high risk of transmission as long as they are highly viraemic, preventive measures, and the importance of notifying partners.[1] The European AIDS Clinical Society (EACS) advises that clinicians should be familiar with local routes to ensure instant referral to an HIV specialised centre to start treatment as soon as possible, and preferably combine this with enrolment into clinical studies investigating HIV curative strategies.[1] Such a study is the Netherlands Cohort Study on Acute HIV Infection (NOVA), part of the H-Team initiative, which intends to promote prompt linkage to care and immediate ART initiation in all PHI patients in the Netherlands. Such initiatives also offer opportunities for a detailed characterisation of the viral reservoir and could provide further insights into the early immune response to HIV. By obtaining a better understanding of the factors related to functional cure, such studies can help optimise treatment strategies and assist in identifying patients who could benefit most from future strategies to achieve post-treatment control, including cure strategies with therapeutic vaccination or specific agents targeting the HIV reservoir. While work on a future cure is in progress, other initiatives to halt onward HIV transmission are needed. For example, pre-exposure prophylaxis has been shown to be highly effective[54,55] and thereby would present an important strategy to reduce the incidence of HIV infection and can aid in HIV elimination.

CONCLUSION

Greater clinical awareness of PHI among clinicians from all disciplines, pro-active and repeated HIV testing, and fast linkage to care in order to facilitate an immediate start of ART merit our attention. First, it helps to prevent onward transmission and could ultimately lead to HIV elimination. Second, it improves an individual patient's health by limiting both reservoir size and immune damage. This could aid future efforts to achieve a functional cure. Ongoing studies involving patients with PHI remain a necessity, however. Thirty-five years on, more than 40 million people have died due to HIV globally. In the Netherlands, approximately 900 people still become infected with HIV every year. PHI remains a clinical and public health emergency that requires early diagnosis and immediate intervention. If we are to finally end the HIV epidemic, PHI should be on the agenda.

DISCLOSURES

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ORIGINAL ARTICLE

Venous thrombosis and coagulation parameters in patients with pure venous malformations

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ABSTRACT

Introduction: Venous malformations (VMs) are ubiquitous, low-flow vascular anomalies known to be occasionally painful due to thrombotic episodes within the lesion. The prevalence of superficial or deep vein thrombosis is unclear.

Methods: A cross-sectional study among outpatients aged ≥ 12 years with pure VMs was performed, quantifying the prevalence of thrombosis by screening all patients with compression ultrasonography (CUS). Additionally, we evaluated whether coagulation alterations were related to thrombosis observed with CUS.

Results: In total, 69 patients with pure VMs were eligible, median age was 30 years (range 12-63) and 52% were female. A total of 68 patients underwent CUS. Superficial vein thrombosis was observed in 10 (15%) cases; 1 patient had a current asymptomatic deep venous thrombosis. Residual superficial or deep thrombosis was observed in 25 patients (36%). In total, 49% had either a history or current signs of a thrombotic event and overall 10% had venous thromboembolism. In approximately 50% of the patients the D-dimer level was above 0.5 mg/l. Median P-selectin and Von Willebrand factor levels were 29 ng/ml (interquartile range (IQR) 21-34) and 108% (IQR 83-132), respectively. No differences were observed in the coagulation parameters between the patients with and without current clots in their VM.

Conclusion: This study shows that superficial or deep vein thrombosis is common among patients with a pure VM. Physicians should be aware of this high incidence, especially if other risk factors for thrombosis are present.

KEYWORDS

Compression ultrasound, superficial vein thrombosis, residual thrombosis, venous malformation, venous thromboembolism

INTRODUCTION

Venous malformations (VMs) are the most prevalent vascular anomalies, with an incidence of almost 2% in the general population. The slow-flow, thin-walled vascular lesions present as bluish or purple lesions, which are mainly localised on the skin and mucosa, but can be found in any tissue or organ. Most of the lesions are asymptomatic, although swelling and pain can occur.[1,2]

Coagulation abnormalities associated with VMs of the extremities are reported as localised intravascular coagulation and are characterised by elevated D-dimer levels. Severe localised intravascular coagulation is associated with elevated D-dimer and low fibrinogen levels. The severity of the activated coagulation state is related to the extent of the malformation.[3,4] Thrombosis may present as a local superficial thrombosis or palpable phlebolith, a stone-like structure due to calcification of the thrombus. VMs usually occur in a pure form; however they can also be part of more complex syndromes, such as the Klippel-Trenaunay syndrome, a low-flow VM of the capillary, venous and lymphatic systems, characterised by a triad of port-wine stains of the affected extremity, and bony and soft tissue hypertrophy. The prevalence of venous thromboembolism in patients with Klippel-Trenaunay

syndrome is high (approximately 20%).[5,6] The prevalence of venous thromboembolism in patients with pure VM is, however, unknown. Similar to patients with Klippel-Trenaunay syndrome, blood stagnation with activation of coagulation within the distorted, enlarged venous blood vessels is also present in patients with pure VMs. It is therefore conceivable that patients with pure VMs similarly have an increased risk of thrombotic complications, such as extension of the superficial vein thrombosis or venous thromboembolism.[3,7] If this is the case, venous thromboembolism could be more common in these patients than presently assumed.

The objectives of this study are 1) to determine the prevalence of superficial vein thrombosis and/or venous thromboembolism, and 2) to assess whether patients with pure VM have a hypercoagulable state.

METHODS

We performed a cross-sectional study among patients with pure VM.

Population

The study population consisted of outpatients of the Department of Plastic, Reconstructive and Hand Surgery, at the Academic Medical Center, Amsterdam, the Netherlands, included between May 2009 and July 2012. Patients were consecutively asked to participate after their elective visit, regardless of whether symptoms of thrombosis were present. Inclusion criteria were patients aged ≥ 12 years with a pure VM. Patients with an VM other than a pure VM, such as patients with Klippel-Trenaunay syndrome, or with a maximum surface area of less than 4 cm^2 with an estimated depth less than 4 cm or patients who refused informed consent were not eligible. The institutional review board approved the study protocol and written informed consent was obtained from all included patients.

Demographic and clinical data were collected, such as age, gender, and details of the symptomatic episodes of the VM. The patient's medical history was carefully considered for a history of thrombotic and major bleeding events, use of anticoagulant therapy and risks for thrombosis such as immobilisation within four weeks prior to inclusion, surgery in the last three months, use of oral contraception, pregnancy or an active malignancy. If prior venous thromboembolism was reported, a copy of the original investigation (ultrasound, CT scan, or other imaging study) was collected. If prior major bleeding was reported, we did not register it specifically, since bleeding was not a predefined outcome of this study.

We did not perform MRI for study purposes. However, when an MRI was performed in patients < 18 years of age within one year prior to enrolment or in patients ≥ 18 years within five years prior to enrolment, the MRI result was used to estimate the surface area of the VM, in combination with physical examination. If no MRI was available, only physical examination was used to estimate the surface area. In case of multiple VMs, we measured the largest malformation to estimate the surface area of the VM.

Compression ultrasonography (CUS)

Flow characteristics of the VM and signs of superficial or deep vein thrombosis or residual thrombosis in the VM were obtained by CUS, performed by one of in total three experienced sonographers. They used the same criteria for thrombosis and residual thrombosis. In case of the latter, another sonographer and one of the researchers were contacted to reach consensus. The CUS was performed on the affected parts of the body after collecting the clinical data, such as current symptoms of thrombosis. If, after physical examination, thrombosis was suspected in a limb not affected by a VM, CUS of that limb was performed as well.

Vein compression was performed in the transverse plane; vein diameter was measured during maximal compression and was expressed in millimetres.

Because this study had a cross-sectional design, we could only compare the results with previous CUS if patients had ever had a thrombosis. In these cases the CUS findings were categorised according to Prandoni and colleagues[8] as negative for deep vein thrombosis or recurrence if both the veins were fully compressible or, in the non-compressible veins, if the residual vein diameter was reduced or unchanged (± 1 mm), compared with the previous assessment; positive for proximal deep vein thrombosis recurrence if a previously normal vein had become non-compressible or if the residual vein diameter in either venous segment had increased in size (> 2 mm) compared with the previous assessment.

If patients had no history of thrombosis, we considered the CUS negative if the veins were fully compressible, and positive for deep vein thrombosis if a vein had become non-compressible or if the residual vein diameter in either venous segment was enlarged (> 2 mm). Furthermore, we made an arbitrary distinction between residual thrombosis and 'fresh' thrombi, depending on the density (old thrombi usually have a larger density compared with fresh thrombi), contour (old thrombi are mostly re-canalised and have lost their irregular shape) and the presence of calcifications or bypasses.

Because this is not a standardised method to report residual thrombus, we reported all CUS findings. Depending on the localisation of the clots, we classified thrombosis as superficial vein thrombosis or deep vein thrombosis.

Coagulation parameters

Blood samples were collected in citrated tubes (Becton Dickinson, San Jose, CA), and centrifuged within 30 minutes for 20 minutes at 1700 g and 15 °C, the plasma was re-centrifuged for 15 minutes at 3000 g and 15 °C. Plasma was stored at -80 °C.

Activated partial thromboplastin time (APTT) and prothrombin time were determined as indicators of the intrinsic and extrinsic pathways, respectively. We also measured D-dimer, a marker of fibrin clot formation and fibrinolysis, Von Willebrand factor, a marker of endothelial activation and involved in the adhesion and aggregation of platelets, and P-selectin, an adhesion receptor on activated platelets for monocytes. The coagulation assays, APTT and prothrombin time, were performed on an automated coagulation analyser (Behring Coagulation System, BCS) with reagents and protocols from the manufacturer (Siemens Healthcare Diagnostics, Marburg, Germany). Von Willebrand factor and P-selectin antigen levels were determined by ELISA using antibodies from Dako (Glostrup, Denmark) and Human SP-selectin/CD62P (R&D Systems), respectively. D-dimer was determined with Innovance D-dimer (Siemens Healthcare Diagnostics).

Statistical analysis

All numbers are expressed as medians with corresponding interquartile ranges (IQR) or ranges, unless otherwise stated. The Mann-Whitney U test was used for nonparametric numeric data; the chi square test was used for categorical data. Statistical analysis was performed using statistical software (SPSS 19.0.2, SPSS, Chicago, IL). Statistical difference was set at $p < 0.05$.

RESULTS

In total 70 patients with pure VM were eligible for the present analysis. One patient was shown to have no VM left after he underwent surgery, so this patient was excluded. The clinical and VM characteristics of the remaining 69 patients are described in *table 1*. Median age was 30 (range 12-63) years and 36 (52%) patients were female. The median estimated surface area of the VMs was 78 cm^2 (IQR 18-240, range 3.4-645 cm^2). The lesions were localised in the following anatomical regions: head and neck (n = 4, 6%), one arm (n = 15, 22%), one leg (n = 38, 55%), trunk (n = 4, 6%), and in more than one region (n = 8, 12%).

A total of 20 patients had a proven previous thrombotic event: 14 patients (20%) had superficial venous thrombosis and 6 patients (8.6%) had a documented venous thromboembolism (6 patients had deep vein thrombosis 1 of whom also had proven pulmonary embolism). The deep vein thrombosis had been located in the region of the VM in 4 of the 6 patients with previous deep vein thrombosis; in the remaining patients the location of the thrombus was not related to the VM.

Nine patients (13%) were using medicine that can affect coagulation: 7 NSAIDs, 1 aspirin and 1 a vitamin K antagonist (phenprocoumon). This last patient was excluded from analysis of the coagulation parameters. None of the patients reported major bleeding in their medical history.

A total of 63 patients (92%) reported intra-lesional pain and/or swelling of the VM. Frequency of the pain episodes ranged from daily (n = 12, 17%) to once a year (n = 3, 4.3%).

Table 1. *Clinical characteristics of the patients with venous malformations*

Characteristic	n = 69
Age in years, median (range)	30 (12-63)
Female, n (%)	36 (52)
Smoking, n (%)	16 (23)
Using anticoagulant medication, n (%)	1 (1.4)
Medical history	
Previous VTE	
• Isolated superficial vein thrombosis, n (%)	14 (20)
• Deep vein thrombosis, n (%)	6 (8.6)
• Pulmonary embolism, n (%)	1 (1.4)
Localisation of the VM	
• One upper limb, n (%)	15 (22)
• One lower limb, n (%)	38 (55)
• > 1 location, n (%)	8 (12)
• Trunk, n (%)	4 (5.7)
• Head, n (%)	4 (5.7)
Surface area, cm^2, median (IQR),	78 (23-242)
Depth, cm, median (IQR), n = 46	3.3 (1.9-3.8)
Available MRI, n (%)	63 (90)
Risk factors for venous thrombosis	
Immobilisation, n (%)	0 (0)
Recent surgery (< 3 months), n (%)	4 (5.8)
Oral contraceptives, n (%)	12 (17)
Pregnancy, n (%)	0 (0)
Known active malignancy, n (%)	0 (0)

IQR = interquartile range, MRI = magnetic resonance imaging, N = number, VM = venous malformation, VTE = venous thromboembolism.

In 78% of the cases, the pain was provoked by physical activity, pressure on the VM, change in temperature, stress or a combination of these factors. None of the patients had symptoms of thrombosis at the time of inclusion, although 40% of the included patients reported their usual, mild chronic pain. The mean and the median intensity of the pain were 1.7 and 0 (scale 0-10) respectively. The surface area of the VM was not related to the severity or frequency of localised pain, neither was the pain correlated to superficial or deep vein thrombosis or a thrombotic event in the past.

Compression ultrasound

A total of 68 out of 69 patients had a CUS result; 1 patient was not able to undergo CUS, because he fainted during blood sampling. Of the 68 remaining patients, 1 patient was using anticoagulant therapy for only a short period. This patient had twice had a deep vein thrombosis; we therefore did not exclude this patient from the CUS analysis. In these 68 patients, superficial vein thrombosis was observed in 10 (15%) cases, in 1 patient an older previously unknown muscle vein thrombosis was found and in another patient asymptomatic deep vein thrombosis was diagnosed (*table 2*). None of the patients with thrombosis, deep vein or superficial, had undergone recent surgery.

Residual thrombosis was observed in 16 patients (24%). In 9 of the 20 patients with a history of a thrombotic event, a residual thrombosis was seen with CUS (*table 2*).

Of the 48 patients with no history of thrombosis, 7 patients had current thrombosis and 7 patients had residual thrombosis on CUS (*table 2*). Hence, in total 29% (14/48) patients either had asymptomatic thrombosis or residual thrombosis on CUS or an older thrombosis which had not been recognised as such by either the patient or physician. None of the patients with thrombosis or residual thrombosis used anticoagulation therapy and 1 of these patients had undergone surgery within the last three months.

When combining the results of medical history and CUS, 34 out of 69 patients (49%) had either a history or current signs of a thrombotic event: 20 patients had a medical history of documented superficial or venous thromboembolism (6 patients with deep vein thrombosis, 1 of whom had documented pulmonary embolism), and 14 patients without a history of thrombosis had current thrombosis or residual thrombosis on CUS. In total, 7 patients in the study population (10%) had venous thromboembolism either in their medical history or at the moment of CUS examination (*table 2*). No relation was found between the size or location of VM and the presence or history of superficial vein thrombosis or venous thromboembolism.

Coagulation parameters

The levels of the coagulation parameters of 67 of the 69 included patients are listed in *table 3*: 1 patient was using phenprocoumon and 1 patient had no CUS result. In order to evaluate whether coagulation parameters differed between patients with and without current thrombosis, patients were categorised by CUS results showing thrombosis (n = 11) or no thrombosis (n = 56) on CUS, regardless the presence of residual thrombosis or whether the thrombosis was deep or superficial.

Median D-dimer level was 0.57 mg/l (IQR 0.3-1.2, range 0.17-16.1). A total of 37 patients (51%) had a D-dimer level above 0.5 mg/l, the usual cut-off level to exclude thrombosis in combination with a clinical decision rule in patients younger than 50 years.[9] Patients with a superficial vein thrombosis or deep vein thrombosis on CUS had similar median D-dimer levels compared with those without, 0.57 versus 0.55 respectively (p = 0.64). The D-dimer levels above the 75th percentile ranged from 1.2-16.1 µg/l. We found a clear association between

Table 2. *Results of the compression ultrasound, categorised by patients with a thrombotic event in medical history*

CUS result	Total n = 68	No thrombotic events in history (n = 48)	Thrombotic events in history (n = 20)	
			Isolated SVT (n = 14)	VTE (n = 6)
SVT	10*	6	1	3*
DVT	1	1	0	0
Residual thrombus	16*	7	6	3*
Total of any thrombus	**25***	**14**	**7**	**4***
No abnormalities	**43**	**34**	**7**	**2**

*Two patients had both current and signs of residual thrombi.
CUS = compression ultrasound, DVT = deep venous thromboembolism, N = number, SVT = superficial venous thrombosis, VTE = venous thromboembolism.

D-dimer levels and extent of the VM (Spearman's r = 0.50, p < 0.0001). Median P-selectin level was 29 ng/ml (IQR 21.5-34.0). Patients with a history of either superficial or venous thromboembolism had a significantly higher median P-selectin level compared with patients with no history of thrombosis (34 ng/l versus 25 ng/l, p < 0.001), whereas the mean age in both groups was comparable (32 years, p = 0.9). A significant correlation was also observed between the surface area of the VM and the level of P-selectin (Spearman's r = 0.53, p < 0.0001). However, the P-selectin levels in the group of VM patients with thrombosis observed on CUS were comparable to those without thrombosis on CUS (p = 0.27) (*table 3*). The median plasma Von Willebrand antigen level was in the middle of the normal range, and the number of patients with a level below 50% was 3 with a median Von Willebrand antigen of 43% (range 29-45).

Because to our knowledge the influence of residual thrombosis on coagulation parameters is uncertain, we additionally categorised patients into neither current thrombi nor residual thrombosis (n = 42) and patients with current and/or signs of residual thrombosis (n = 25). This categorisation gave comparable results for the median D-dimer and Von Willebrand antigen level (*table 3*). However, median (IQR) P-selectin levels were significantly higher in patients with a residual, superficial vein thrombosis or deep vein thrombosis on CUS 32 ng/ml (24-48) versus 26 (20-33) in patients with no thrombosis (p = 0.03).

DISCUSSION

In this cohort of patients with pure VM we observed that almost half of the patients had either a history of thrombosis or current signs of a thrombotic event, including superficial vein thrombosis and deep venous thromboembolism. Furthermore, in patients without a thrombotic event in their medical history, CUS showed the presence of thrombosis or residual thrombosis on CUS in 14/48 (29%), which may indicate that many thrombotic events happen asymptomatically.

This number of patients with asymptomatic events is higher than the 5.5% (95% confidence interval, 3.1-9.5%) in the normal population.[10] Also the number of previous or current venous thromboembolisms (7/69, 10%) is higher than what may be expected for a cohort of patients with a median age of 30 years. In the normal population the

Table 3. *Results of markers of coagulation activation, classified by patients with or without current thrombi in the VM observed by CUS and by patients with or without current thrombi and/or signs of residual thrombi in the VM, observed by CUS*

	Total (n = 67)*	No thrombi in the VM (n = 56)	Thrombi in the VM (n = 11)	P-value	No thrombi or signs of residual thrombi in the VM (n = 42)	Thrombi or signs of residual thrombi the VM (n = 25)	P-value
Age, median (range)	29 (12-63)	29 (12-63)	30 (12-61)	0.8	30 (13-63)	29 (12-63)	0.2
Female, n (%)	35 (52)	28 (50)	7 (64)	0.4	20 (48)	15 (60)	0.1
History of SVT/ DVT n (%)	19 (28)	14 (25)	5 (46)	0.3	7 (17)	12 (48)	0.008
PT (sec), median (IQR)	11.0 (10.8-11.7)	11.0 (10.7-11.7)	11.5 (11.0-11.9)	0.3	11.0 (10.7-11.6)	11.0 (10.9-12.1)	0.2
APTT (sec), median (IQR)	30.7 (29.1-32.5)	30.7 (29.3-32.4)	31.0 (28.9-35.5)	0.3	30.9 (30.0-31.8)	30.3 (28.4-33.0)	0.9
D-dimer (mg/l), median (IQR)	0.57 (0.30-1.2)	0.56 (0.31-1.1)	0.57 (0.30-1.4)	0.8	0.45 (0.30-1.0)	0.63 (0.39-1.4)	0.2
P-selectin (ng/ml), median (IQR)	29 (22-34)	28 (22-34)	33 (19-47)	0.3	26 (20-33)	32.0 (24-475)	0.03
Von Willebrand factor (%), median (IQR)	108 (84-132)	109 (85-133)	92 (66-142)	0.2	109 (84-131)	105 (83-138)	0.8

APTT = activated partial thromboplastin time, CUS = compression ultrasound, DVT = deep venous thromboembolism, N = number, SVT = superficial venous thromboembolism, IQR = interquartile range, PT = prothrombin time, VM = venous malformation.
*Two out of 69 patients were excluded for this analysis: in 1 patient a CUS result was lacking and one patient was using a vitamin K antagonist.

incidence rate of venous thromboembolism is 0.005% in childhood to nearly 0.5-0.4% in patients aged 60-64 years.[11,12] The number of patients with any superficial vein thrombosis was also much higher. This is relevant since superficial vein thrombosis may extend and progress to deep vein thrombosis.[13] The median D-dimer level was higher than 0.5 mg/l, the usual cut-off value to exclude thrombosis in the normal population younger than 50 years,[9] while some patients had very high levels. We only had a few patients with a low Von Willebrand factor. Finally, D-dimer values and P-selectin were clearly related to the extent of the VMs, suggesting the bigger the VM, the more coagulable.

Until now, only a few studies have addressed the coagulation parameters of patients with pure VM. The D-dimer level in patients with pure VM was investigated in two studies[14,15] and the rates of a D-dimer level higher than 0.5 mg/ were 43% and 58%, respectively, which is comparable with the rate of 53% in our study. Oduber and colleagues[16] quantified the frequency of venous thromboembolism in a cohort of 75 patients with Klippel-Trenaunay syndrome (median age 24) with CUS. Additionally, they performed a case-control study to evaluate whether coagulation alterations were related to venous thromboembolism and magnitude of VMs. A total of 29 (39%) patients had signs of current or previous venous thromboembolism, including superficial venous thrombosis, and 6 (8%) had ever had venous thromboembolism, comparable with our cohort of pure VM. Compared with the age-matched controls (n = 105, median age 33 years) D-dimer levels were also higher: 0.46 mg/l (IQR 0.27-3.84) versus 0.27 mg/l (IQR 0.20-0.36) and comparable with our median of 0.54 mg/l. The extent of the vascular malformations on MRI was, similar to our results, positively correlated with D-dimer plasma levels ($r = 0.33$; $p < 0.05$). Other studies have demonstrated that high plasma levels of soluble P-selectin are strongly associated with venous thromboembolism.[17-20] In our cohort, P-selectin levels were higher in patients with thrombi compared with patients with no thrombi in their VM; nevertheless, this difference did not reach significance. The shift towards significance in patients with thrombosis or residual thrombosis versus patients with no thrombosis is probably due to power. The patient with current deep vein thrombosis observed on CUS, however, had a high P-selectin level of 57 ng/ml, suggesting that platelet activation in VM only occurs in case of deep venous or superficial thrombosis.

Some aspects of the study require comment. First, we did not perform MRI in this study and we could only determine the size of the VM and the tissue types involved of the 63 patients (91%) who underwent an MRI for clinical reasons before inclusion. Second, we did not recruit a matched control group of patients without VM, Klippel-Trenaunay syndrome or thrombosis to compare our results with. However, the laboratory results may be compared with the results of Oduber and colleagues,[16] since they used a control group which was comparable to our cohort and used similar laboratory assays. Furthermore, due to practical issues, we did not standardly perform CUS of all limbs irrespective of the location of the VM. Consequently, we may have even underestimated the number of asymptomatic thrombotic events. Moreover, patients were asked to participate after their elective visit to the plastic surgery outpatient clinic, regardless of their current complaints. We did not, however, report an exclusion list of patients who were not able to participate, which may have masked an inclusion bias. Also, our results should be interpreted with caution because of the moderate sample size. Last, the distinction between thrombosis and residual thrombosis is arbitrary. The definition of residual thrombosis, made by Prandoni et al.[8] was in patients with proven deep vein thrombosis in contrast to our cross-sectional design in a high-risk group for thrombosis. However, we think this distinction makes our interpretation a more accurate reflection of clinical practice, because residual and fresh thrombi have a different appearance on CUS. Because of this arbitrary distinction, we have shown all the data. We consider that this is more complete than only reporting the new thrombi. When we performed analyses including and excluding residual thrombosis our main findings did not change. However, this arbitrary distinction makes our results less generalisable. And, although the interobserver concordance rate of residual vein thrombosis on CUS is high ($\kappa = 0.92$),[21] the interobserver reliability in the measurement of residual thrombosis in VMs is unknown.

In conclusion, superficial vein thrombosis and venous thromboembolism are common in this cohort of apparently healthy and young patients with pure VM and a significant proportion of these patients have high D-dimer levels. Treating physicians should be aware of this, especially in those pure VM patients with exposure to risk factors for venous thromboembolism.

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DISCLOSURES

There are no conflicts of interests to disclose.

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ORIGINAL ARTICLE

Improving care for older patients in the acute setting: a qualitative study with healthcare providers

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ABSTRACT

Background: The proportion of older people needing acute care is rapidly growing, thereby posing an increased burden on the acute care chain. The aim of this study is to gain more insight into the obstacles and potential improvement opportunities of the acute care process for older patients arriving at the hospital.

Methods: Semi-structured interviews were conducted to determine the experiences of 18 different primary (i.e. general practitioner, community nurse) and secondary healthcare professionals (i.e. emergency department (ED) nurse, ED physician, geriatric physician, geriatric nurse, ambulance nurse, acute medical unit nurse), and three experts (2 researchers, 1 older adult advisor).

Results: Four core themes emerged from the interviews: 1) The concept of frailty, awareness concerning frail older patients, and identification of frailty, 2) Barriers in the care process of older patients within the acute care chain, 3) Optimising the discharge process of older patients, and 4) Improvement opportunities suggested by the respondents. Early identification of frailty, improving the continuity of care by means of structured information exchange between care providers in the acute care chain, and a more generalist approach were considered important by the respondents in order to deliver appropriate care to older patients.

Conclusion: This explorative study identified several barriers and improvement opportunities which are important to improve the quality, efficacy and appropriateness of the acute care of older patients. More seems needed in the future in order to share experiences, expertise and develop potential improvement strategies for the acute care of older patients.

KEYWORDS

Older patients, frailty, qualitative research, caregiver experience, acute care, emergency department, quality of care

INTRODUCTION

Older patients represent an increasing proportion of emergency department (ED) admissions.[1] Of the 90 EDs in the Netherlands, 75% report a structural increase in the admission of older patients.[2]

The increase in hospital admissions of older patients is a complex and challenging issue.[3] Originally the EDs were designed and organised to treat and care for patients with a single acute illness. However, a large proportion of older patients suffer from multiple chronic diseases.[1,4-6] In addition, the early identification of frail older patients as part of standard of care appears to be difficult in an emergency setting due to the hectic work environment,[7] while this is thought to be essential to optimise the care provision for these patients.[7-10]

Frailty can be defined as the inability to withstand illness (or a stressor event) without loss of function or a loss of functional homeostasis.[11,12] It is a dynamic state affecting

Table 1. *Characteristics of the respondents*

Respondent #	Gender	Job title
1	M	Older adult advisor
2	M	General practitioner
3	F	Geriatric specialist
4	M	Ambulance nurse
5	F	Geriatric nurse
6	F	Researcher
7	M	Ambulance nurse
8	F	ED physician
9	M	Geriatric specialist
10	M	Acute medical unit nurse
11	F	Community home care nurse
12	M	ED nurse
13	F	Geriatric specialist
14	F	Geriatric specialist
15	F	ED physician
16	M	Acute medical unit staff member
17	F	Trauma surgeon
18	F	Geriatric specialist
19	F	Researcher
20	M	Acute medical unit nurse
21	M	General practitioner

an individual who experiences losses in one or more domains of human functioning (physical, psychological, social).[13] Older patients who are frail do not cope well with change and disruptions,[14] thereby increasing their risk of developing adverse events, dependence, morbidity, relapse, entry into a nursing home, or death.[1,4,15,16] As a reaction to this, frailty instruments such as the Clinical Frailty Scale (CFS) and the Identification of Seniors at Risk (ISAR) score have been developed to determine existing geriatric vulnerabilities, such as functional and cognitive impairment.[16] However, neither of these tools seem suitable to identify high-risk patients in an acute setting.[17,18]

Another issue while treating older patients is that they often receive care from multiple healthcare professionals from inside and outside the hospital, leading to a fragmentation of care and inefficiency in the acute care chain between the general practitioner, homecare, ambulance services, and the EDs and Acute Medical Units (AMUs) in the hospital. This increases suboptimal communication, the chance of errors, and delay in diagnosis and treatment.[10] In contrast to elective care, there is also a scarcity of interventions (i.e. organisational, patient and next of kin-orientated, and professional-orientated interventions) which are developed and feasible for use in acute care.[19] The reasons for this seem to be the focus on acute care, time pressures, and lack of resources.[1] Hence, it seems there is no unambiguous answer on how to improve the acute care of older patients. The aim of this study is to start by involving the perspectives of healthcare professionals and other experts working in the acute care chain to gain more insight into the barriers and potential improvement opportunities of the different aspects of acute care. The main focus of the study will be on healthcare professionals working in secondary care who are involved in the triage process, the care process, and the discharge process of older patients.[20] These insights may add to the knowledge needed to optimise or develop interventions that can help frail older patients with the transition of care and provide simple and time-saving tools which can support caregivers on the work floor.[21]

METHODS

Research setting and design

Twenty-two semi-structured interviews were conducted between March 2016 and May 2016 with healthcare professionals working in the acute care chain. We also included individuals who are experts on the topic of frailty and ageing in order to obtain a better understanding of current research and activities that are already being conducted to improve the acute care of older patients. Since the main focus was on secondary care, the majority of the interviews were conducted at the EDs of two hospitals in Amsterdam: an urban academic hospital with a level 1 trauma centre and a tertiary teaching hospital. However, as many older patients are referred to the ED by their general practitioner or arrive at the ED by ambulance also these primary healthcare professionals were invited to participate. In addition, a representative of a large community home care organisation in Amsterdam was approached for participation to gain more information on the discharge process from the hospital to home.

The academic hospital has a capacity of 733 beds, with approximately 55,000 hospital admissions each year and 31,000 ED visits a year. The tertiary teaching hospital has a capacity of 921 beds, with approximately 46,000 hospital admissions each year, and approximately 75,000 ED visits a year. The acute care of the academic hospital includes the ED and the acute medical unit.

Participant selection

A brainstorm session was used to compose an inventory list of healthcare professionals and experts who would

be eligible for participation. The different healthcare professionals and experts were contacted by mail or telephone to explain the goal of the project and to invite them to participate in the interview. All healthcare professionals and experts who were contacted agreed to take part in the study. Eighteen respondents were healthcare professionals working in primary (2 general practitioners, 1 community nurse) or secondary care (1 ED nurse, 2 ED physicians, 1 trauma surgeon, 5 geriatric physicians, 1 geriatric nurse, 2 ambulance nurses, 2 AMU nurses, 1 AMU physician). Three other respondents were experts working in the field of ageing, gerontology and geriatrics (2 researchers), one of whom participated in the organisation of activities and services dedicated to the Senior Friendly Hospital program (older adult advisor). Of the 21 respondents, two respondents were working in the tertiary teaching hospital. Upon agreement to participate, the researcher scheduled the date and location for the interview. The aim was to enrol enough healthcare professionals from secondary care to achieve data saturation.[22] Data saturation was not achieved for the experts and the primary care providers due to the low number of respondents. The gender, job title and workplace of the respondents can be found in *table 1*.

Data collection

To gain insight into the experience of the respondents concerning the care of frail older patients a topic list was constructed for the interviews using recent literature regarding challenges in the delivery of acute care to older patients and interventions to improve the care of older patients (see *Appendix*). In addition, respondents were asked if they had any suggestions for improvement in the care of frail older patients. All the questions were open ended to enable the respondents to express their experiences and perspectives freely and in their own words. The interviews lasted 20 to 60 minutes (mean = 37 minutes). After obtaining the respondent's consent, the interviews were audio-recorded and transcribed verbatim with support of the software program MAXQDA® 12 (VERBI software GmBH, Germany).

Data analysis

A thematic analysis was conducted in order to systematically pinpoint, examine, and record patterns (or 'themes') within the data. Thematic analysis is performed through the process of coding in six phases to create established, meaningful patterns. These phases are: familiarisation with data, generating initial codes, searching for themes among codes, reviewing themes, defining and naming themes, and producing the final report.[23] To increase the reliability of the coding process, triangulation was used. Two researchers read, reread and coded two interviews individually (double-check) (DH and CB). The defining and naming of the codes were discussed by the researchers and an advisor from the acute care network, after conducting the first five interviews and after conducting all the interviews, until consensus was achieved (DH, CB, TW and HM). Eventually all codes were clustered together into main themes.

RESULTS

The following main themes were identified based on the data: 1) The concept of frailty, awareness concerning frail older patients, and identification of frailty, 2) Barriers in the care process of older patients within the acute care chain, 3) Optimising the discharge process of older patients, and 4) Improvement opportunities suggested by the respondents. The themes are illustrated by quotes that were translated into English.

Concept of frailty, awareness concerning frail older patients and identification of frailty

All respondents were positive about the fact that there has lately been an increased focus and awareness on improving the care of frail older patients. This focus, in their opinion, had been insufficient in the past.

'Yes it is very positive, but I think the level of awareness is still too low. I notice that we struggle to improve this issue [....]. We know it is a must, but the older patient is still bogged down in daily practice.' (R17, Trauma surgeon)

A large number of respondents stated that the identification of frailty is a major problem in the care of older patients. However, there was no consensus between respondents on the best way of identifying frailty. Some recommended the use of screening tools which are provided by the national improvement program for hospitals, or physical strength tests. Other respondents mentioned that in everyday practice they solely use their clinical acuity and intuition.

'You use a different way of observing older patients. You look at the 'normal' patient history but you should also use a broader perspective. So you really need more tools to identify older frail people. It is less straightforward compared with the care of younger patients.' (R13 Head of Geriatric Unit, Geriatric specialist, Academic Hospital)

Additionally, respondents mentioned different aspects of the term 'frailty'. The four domains represented in the literature – physical, mental, social and cognition – were mentioned independently of each other. Respondents indicated that frailty was a difficult concept to explain due to the fact that the different aspects of frailty are

interconnected. A few respondents mentioned all four domains. The domain 'physical' was mentioned by most respondents as an important aspect of frailty, in particular problems concerning comorbidity, but also aspects such as the risk of falling, level of mobility and the ability to take part in a conversation were mentioned.
The second main aspect of frailty commented on by many respondents is the social aspect. The living situation of older people: whether they live alone and whether they have a strong social network has a strong effect on frailty. Besides the social network, also the socioeconomic status is mentioned by respondents, whereby a higher socioeconomic status has a direct influence on the capability to organise care. Cognition was mentioned by a few respondents, while cognition is known to be associated with medication compliance and self-management.[24] The mental aspect of frailty was also mentioned by some of the respondents as a factor that influences frailty. These respondents described the mental aspect of frailty as the perceived willpower and drive to live.

'Yes, it is always very difficult, because frailty is a very broad concept. I think an older person is frail when there are deficiencies on multiple domains: physical, mental, social, functional. And even if you are so physically ill, you may not be frail when you are functioning well in the other domains. Frail people often have problems on multiple domains.' (R13, Head of Geriatric Unit, Geriatric specialist, Academic Hospital)

Barriers in the care process of older patients within the acute care chain

Most respondents mentioned that they experienced differences in the care process between older patients and other patients. This difference was due to an increased focus on polypharmacy, drug rehabilitation, and challenges related to communication when treating older patients.

Communication barriers: 'There are doctors who talk too fast, talk too loud, have a poor articulation, and who use difficult words. Well those are a few factors that are not really adapted to older patients.' (R1, Advisor for older patients)

Communication barriers: 'When I look at the interns and residents I get shivers down my spine. Once they recognise frailty, they set a tone of 'well sir…'. A person may be delirious or may not understand everything, but they do not like the patronising way physicians speak. […] If someone has dementia, I still think the communication should be in a mature manner. There is a lot to gain by involving older people in the right way.' (R9, Geriatric specialist)

Communication barriers: 'Yes, I notice that older people want paternalism, where the doctor makes all the decisions. Young people are often more critical concerning their care. For older people this could be a pitfall, because older people are afraid to speak out if they have doubts about something…. (R19, Researcher)

The bottlenecks mentioned were mostly capacity problems of the acute care chain, staff limitations and capacity, challenges related to the continuity of care, a lack of facilities suited to older patients, and the lack of a generalist approach. Due to staff limitations, it is not always possible to ask a geriatric specialist for a consult at the ED, which is sometimes preferred when there is a suspicion of malnutrition, delirium or an increased fall risk. A few respondents also commented that there are differences in the quality of care throughout the week due to the limited availability of experienced professionals during non-office hours. Four respondents mentioned the lack of facilities for older patients with impaired mobility or cognitive capacity. These patients could benefit from adjusted toilets, private examining rooms and special patient leaflets. The lack of a generalist approach results in an accumulation of consultations by different specialists which can lead to incorrect or incomplete information in the patient record, for example about the choice of treatment or whether to treat or not.

Capacity problems: 'The number of patients arriving at the ED is sometimes so large that we reach our maximum capacity. And sometimes we must refuse an older patient, which means that the older patient must go to another hospital. Well that can also be a risk, the other hospital is not quite familiar with the patient. The transfer to the other hospital, in itself, may also not always be beneficial for the patient. The whole region struggles with this, certainly in the winter months.' (R8, ED staff member, Academic Hospital)

Continuity of care: '….Most patients arrive at the ED during office hours, but for those patients arriving in the evening or in the weekend it is very difficult to arrange aftercare. I think the contact with the primary caregivers in the weekend and evening is completely disconnected. Or the contact is very one sided. […].' (R17, Trauma surgeon)

The need for information and tools for treating older patients: 'Especially when we realise that 25% of the ambulance rides concerns geriatric patients, it would be useful to have a protocol or, at least, alarm signals, key features, small interventions, what are you supposed to do or not to do.' (R15, Medical manager ambulance, ED specialist, Peripheral Hospital)

Only two respondents, the advisor of older patients in the academic hospital and the geriatric specialist, mentioned the social aspect as a very important aspect in the care process. The advisor of older patients also mentioned the

attention of care providers for the human element in the care process.

'If you are an older person, then who is caring for the plants? That is very important for an older patient,... or who takes care of the dog or cat. If there is interest for these things, then the human aspect is emphasised. The human aspect, such as family, animals, plants, is important to consider in the care process. Not only if you have taken your medication.' (R1, Advisor for older patients, Academic Hospital)

Optimising the discharge process for older patients

The respondents mentioned several elements they considered important in the discharge process of older patients. Two respondents commented that involving a transfer nurse in the discharge process was imperative for a smooth transition from hospital back home or to a nursing home. The majority of respondents also mentioned the importance of obtaining an overview of the home situation of the older patient before discharge. A few respondents emphasised the importance of a standardised discharge process since, in the current situation, there is often too little time for an extensive discharge conversation and the discharge letter is often delayed or incomplete, especially with respect to contextual and personal information.

'Especially the communication, the anticipation, the available time for discharge and how to discharge, these parts should be improved.' (R16, Medical manager AMU, internist, Academic Hospital)

Many respondents mentioned a lack of agreement between the primary and secondary care providers concerning the responsibility for initiating contact. Arranging the transfer of patients is also experienced as a laborious undertaking, for example because the accessibility of rehabilitation centres is problematic and because of the complex paper-based process. As a result, patients often have to stay longer in the hospital than desired while they are not in need of medical treatment.

'The AMU is also an "extension tube". This entails that there are people in the hospital who could be discharged but for whom there is no room available in a rehabilitation centre and nursing home. That I think is also a concern.' (R10, Nursing head of AMU, nurse, Academic Hospital).

'Well I have to say honestly, when an older patient has to be admitted to the hospital, I am also not the first to contact the secondary care providers to say that I changed the medication yesterday. Let me be honest, I can improve on this. Although I think secondary care has to improve more than we do. This is due to the role distribution. The general practitioner should get the central role, but that only works if everyone is reporting back. (R21, General practitioner)

Improvement opportunities suggested by the respondents

During the interviews several interventions were mentioned which could potentially improve the care of older patients. In order to achieve a more holistic approach and thereby improve the care of older patients, respondents argued that regular consultations with geriatric specialists could be beneficial. Also the stimulation of interdisciplinary teamwork between departments which have a high number of frail older patients such as neurology, internal medicine, traumatology, orthopaedics and the AMU was mentioned as a possibility to increase the efficiency and quality of care. The ambulance personnel mentioned the implementation of a special protocol for older patients who are transported by ambulance. While there are special protocols for children there is no protocol or guideline for older patients. The respondents also argued that it would be helpful if older patients were to carry some kind of 'medical passport' in which essential information about their health is documented, such as medication, allergies, hearing, walking and visual aids, and advance directives).

To improve the communication and information between primary and secondary care, respondents mentioned that, especially during the weekends, the preferred contact options (phone/fax) between the ED, the general practitioner and home care about follow-up care should be more transparent and easily available. Another respondent suggested the use of the SBAR (Situation, Background, Assessment and Recommendations) technique[25] to streamline information and improve the communication and collaboration between care providers in primary and secondary care. The discharge letter also plays an important role in the information exchange between care providers. Currently, respondents argue that the discharge letter is often incomplete or sent out too late which can lead to delay in follow-up.

Finally, in relation to the communication between older patients and care providers, a few of the respondents suggested that a consult by phone with the patient after discharge could be an effective way to provide aftercare while simultaneously creating the opportunity to check whether the patient has understood all the information given during discharge (i.e. follow-up appointments, medication changes, changes in home care, provide contact details in case of questions after discharge, and points of attention when arriving at home).

DISCUSSION

An important conclusion emerging from this study is that despite the many challenges faced by the different healthcare professionals when treating older patients there is a lot of common ground which offers the opportunity to work together on improving acute care for frail older patients. Based on the interviews, four aspects could be identified within the themes which are critical for improving the acute care of older patients in the hospital, namely: early identification of frailty, optimising the continuity of care, structured information exchange between care providers in the acute care chain, and a more generalist and holistic approach. Since this study has an explorative design the improvements suggested are not evidence-based but based on the opinion of the healthcare professionals and experts. Despite this fact we would like to compare our findings with the existing literature.

There is general consensus that the currently used models of emergency care units (disease-oriented instead of patient-oriented) do not adequately respond to the complex and changing care needs of older patients.[26,27] The lack of a generalist and holistic approach in the acute care chain is in concordance with the literature and can lead to a significant delay in the process of decision making, resulting in a prolonged ED stay and undertriage, especially in vulnerable and older (> 65 years) patients.[28,29] The Royal College of Physicians recommended that hospitals will need more generalists and fewer specialists in acute inpatient care in order to deal with patients with multiple chronic diseases.[30] This will create a team of clinicians who will promote timely, holistic and integrated hospital care. Especially the holistic aspect of care was considered to be important by the geriatric physicians and older adult advisor. They argued that in acute care, the human element of care is often missing, while this is very important for older patients who are often anxious and have difficulty understanding all the information. Hence, there seems a lot to gain by optimising the communication and care towards older patients, as healthcare professionals tend to be too paternalistic or patronising when caring for older patients.

To improve the information exchange there is a need for more uniformity and structure. The SBAR technique, which was also suggested by one of the respondents, has proven to be beneficial in improving the standardisation of communication in several studies conducted in hospitals and rehabilitation centres.[25,31-33] Respondents reported that they need a truly collaborative team environment to improve the information transfer, but also training to obtain the right skills. This finding is in line with other studies that underline the importance of teamwork and communication in providing safe care.[34,35] This has resulted in an increase in the use of, for example, crew resource management training to train healthcare professionals in non-technical skills,[36] but also in the introduction of 'transition coaches' who can help streamline the information exchange between primary and secondary care.[37,38]

Regarding the identification of frailty, many of the healthcare professionals mentioned the need for interventions which increase awareness and knowledge regarding the identification of frail older patients. Evidence confirms that increased knowledge and awareness by healthcare professionals is a prerequisite to achieve a change in a working routine, such as making the identification of frailty a routine care step at the ED.[34,39-41] In some cases it seems a geriatric specialists can help in improving the knowledge of the ED staff concerning the identification of frailty. Also, developing easy-to-use standardised geriatric assessments tools, such as the frailty index, questionnaires or indicators, for the identification of frailty in an acute care setting could potentially be beneficial.[21] A recent study showed that directly available clinical data describing disease severity and geriatric vulnerability can be used for prediction in hospitalised older patients,[42] and that a combined outcome measure can successfully predict 90-day composite outcome and 90-day mortality in older emergency patients.[42] In addition, the use of broad multidisciplinary teams to assess, organise and coordinate the care of older patient groups (referred to as comprehensive geriatric assessment) are being used for the identification of frailty in hospital EDs worldwide.[10]

Strengths and limitations

Some strengths and limitations need to be addressed. First, a strength of this study is that we included many different healthcare professionals and experts working in acute care. Secondly, the qualitative approach of this study offers a perspective of the respondents' behaviour, needs, and desires. This study also has some limitations. First, the diversity and full scope of the acute care chain might not be perfectly reflected, since only three respondents were working in primary care, and the respondents working in secondary care were almost all from the same hospital. In the Netherlands there is a considerable difference in the hospital population of an academic hospital and peripheral hospital. Peripheral hospitals in rural settings often have more direct communication with primary care organisations, which makes it easier to communicate and organise appropriate care for older patients.[43] Secondly, translation of the quotes from Dutch to English may have affected the context and meaning of the quotes. Hence, this exploratory study with in-depth interviews on the acute care chain for frail older patients should be replicated in other districts in the Netherlands to see if there are differences in findings.

CONCLUSION

Early identification of frailty, improving continuity of care by means of structured information exchange between care providers, and a more generalist care approach were identified as the most important improvement opportunities in the acute care of older patients. More collaboration seems to be needed in the future in order to share experiences, expertise and develop potential improvement strategies for the acute care of older patients.

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DISCLOSURES

All respondents provided consent to participate prior to the start of the interview. Ethics approval by an ethics committee was not applicable.
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All data are available from authors upon request.

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APPENDIX

Topic list

Topic	Optional questions
Introduction	• Explain purpose of interview • Provide estimate regarding the duration of the interview • Provide information regarding the transcription process and anonymisation of the data
Get acquainted with the respondent	• What is your function? • Can you tell me something about your work experience? • How much contact do you have with older patients during your work? • Do you consider the increasing number of older patients visiting the ED as a major healthcare problem? If yes/no, why?
Frailty	• What does frailty mean to you? • What makes older patients frail? • What do you do to recognise frailty in daily practice? • Do you think it is important to identify frailty? • Which barriers do you perceive in the process of identifying frailty?
Care process and continuity of care	• Are there differences in the care process between older patients and other patients? • What do you believe are specific care needs for older patients? • How do you adapt to these needs? • How do you deal with medication-related issues, delirium, nutritional status in older patients? • What is going well in the care process of older patients? • Where in the care process can there be improvement? • Do you experience a difference in the care process in the weekends vs. working days?
Information provision towards older patients	• How is the information provision organised for older patients? • What is going well? • What could be improved?
Communication in the acute care chain	Specific questions per respondent: *ED* • How is the transfer of older patients arranged after discharge from the ED? • How good is the communication between the ED and the transfer unit? • To what degree do you think you are responsible for the transfer of information between primary and secondary care and improving this communication? *Pharmacist* • How is transfer of information arranged between the local pharmacy and the hospital pharmacy? And between the hospital pharmacy and other care professionals in primary care? *GP* • Do you get notified if one of your patients is hospitalised? If yes, by whom? • What kind of support or information do you need to improve the detection and care of older patients? • To what degree do you think you are responsible for the transfer of information between primary and secondary care and improving this communication? *Homecare* • How satisfied are you with the communication between homecare and the ED and GP? What do you think could be improved?
Existing interventions for improving the care of older patients	• Are you familiar with interventions that can improve the care of older patients? If yes, what kind of interventions?

ORIGINAL ARTICLE

Prevalence of iron deficiency in a Dutch geriatric migrant population

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ABSTRACT

Background: The prevalence of iron deficiency anaemia (IDA) rises with age. Migrants are potentially at higher risk for IDA because of differences in intake and uptake as well as their higher comorbid status. We assessed whether geriatric Turkish and Moroccan migrants have a higher prevalence of low iron status and IDA.

Methods: Retrospective case-control study in a geriatric outpatient clinic (2012-2015). In total, 188 consecutive Turkish and Moroccan migrants aged ≥ 65 years were included and matched with 188 Dutch controls. Matching was based on the visiting date of the patients. Main outcome measures were serum ferritin level (below 15 µg/l) and IDA. IDA was defined as anaemia according to the WHO definition, with a serum ferritin level below 15 µg/l and serum CRP below 10 mg/l. Multivariate logistic regression was performed to correct for confounders.

Results: Mean serum ferritin level was significantly lower in migrants (83.46 µg/l, SD 106.8 vs. 164.94 µg/l, SD 160.1, ($p < 0.05$)). In total, 7.4% met the IDA criteria, of these 5.6% were migrants and 1.8% were Dutch ($p < 0.05$). After correction for age, gender, BMI, and use of NSAIDs, a low ferritin level was associated with migrant status (OR 3.0, 95% CI 1.0-8.9) as was IDA (OR 2.9, 95% CI 1.2-7.2).

Conclusion: Prevalence of low serum ferritin and IDA is increased in the first-generation Turkish and Moroccan geriatric migrant population. This might be caused by differences in iron intake or uptake from nutrition between the populations or because of gastrointestinal pathology; further study is warranted.

KEYWORDS

Ferritin, geriatric, iron deficiency anaemia, migrants

INTRODUCTION

In an older population, anaemia is a frequent finding. The prevalence of anaemia rises with age and is about 25% in persons aged ≥ 85 years.[1] This is of clinical relevance since, corrected for comorbidity, in elderly persons anaemia is associated with poor physical performance, hospital admissions, a diminished quality of life and mortality.[2,3] In patients > 65 years with anaemia, 36% is caused by iron deficiency.[4] Iron uptake can be insufficient as a consequence of dietary deficiency or an uptake problem such as coeliac disease. Another more frequent cause in the Western world is salient blood loss. In elderly patients, the blood loss mostly occurs within the gastrointestinal tract.[5] Causes are often non-malignant such as an erosive lesion or angiodysplasia of the colon. Nevertheless, 2-15% of elderly patients with IDA are diagnosed with colorectal cancer, and 2-6% are diagnosed with a malignancy of the upper gastrointestinal tract.[6] The diagnosis IDA affects both the morbidity and mortality of patients, while it might also have consequences for the diagnostic procedures. Since IDA is often caused by blood loss in the gastrointestinal tract, invasive diagnostic procedures such as gastroscopy or colonoscopy are regularly performed. Although it is important to exclude the possibility of a malignancy, the potential risks of such procedures, especially in the geriatric population, need to be taken into account.[5]

In the Netherlands, a growing part of the elderly population consists of first-generation migrants originating from Turkey and Morocco. Expectations are that the population with a Turkish and Moroccan background older than 65 years will grow from 32,345 in 2010 to 91,947 in 2030.[7,8] A study by the Netherlands Institute of Social Research showed that migrants from Morocco and Turkey aged > 65 years report more chronic diseases compared with the Dutch elderly, including diabetes mellitus, obesity, chronic obstructive pulmonary disease and cardiovascular

diseases.[7] Similarly to these chronic diseases, IDA might also have a higher prevalence in this population.
If there is a pre-existing higher prevalence of low ferritin levels and IDA in the Turkish and Moroccan migrant population, it is possible that the current diagnostic pathway is not the most favourable for this patient group. For the clinician, knowing that the migrant geriatric population on average has a lower ferritin level than the Dutch elderly could influence the decision to perform invasive diagnostic procedures. As it is not yet known to what extent low ferritin and IDA occur in the Turkish and Moroccan migrant population, we assessed this in a cohort of geriatric outpatients.

METHODS

Study population

Cases were defined as Turkish and Moroccan new referrals visiting the outpatient geriatric clinic of a Dutch teaching hospital in Amsterdam. The total study population was referred for combinations of cognitive and/or functional decline. All consecutive patients were screened for eligibility if they visited the outpatient clinic for the first time in the period from 01-01-2012 until 31-12-2015. Patients were excluded if they were < 65 years. The control group was matched 1:1 for visiting the geriatric outpatient clinic on the same or consecutive date of first visit as the study population. The control group was not age- or gender-matched. The controls were defined as new referrals of ≥ 65 years who were born in the Netherlands. This study was performed according to the ethical principles of the Declaration of Helsinki. The Medical Ethics Committee of the MC Slotervaart in Amsterdam, the Netherlands, waived the necessity of informed consent because of the observational design.

Design

This study was a retrospective case-control study. Socio-demographic, medication and laboratory data were collected from patient files. All included patients had visited the outpatient clinic and were subjected to a complete comprehensive geriatric assessment. The consultation with the migrant population was done in the presence of a professional interpreter.

Covariables

The sociodemographic information gathered from each patient included the following: age, gender, country of origin, body mass index (BMI) and Charlson Comorbidity Index (CCI).[9] Use of the following medications was determined from the medical files: vitamin K antagonist, platelet aggregation inhibitors, new oral anticoagulants (NOAC), iron supplementation and non-steroidal anti-inflammatory drugs (NSAIDs). The dosages were not specified. All indications and outcomes of the performed gastrointestinal diagnostic procedures, such as gastroscopies and colonoscopies, were reviewed. Finally, the following laboratory outcomes were routinely collected: leucocytes, C-reactive protein (CRP), creatinine, glomerular filtration rate (GFR), thyroid stimulating hormone (TSH), vitamin B12, and folic acid.

Primary and secondary outcome measures

Primary outcome was serum ferritin level. The level of serum ferritin is known to increase with age, therefore we used two different definitions for low ferritin level.[10] The first is the overall definition defined by the World Health Organisation (WHO), with a cut-off value of < 15 µg/l.[11] The second definition has a cut-off value of serum ferritin < 25 µg/l, which was suggested by Hamaker et al. as a more appropriate cut-off value for elderly patients.[6] In our study serum ferritin was assessed by electrochemiluminescence immunoassay (sandwich principle).[12]
Secondary outcome measure was IDA, which was defined as a haemoglobin level < 8.1 mmol/l for men and < 7.5 mmol/l for women, with a serum ferritin level < 15 µg/l and serum CRP < 10 mg/l.[13] The definition of anaemia was in accordance with that of the WHO.[14] Haemoglobin was established in the laboratory by spectrophotometry on automatised analysers after haemolysis of the erythrocytes.[12]
Another secondary outcome measure was the indications for and outcomes of performed gastrointestinal diagnostic procedures such as gastroscopies and colonoscopies.

Statistical analysis

Descriptive statistics were used for baseline characteristics of the cohort. For comparisons between participant groups, a chi-square test was used for nominal and ordinal variables. To establish whether continuous variables were normally distributed, a histogram was created. If the variates were not normally distributed, they were transformed with a log transformation. A Student's t-test was used for continuous variables with a normal distribution or transformed data, and a Mann-Whitney test was used for the analysis of estimated glomerular filtration rate. A p-value < 0.05 was considered statistically significant.
Subsequently, multivariate logistic regression was used to adjust for potential confounders. Covariates that changed point estimate more than 10% were added to the final model. The following covariates were considered for potential confounding: CCI, BMI, vitamin B12, folic acid, use of anticoagulants (platelet aggregation inhibitors and vitamin K antagonist), use of iron supplementation and use

of NSAIDs. All analysis was performed using SPSS version 22 (IBM, Chicago, IL).

RESULTS

Characteristics of the study population

In total, 188 cases and 188 controls were included. Among the 376 participants, 152 (40.4%) were male and 224 (59.6%) were female. Among the migrants, there were 86 (45.7%) Turks and 102 (54.3%) Moroccans. The mean age of the study population was 78.4 years (SD 7.4). The mean age of the migrant population was 73.9 years (SD 5.2), nearly 9 years younger compared with the Dutch population with a mean of 82.7 years (SD 6.6). The CCI showed an average of 2.43 points (SD 1.8) for the total study population. The difference in CCI between the migrant and Dutch population, 2.6 (SD 1.9) and 2.3 (SD 1.7) respectively, was not statistically significant ($p < 0.05$). The BMI for the migrant and Dutch population was 30.1 (SD 5.3) and 24.8 (SD 4.8) respectively ($p < 0.05$). Except for BMI (31.5 vs. 28.8 $p < 0.05$) no significant differences between Turkish and Moroccan elderly were found. Baseline characteristics are shown in *table 1*.

In total, ferritin samples were available for 368 (97.9%) patients. In the migrant population, the mean serum ferritin level proved significantly lower at 83.46 µg/l (SD 106.8), compared with 164.94 µg/l (SD 160.1) in the Dutch population ($p < 0.05$). When using the strictest definition of low ferritin (< 15 µg/l), there were 25 (6.6%) migrant and 9 (2.4%) Dutch patients with low ferritin; this was significantly different ($p < 0.05$). The elderly-specific definition of low ferritin (< 25 µg/l) resulted in 58 (15.4%) migrant and 17 (4.5%) Dutch patients who met the criteria for low ferritin; this was significantly different ($p < 0.05$).

In the total study population, 28 patients (7.4%) met the criteria of IDA. Of these patients, 21 (5.6%) were migrants and 7 (1.8%) were Dutch ($p < 0.05$). In total, 106 patients (28.2%) met the definition of anaemia, of these patients 60 (16%) were migrants and 46 (12.2%) were Dutch ($p = 0.109$) (*figure 1*).

Logistic regression analyses

In the univariate analyses, the risk of iron deficiency with ferritin levels < 15 µg/l had an odds ratio (OR) of 2.99 (95% CI 1.35-6.59) according to migrant status, with ferritin levels < 25 µg/l the OR was 4.40 (95% CI 2.44-7.92). The risk of iron deficiency anaemia in the univariate analyses had an OR of 3.22 (95% CI 1.33-7.76).

After correction for the BMI and use of NSAIDs the multivariate analyses remained significant, iron deficiency defined as ferritin levels < 15 µg/l had an OR of 3.00 (95% CI 1.01-8.97). Iron deficiency defined as ferritin levels < 25 µg/l had an OR of 3.92 (95% CI 2.15-7.13). In the multivariate analyses iron deficiency anaemia had an OR of 2.94 (95% CI 1.20-7.17). All the data of the multivariate analysis are shown in *table 2*.

Gastrointestinal diagnostics studies

In the migrant population 14% underwent endoscopic procedures compared with 5% of the Dutch population. Because of the small absolute number, no statistical analyses were performed. The data are shown in *table 3*.

DISCUSSION

This study shows that the mean serum ferritin level in the geriatric migrant population was significantly lower compared with the Dutch geriatric population. Consequently, the patients in the migrant population were significantly more often diagnosed with IDA. The multivariate analyses showed that the migrant population had an increased risk of developing iron deficiency anaemia with an OR of 2.9.

To our knowledge this is the first study addressing the prevalence of IDA in migrant populations. As such, the potential underlying cause of the significantly lower mean serum ferritin levels and the higher prevalence of IDA in the migrant population has not yet been studied. Looking at the known mechanisms behind iron deficiency and IDA, different mechanisms for this difference can be hypothesised. In the Western geriatric population, IDA is mainly caused by gastrointestinal bleeding.[15] It might be that the migrant population has more gastrointestinal bleeding compared with the Dutch population. This could possibly be caused by a higher prevalence of, for example, *Helicobacter pylori* infections.[16] On the other hand, our limited data on gastroscopy and colonoscopy outcomes do not suggest that the migrant population has more gastrointestinal pathology. Besides bleeding, other known mechanisms for developing iron deficiency (anaemia) are intake and uptake problems. Iron deficiency is known to be the most common and widespread nutritional disorder in de world.[13] The level of iron intake has been shown to differ between women with different ethnic backgrounds living in the Netherlands. The recommended dietary allowance for people > 65 years is 9.0 mg for man and 8.0 mg for women. Women with a Moroccan background had the lowest iron intake (7.2 mg a day), Dutch women had an average intake of 10.3 mg a day, while women with a Turkish background had a daily iron intake of 8.8 mg.[17] This might be an explanation for the higher prevalence of iron deficiency anaemia.

Table 1. *Baseline characteristics of the study population*

Characteristic	Total population n = 376	Migrants n = 188	Dutch n = 188
Age, years, median (SD)	78.4 (7.4)	73.9 (5.2)	82.8 (6.7)*
Gender, male, no. (%)	152 (40.4)	83 (22.0)	69 (18.4)
CCI, median (SD)	2.4 (1.8)	2.6 (1.9)	2.3 (1.7)
CCI-age, median (SD)	5.5 (2.6)	5.3 (2.4)	5.6 (2.7)
BMI, median (SD)	27.4 (5.7)	30.1 (5.4)	24.8 (4.8)*
Laboratory results			
Haemoglobin, mmol/l, median (SD)	8.2 (1.0)	8.1 (0.9)	8.2 (1.0)
MCV, fl, median (SD)	90.4 (6.8)	88.2 (6)	92.6 (6.8)*
Ferritin, µg/l, median (SD)	123.8 (141.6)	83.5 (106.8)	164.9 (160.1)*
Iron, mmol/l, median (SD)	12.7 (5.0)	11.9 (4.5)	13.7 (5.4)*
Transferrin, g/l, median (SD)	2.5 (0.5)	2.6 (0.5)	2.4 (0.4)*
CRP, mg/l, median (SD)	7.8 (17.3)	5.0 (8.4)	10.7 (22.7)*
Leucocyte, $x10^9$/l, median (SD)	7.3 (2.3)	7.1 (2.6)	7.4 (2.0)
Creatinine, µmol/l, median (SD)	89.6 (33.4)	86.8 (26.9)	92.5 (38.6)
eGFR, median (SD)	55.0 (9.1)	56.1 (8.1)	53.9 (10.0)*
TSH, mU/l, median (SD)	2.3 (2.0)	2.4 (1.9)	2.3 (2.1)
Vitamin B12, nmol/l, median (SD)	337.9 (249.7)	301.6 (216.3)	374.5 (275.2)*
Folic acid, nmol/l, median (SD)	18.4 (19.7)	17.1 (12.2)	19.7 (24.9)
Medication			
NSAID, use, no. (%)	39 (10.4)	21 (5.6)	18 (4.8)
NSAID, used daily, no. (%)	21 (5.6)	14 (3.7)	7 (1.9)
NSAID, not used daily, no. (%)	18 (4.8)	7 (1.9)	11 (2.9)
Platelet aggregation inhibitors, use, no. (%)	91 (24.2)	43 (11.4)	48 (12.8)
Vitamin K antagonist, use, no. (%)	60 (16)	19 (10.1)	41 (21.8)*
Iron supplementation, use, no. (%)	27 (7.2)	16 (8.5)	11 (5.9)
Gastrointestinal diagnostics			
Colonoscopy, total no. (%)	15 (4.0)	10 (2.7)	5 (1.3)
Gastroscopy, total no. (%)	17 (4.5)	12 (3.2)	5 (1.3)

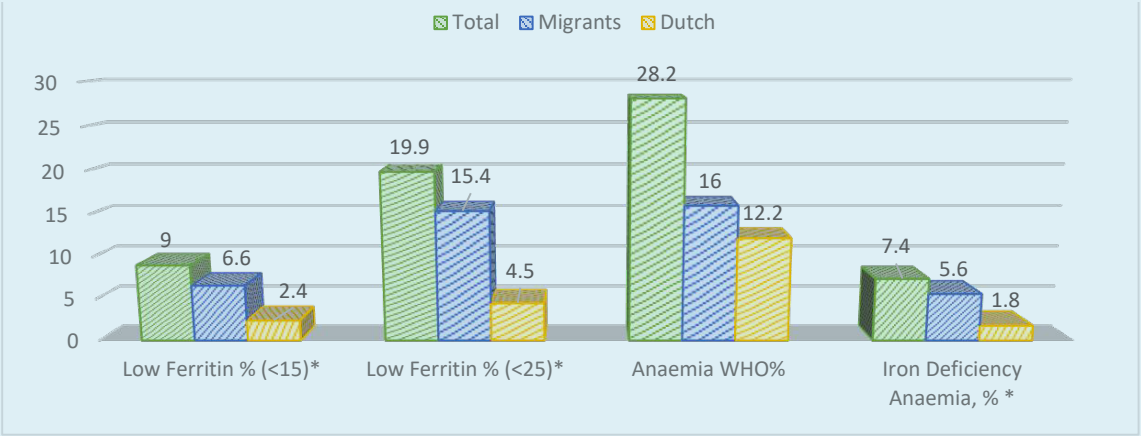
For continuous variables, Student's t-test was used if normally distributed otherwise a Mann-Whitney test was used. For nominal variables a chi-square test was used. *P-value is statistically significant (< 0.05)
CCI = Charlson Comorbidity Index, BMI = body mass index, MCV = mean corpuscular volume, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, TSH= thyroid-stimulating hormone, NSAID = non-steroidal anti-inflammatory drug.

Iron absorption can vary from 1% to 40%, depending on the mix of enhancers and inhibitors in the meal.[13,18] A survey in Denmark of 80-year-old healthy persons showed a positive correlation between dietary iron intake and serum ferritin.[18] Noteworthy was the negative correlation between serum ferritin and the consumption of tea.[19]

Limitations

A noteworthy result is the difference in age of the populations; this study showed that the migrant population was nine years younger than the Dutch population. Although this difference is considerable and could be a limitation of the study, we were able to correct for

Figure 1. *Diagnosis of iron deficiency*



Diagnosis of iron deficiency	Total	Migrants	Dutch
Low Ferritin WHO [a], no. (%)	34 (9.0)	25 (6.6)	9 (2.4) *
Low Ferritin [b] (< 25), no. (%)	75 (19.9)	58 (15.4)	17 (4.5) *
Anaemia WHO [c], no. (%)	106 (28.2)	60 (16)	46 (12.2)
Iron Deficiency Anaemia [d], no. (%)	28 (7.4)	21 (5.6)	7 (1.8) *

For continuous variables, Student's t-test was used if normally distributed otherwise a Mann-Whitney test was used. For nominal variables a chi-square test was used. *P-value is statistically significant (< 0.05)
[a] Low ferritin according to the World Health Organisation, defined as serum ferritin level < 15 µg/l[11]
[b] Low ferritin according to Hamaker et al., defined as serum ferritin level < 25 µg/l[6]
[c] Anaemia according to the World Health Organisation, defined as serum haemoglobin for males and females of 8.1 mmol/l and 7.5 mmol/l respectively [14]
[d] Iron deficiency anaemia according to the World Health Organisation, defined as anaemia, serum ferritin level < 15 µg/l and CRP < 10 [13]

Table 2. *Logistic regression model*

Outcome	Model 1 OR	95% CI	Model 2 OR	95% CI
Ferritin < 15 [a]	2.99*	1.35 – 6.59	3.00*	1.01 – 8.97
Ferritin < 25 [b]	4.40*	2.44 – 7.92	3.92*	2.15 – 7.13
Iron deficiency anaemia [c]	3.22*	1.33 – 7.76	2.94*	1.20 – 7.17

Logistic multivariate analyses was used.
Model 1 included variables: age and gender.
Model 2 included variables: age, gender, BMI and NSAID use
Ferritin < 15: NSAID use
Ferritin < 25: BMI and NSAID use
IDA: BMI
*P-value is statistically significant (< 0.05)
CI = 95% confidence interval
[a] Low ferritin according to the World Health Organisation, defined as serum ferritin level < 15 µg/l [11]
[b] Low ferritin according to Hamaker et al., defined as serum ferritin level < 25 µg/l[6]
[c] Iron deficiency anaemia according to the World Health Organisation, defined as anaemia, serum ferritin level < 15 µg/l and CRP < 10.[13]

this in the multivariate analysis. Also of note, the CCI, a measurement for the degree of comorbidity, was not significantly different. This suggests that – despite the nine years difference in age – the burden of comorbidity between the populations was equal.

Furthermore, ferritin is highly specific for iron deficiency; however sensitivity is low, and a normal ferritin level thus does not necessarily preclude that iron stores are low.[6] Interpretation of ferritin in older adults is complicated due to the serum ferritin level increasing with age and concomitant chronic disorders.[10] As ferritin and CRP are both acute phase proteins, they are associated. The mean CRP level was significantly different between the two groups in this study. This could influence the mean ferritin

Table 3. *Gastrointestinal diagnostics*

Gastrointestinal diagnostics	Total n = 32	Migrants n = 22	Dutch n = 10
Colonoscopy, cause found, no. (%)	4 (1.1)	1 (0.3)	3 (0.8)
Colonoscopy, cause not found, no. (%)	11 (2.9)	9 (2.4)	2 (0.5)
Gastroscopy, cause found, no. (%)	4 (1.1)	3 (0.8)	1 (0.3)
Gastroscopy, cause not found, no. (%)	13 (3.5)	9 (2.4)	4 (1.1)

Colonoscopies and gastroscopies divided into whether the cause of iron deficiency and/or iron deficiency anaemia was found. In numbers followed by the total of colonoscopies or gastroscopies and in percentages.

levels. However, to our knowledge, there is no direct evidence suggesting that a difference of 5 mg/l in the CRP concentration significantly affects ferritin levels, especially if they are both within the normal range.

Another limitation is that the exact reason for referral of the study population remains broad, possibly causing referral bias. However, the overall impression at the outpatient clinic is that the migrants are more often referred for cognitive problems, and the Dutch population is more often referred for somatic problems. As CCI was comparable and was corrected for, we assume that underlying differences in somatic disorders did not play a role in the association.

With regard to potential explanative analyses, more information regarding the diet of the study population, for example the Mini Nutritional Assessment (MNA), or iron intake would be interesting. Further studies are needed to evaluate the iron intake of the migrant population. Lastly, we had relatively limited information about the use of over-the-counter medication, especially NSAIDs. It is possible that these results are an underestimation because NSAIDs are available without prescription in the Netherlands. In the geriatric population in the Netherlands 7% use NSAIDs that are purchased over the counter.[20] The use of NSAIDs might be more frequent in the migrant population, although this has not been confirmed in the literature. This could cause an underestimation of the influence of the use of NSAIDs.

CONCLUSION

In the Netherlands, the prevalence of a low serum ferritin and iron deficiency anaemia appears to be more frequent in the geriatric migrant population, first-generation Turks and Moroccans, compared with the geriatric native Dutch population. The cause of this difference is not yet known. Potentially the difference in iron intake or uptake from nutrition between the populations may be underlying or it might be because of more gastrointestinal pathology in the migrant population, although our study outcomes do not point this way. For the clinician, knowing that the migrant geriatric population on average has a lower ferritin level than the Dutch elderly could influence the decision to perform invasive diagnostic procedures. Further research is needed to evaluate potential underlying pathways, including studies regarding the gastrointestinal pathology and the dietary specifications in the elderly migrant population.

DISCLOSURES

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CASE REPORT

A rare case of Waterhouse-Friderichsen syndrome during primary Varicella zoster infection

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ABSTRACT

Primary *Varicella zoster* virus infection in adults is associated with a higher risk of complications when compared with the benign disease course of primary infection during childhood. We present a rare complication of adult primary *Varicella zoster* in the form of acute, irreversible adrenal insufficiency due to bilateral adrenal haemorrhage, which is also known as the Waterhouse-Friderichsen syndrome.

KEYWORDS

Adrenal insufficiency, adrenal haemorrhage, *Varicella zoster*, Waterhouse-Friderichsen syndrome

What was known on this topic?
Waterhouse-Friderichsen syndrome is defined as bilateral adrenal haemorrhage with subsequent adrenal insufficiency due to an infectious disease, most commonly meningococcal sepsis. Primary *Varicella zoster* infection is most common in children, where it usually has a benign and self-limiting course.

What does this add?
In presenting this rare and serious complication of Waterhouse-Friderichsen syndrome due to primary *Varicella zoster* infection, we hope to illustrate the unexpected way in which adrenal insufficiency may present as well as to emphasise the different and more serious clinical course of primary *Varicella zoster* infection in adulthood.

INTRODUCTION

Waterhouse-Friderichsen syndrome is a classic disease entity in which bilateral adrenal haemorrhage causes irreversible adrenal insufficiency in the course of an infectious disease, and is most commonly reported in relation to meningococcal sepsis. We describe a case of Waterhouse-Friderichsen syndrome caused by primary *Varicella zoster* virus (VZV) infection in a male adult patient. To our knowledge this is the first case of Waterhouse-Friderichsen syndrome occurring in the setting of VZV infection to be described in over 40 years, and only the second case reported in an adult patient.[1]

CASE REPORT

A 53-year-old man of African Caribbean descent, with a previous medical history of hypertension and paroxysmal atrial fibrillation not treated with anticoagulants, presented to the emergency department with a sharp umbilical pain. The pain was accompanied by the feeling of general weakness. His temperature was normal at 36.7 °C. His blood pressure was 170/90 mmHg with a pulse rate of 58/minute. His abdomen was tender with right-sided pain upon palpation. No skin abnormalities were noted at first presentation. The complete blood count including thrombocytes was normal, except for a mild lymphopenia of 0.66 x 10^9/l. The prothrombin time was 11.1 seconds, while the activated partial thromboplastin time was not measured at presentation. Kidney function was within the normal range (an estimated glomerular filtration rate (eGFR) of 106 ml/min/1.73m^2) and the C-reactive protein was 12 mg/l. There was a slight hyponatraemia of 132 mmol/l and hyperkalaemia of 5.0 mmol/l.
A computed tomography (CT) scan of the abdomen with intravenous contrast demonstrated diffuse swelling and

strong enhancement of both the adrenal glands with inflammatory changes in the surrounding retroperitoneal fat (*figures 1a and 1b*).

Due to persistent pain and a new, rapidly progressive, non-itching and vesicular generalised rash an additional CT scan was performed the next day, which demonstrated hyperdense round masses strongly suggestive of bilateral adrenal haemorrhage (*figure 1c*). Polymerase chain reaction (PCR) on fluid from a skin lesion was positive for VZV, serological testing showed a positive IgG and weak positive IgM for VZV and PCR on plasma was positive for VZV genome after nucleic acid amplification testing, which confirmed the diagnosis of primary VZV. The patient was admitted under the diagnosis of primary VZV infection complicated by bilateral adrenal haemorrhage, for which he was treated with intravenous aciclovir (10 mg/kg thrice daily).

During admission the patient's blood pressure fell to 76/50 mmHg and a random cortisol measurement was significantly decreased at 41 nmol/l (150-700 nmol/l). The diagnosis of adrenal insufficiency was made after which substitution of glucocorticoid and mineralocorticoid steroids was initiated. The substitution consisted of a bolus of 100 mg hydrocortisone intravenously followed by 50 mg thrice daily and fludrocortisone 100 µg orally. He developed marked acute renal failure with an eGFR nadir of 16 ml/min/1.73 m^2, which resolved over the next few days after aggressive fluid resuscitation. The sodium and potassium normalised to 136 mmol/l and 4.5 mmol/l respectively. The vesicular skin lesions resolved completely after treatment. Standard adrenocorticotropic hormone (ACTH) stimulation testing with 250 µg synthetic ACTH 5 months after the initial diagnosis with a baseline cortisol of 0.036 µmol/l resulted in cortisol levels of 0.040 µmol/l 30 minutes after stimulation and 0.043 µmol/l 60 minutes after stimulation, which in accordance with a cut-off value of > 0.43 µmol/l confirmed permanent hypocortisolism. Renin/aldosterone testing was not performed. The patient's maintenance therapy consisted of hydrocortisone orally in a standard dose of 10 mg in the morning, followed by 5 mg in the afternoon and evening as well as fludrocortisone 100 µg orally.

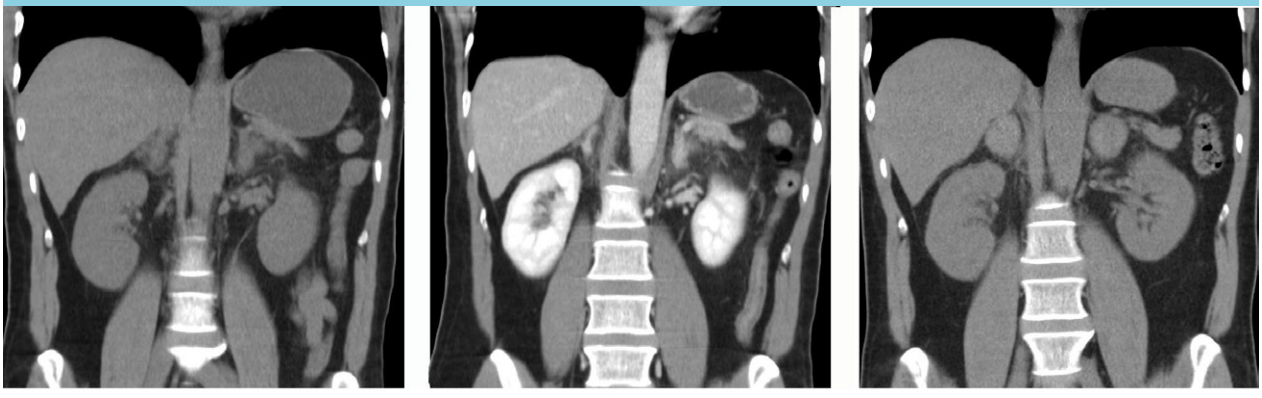
DISCUSSION

VZV (or human herpesvirus type 3) infection is a common viral infection. Primary infection results in a generalised maculovesicular rash (varicella or chickenpox); endogenous reactivation of latent VZV causes herpes zoster (shingles). In the Netherlands, primary VZV infection most commonly occurs in childhood with a benign and self-limiting course. However, the adult disease course can be more complex and infected adults have a six-fold higher hospitalisation rate, usually due to pneumonia.[2] National surveillance data estimate that 98-100% of the Dutch adult general population[3] test positive for VZV IgG antibodies.

In tropical climates approximately 50% of the adult population is estimated to be seronegative for VZV IgG. The adult immigrant population therefore has a greater risk of contracting the disease during adulthood with an increased risk of severe morbidity. In a cross-sectional survey of the Amsterdam population, ethnic origin and first-generation immigrants were positive predictors for IgG seronegativity to VZV, with 91% of adults of Surinamese and Caribbean descent being seropositive for VZV IgG.[4]

Awareness of these substantial differences in immunity is important in recognising and managing primary VZV in adults, as our case clearly demonstrates.

Figure 1. *A) A CT scan of the abdomen before intravenous contrast demonstrates diffuse swelling of both adrenal glands with fuzzy margins and inflammatory changes in the surrounding retroperitoneal fat. B) The same CT scan after injection of intravenous contrast, demonstrating strong enhancement of both adrenal glands. C) Subsequent imaging showing bilateral, slightly hyperdense round masses, strongly suggestive of bilateral adrenal haemorrhage*



Bilateral adrenal haemorrhage with subsequent adrenal insufficiency occurring in the setting of an infectious disease is known as the Waterhouse-Friderichsen syndrome. Waterhouse-Friderichsen syndrome is classically associated with meningococcal disease but has also been described in the clinical course of various other infectious diseases, and if unrecognised and left untreated often has a fatal outcome.[5,6] Patients may present with abdominal pain and shock which is only preceded by hypotension in approximately half of all patients,[7] which may explain the fact that our patient presented with hypertension rather than the expected distributive shock that many clinicians associate with hypoadrenalism. The exact pathogenic mechanism responsible for adrenal haemorrhage in Waterhouse-Friderichsen syndrome is still unknown, but may be related to the adrenal gland's inherent vulnerability to haemorrhage due to its unique blood supply, where an arterial subcapsular plexus drains on relatively few venules.

Other case reports have described haemorrhagic transformation after thrombosis as a cause of bilateral adrenal bleeding in the setting of an antiphospholipid syndrome,[8] while spontaneous haemorrhage has been reported as well.[9] In a case series describing 65 cases of fatal bacterial infections in which bilateral adrenal gland haemorrhage occurred in 60% of cases, 36% of cases showed haemorrhages in other internal organs as well, possibly representing the presence of disseminated intravascular coagulation.[10] Based on the subsequent imaging available in our case, where haemorrhage was preceded by swelling and enhancement of both adrenals, we hypothesised that haemorrhagic transformation of the adrenal glands may have been preceded by venous backflow into this vulnerable vascular network due to stress-mediated venoconstriction and/or thrombosis.[11]

CONCLUSION

Despite its rarity, this unique case highlights the importance of awareness of possible complications in adult primary VZV infection. It also illustrates the treacherous way in which adrenal insufficiency may present in the course of an infectious disease. This is especially important in an increasingly global setting where *Varicella* immunity among adults varies greatly.

DISCLOSURES

The authors have nothing to disclose.

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CASE REPORT

Female urothelial cell carcinoma in a failed kidney graft of a male recipient

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ABSTRACT

We present a case of a male kidney transplant patient harbouring two kidney grafts of which one is functional. In the failed graft, he developed urothelial cell carcinoma with cells containing XX-chromosome, and female tumour cells were also found in the bladder. The patient underwent donor nephrectomy, was treated with epirubicin bladder instillations, and immunosuppression was tapered. Less than a year before re-transplantation a CT scan showed no abnormalities of the first graft. Transplantectomy before a second kidney transplantation is debated.

KEYWORDS

Donor-derived tumour, kidney transplantation, FISH, cancer, nephrectomy.

What was known on this topic?
There are several reports of malignancies in renal transplant grafts. In this case report a malignancy is described in a failed graft shortly after re-transplantation.

What does this add?
This case report describes the relevance of interphase cytogenetics in identifying the origin of a urothelial cell carcinoma originating from a failed kidney graft many years after transplantation. It may add to the discussion about screening protocols for malignancy after transplantation since a CT scan without IV contrast less than a year before re-transplantation showed no abnormalities.

INTRODUCTION

After kidney transplantation, there is an increased risk for development of urothelial cell carcinomas including graft tumours.[1] We present a case of a male recipient with two consecutive kidney grafts in which a donor-derived urothelial cell carcinoma in the first graft and in the bladder was found harbouring a XX genotype, as detected by FISH, thus indicating that the tumour originated from the maternal donor.

Apart from a report identifying Y-chromosome status in female post-transplant non-small cell lung carcinoma patients[2] and two cases of sex chromosome discrepancy in kidney transplantation patients with urothelial carcinoma,[3,4] to our knowledge, there are no other reports after organ re-transplantation about late-onset tumours where the origin of the tumours from donor cells was proven.

CASE REPORT

Nine months after kidney transplantation from a 59-year-old female, a 47-year-old man was seen in our outpatient nephrology clinic for a regular check-up. In the last few days, the patient had developed macroscopic haematuria. His medication consisted of tacrolimus, mycophenolate, metoprolol, felodipine, enalapril, and atorvastatin. The patient used no alcohol or illicit drugs and had smoked 20 cigarettes a day for the last 17 years.

Medical history included end-stage renal disease probably due to hypertension in 2006, followed by transplantation of a kidney donated by his then 70-year-old mother with immediate graft function. In 2012 graft function deteriorated due to membranous glomerulonephritis. In January 2013, the patient was re-transplanted pre-emptively with a kidney from another living donor. Prior to re-transplantation, computed tomography (CT) scanning of the first kidney graft showed no abnormalities.

The patient had no other symptoms besides haematuria. There was no dysuria, no fever and no weight loss. Physical examination revealed no abnormalities. The urine showed > 200 erythrocytes/ µl without dysmorphic erythrocytes, 51-140/µl leucocytes and a 24-hour urine collection showed 0.24 g/l protein with a creatinine of 11.1 mmol/l. A urine culture showed no bacterial growth. The serum creatinine was stable at 136 µmol/l.

The patient was referred to a urologist. A cystoscopy was performed and showed a papillary lesion on the left posterior bladder wall, without lesions around any of the four ureteral ostia. CT-intravenous pyelogram showed shrunken native kidneys and a tumour in the renal pelvis of the first kidney graft without lymph node metastasis. The functioning graft showed no abnormalities.

The patient underwent transplantectomy of the failed first kidney graft. The kidney graft showed a high-grade pT3 papillary urothelial cell carcinoma of the renal pelvis with infiltration into the kidney, however not in the ureter.

Because of the malignancy, immunosuppression was tapered to tacrolimus monotherapy, after a biopsy of the functioning kidney graft was performed and showed no signs of rejection. A transurethral bladder resection (TUR) showed a pTaG2 papillary urothelial cell carcinoma of the right posterior bladder wall.

Chromosome copy number analysis of the explanted graft and bladder tumour by FISH using a chromosome X and Y probe mixture (Aneuvysion Multicolor DNA Probe Kit, Abbott Molecular, Hoofddorp, NL)[5] showed malignant cells with a XX genotype and no Y chromosome, indicating that not only the graft tumour, but also the bladder tumour originated from cells of the maternal donor kidney (*figure 1*). Subsequent screening of the donor was negative for urothelial carcinoma.

The patient was treated with epirubicin instillations of the bladder. Two months later, a cystoscopy showed no abnormalities. Six months later, ten small papillary urothelial cell carcinomas were removed from the bladder wall, again with XX genotype, followed by new prophylactic epirubicin instillations. During the next year, the patient received multiple epirubicin instillations and underwent regular cystoscopies, which showed no recurrences. The patient remained on tacrolimus monotherapy with stable kidney graft function (creatinine 130 µmol/l).

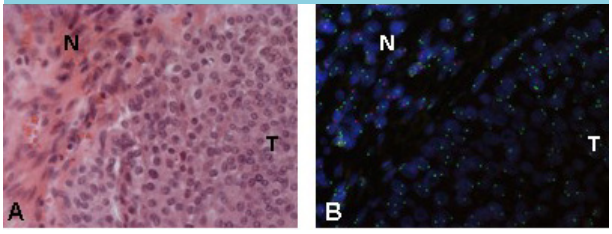
In March 2016, the patient developed painful pathological inguinal lymph nodes. MRI of the lower abdomen and pelvis revealed enlarged inguinal, iliac and aortic lymph nodes and thickening of the bladder wall, suspect for tumour infiltration. A new TUR of the bladder wall was performed and a lymph node was removed, showing metastasis of urothelial cell carcinoma, again with XX genotype. A CT scan showed multiple millimetric nodules in the lungs and one lesion in the liver. A diagnosis of metastasised urothelial cell carcinoma was made. The patient was referred to an oncologist, who started palliative chemotherapy consisting of six cycles of gemcitabine/ carboplatin.

DISCUSSION

This case shows a patient who received a living related donor kidney from his mother and subsequently developed urothelial cell carcinoma in that graft kidney and in the bladder, after he had already undergone a second transplantation because of graft failure. We provided evidence, using XY-specific FISH analysis of the malignant cells, that both the original tumour and the recurrent bladder tumours originated from cells from the maternal graft.

Current literature does not recommend standard imaging[6] or transplantectomy without a clinical indication after graft failure,[7] which might have improved the prognosis of this patient. The decision regarding transplantectomy before a re-transplantation is complicated. Careful consideration of the advantages and disadvantages for the individual patient is needed. Our patient was re-transplanted pre-emptively. It was decided not to perform transplantectomy, because this would have led to a period of dialysis and possibly more operative risks and also possible HLA immunisation against the new donor.

Figure 1. *Representative images of A) a haematoxylin-eosin stained formalin fixed, paraffin embedded tissue section of the urothelial cell carcinoma (T) and flanking normal stromal cells (N), and B) FISH analysis showing the XX genotype (two gene signals/cell nucleus) of the female tumour cells and the XY genotype (a green and a red signal per nucleus, respectively) of the host stromal cells*



Screening for tumours in a failed graft and transplantectomy of a first graft before re-transplantation remains a difficult issue. In our clinic, CT scanning of the abdomen without IV contrast in the preparation before re-transplantation is a standard procedure. The CT scan without IV contrast preceding re-transplantation showed no abnormalities of the first kidney graft. IV contrast is relatively contraindicated for many patients with a kidney graft. The relevance of regular screening with ultrasound and/or PET-CT in early detection of renal graft tumours is also unclear. In our centre, we generally remove failed kidney grafts when patients are dependent on dialysis and have oliguria. In other centres, the failed graft remains in situ. Hence, with regard to transplantectomy of failed kidney grafts, there is also no consensus.

In conclusion, we have proven the relevance of interphase cytogenetics to identify the origin of a tumour in organ transplant recipients, especially after re-transplantation with two donor organs in situ. At this time, the value of screening for graft tumours is unproven.

DISCLOSURES

All authors declare no conflict of interest. No funding or financial support was received.

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PHOTO QUIZ

Spontaneous rupture of a splenic artery aneurysm in a male patient

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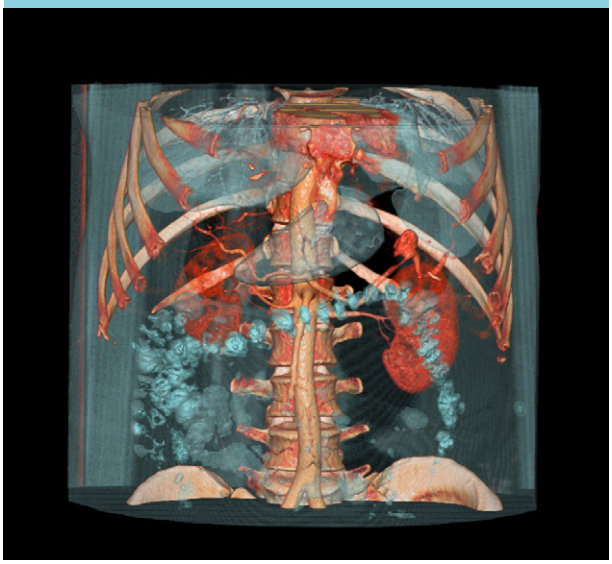
CASE REPORT

A 51-year-old male was admitted to our hospital with intensive abdominal pain that started three days earlier during lawn mowing. The pain intensified on the day of admission. He had pale skin and mucosa, diaphoresis, and presented with hypotension of 83/60 mmHg and abdominal tenderness. A multislice computed tomography angiography scan was performed (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 358 for the answer to this photo quiz.

Figure 1. *3D multislice tomography angiography on the day of admission with the splenic artery aneurysm in the distal third of the splenic artery*



ANSWER TO PHOTO QUIZ (PAGE 357)

SPONTANEOUS RUPTURE OF A SPLENIC ARTERY ANEURYSM IN A MALE PATIENT

DIAGNOSIS

The multislice computed tomography angiography revealed a splenic artery aneurysm (SAA) measuring 23 x 20 mm, 40 mm from the splenic hilum. A small trace of contrast extended caudally and medially from the aneurysm indicating actual bleeding.

The emergency operation was performed through a medial laparotomy. A large amount of blood in the free intra-abdominal cavity (at least 1000 ml) and a retroperitoneal haematoma which was lifting central and left retroperitoneum were found. The aneurysm was found at the bifurcation of the splenic artery. After controlling the haemorrhage, an aneurysmorrhaphy and splenectomy were carried out. The postoperative course was uneventful and the patient was discharged on the 12th day of hospitalisation (*figure 2A and B*).

True SAAs are rare with an incidence of 0.01-0.98% in large autopsy studies.[1] They appear mainly in female patients with a female-to-male ratio of 4:1.[2] The risk of rupture is 5% and the risk factors are pregnancy, portal hypertension, medial fibrodysplasia, splenomegaly, orthotopic liver transplantation, pancreatitis, vasculitis and degenerative atherosclerosis. None of these were found in the patient's medical history. We present here a rare case of spontaneous rupture in a previously healthy male patient. Indications for treatment are symptoms, aneurysms measuring more than 20 mm, pregnancy and patients who have undergone previous major upper abdominal surgery.[3] According to Van Rijn et al.[2] the smallest spontaneously ruptured splenic aneurysm in their study was 23 mm. Aydın et al. report an SAA measuring 20 mm[4] and here a 23 mm SAA is described as well. This raises a question of whether the size of visceral artery aneurysms plays a role in the risk of rupture.

Most of the patients with SAAs are asymptomatic; it is an incidental finding on cross-sectional imaging.[2] However, the first symptoms occurring can be symptoms of hypovolaemic shock. The case above describes a classic double rupture phenomenon after which catastrophic symptoms of shock appeared.

The main treatment option in elective cases is an endovascular procedure. In emergency settings with massive intraperitoneal haemorrhage, open surgery remains the main treatment option.[2] In case of a distal artery aneurysm, both aneurysmectomy or aneurysmorrhaphy in combination with splenectomy are possible.

The high morbidity associated with SAA rupture compared with the significantly lower morbidity of elective treatment[2] indicates that SAAs should be treated as diagnosed.

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Figure 2. *A. Multislice computed tomography angiography on the day of admission. B. Multislice computed tomography angiography after splenectomy*

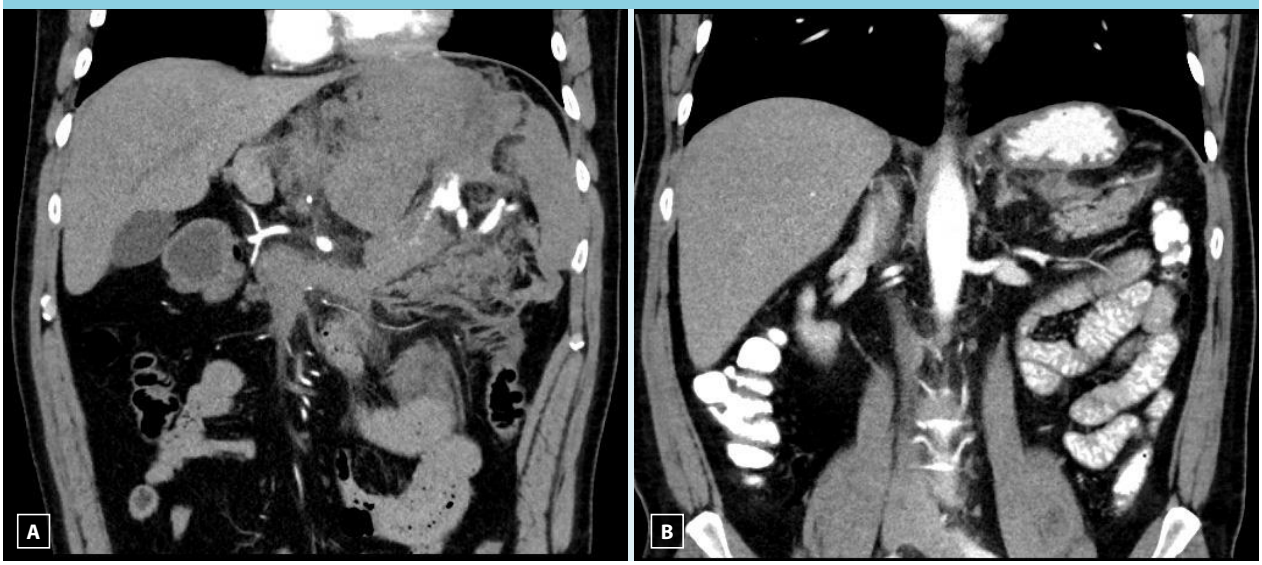

PHOTO QUIZ

A 52-year-old oncology patient with acute severe abdominal pain

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CASE REPORT

A 52-year-old man with a myocardial infarction and percutaneous coronary intervention in his medical history underwent perioperative chemotherapy and a gastrectomy because of a poorly differentiated adenocarcinoma of the stomach. Unfortunately, two months later metastatic disease was diagnosed in his diaphragm and peritoneum with malignant ascites. The patient was not eligible for palliative chemotherapy because of a low performance status. Four weeks later, he was admitted to the hospital because of a severe but symptom-free hypopotassaemia caused by persistent vomiting due to a soft tissue swelling suspicious for local recurrence in the stomach. The hypopotassaemia was corrected with supplements and the vomiting decreased slowly. However, two days after admission, acute severe generalised abdominal pain developed and imaging of the abdomen was performed (*figures 1 and 2*).

WHAT IS YOUR DIAGNOSIS?

See page 360 for the answer to this photo quiz.

Figure 1. *Abdominal CT scan – transverse view*

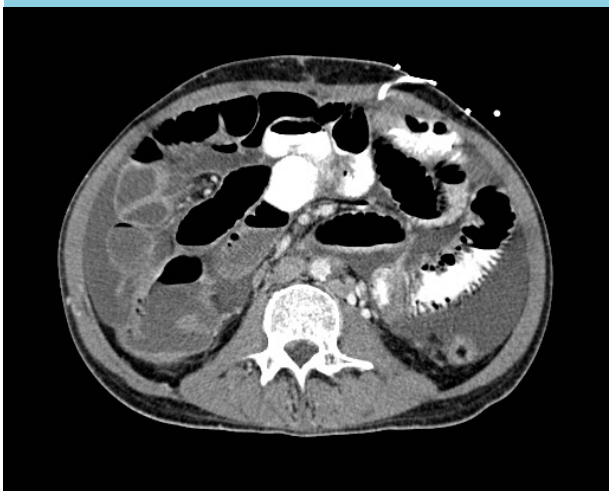
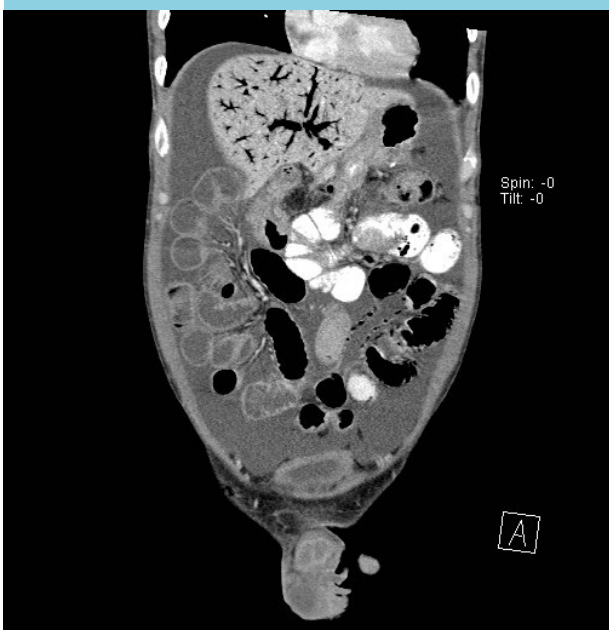


Figure 2. *Abdominal CT scan – coronal view*



ANSWER TO PHOTO QUIZ (PAGE 359)

A 52-YEAR-OLD ONCOLOGY PATIENT WITH ACUTE SEVERE ABDOMINAL PAIN

DIAGNOSIS

In addition to liver metastases and ascites, the abdominal CT scan showed extensive pneumatosis intestinalis of the jejunal loops (*figure 1*) and gas filling of the mesenteric and portal veins (*figure 2*). There was no perforation of the bowel. Pneumatosis intestinalis is defined as the presence of gas in the bowel wall and is suspicious for bowel ischaemia; in this case it is probably related to advanced malignancy and malignancy-induced hypercoagulability.[1,2] Gas in the portal system, a so-called pneumoportogram, is a rare finding. It is due to accumulation of gas in the portal veins and its branches and has to be distinguished from air in the biliary tree (pneumobilia or aerobilia), which is more centrally located and does not extend to the liver capsule (to within 2 cm) as gas in the portal veins does.[3-5] Portal vein gas and mesenteric vein gas are sometimes reported as two separate entities, but they are usually found together.[5] The precise pathophysiology is still unclear, but predisposing factors that are associated with the development of portomesenteric vein gas are intestinal wall alterations, bowel distention an abcess and gas-forming organisms in the bowel lumen or in the portal venous system in case of sepsis.[4,5] Intestinal wall alterations are commonly caused by bowel ischaemia and permit passage of intraluminal gas into the portomesenteric venous system.[5] Portomesenteric vein gas is not a specific disease but a diagnostic clue and an important sign that is often caused by underlying acute and severe abdominal pathology, but a range of benign diseases have also been described.[2,4] The most serious and frequent cause of portomesenteric vein gas in adults is bowel ischaemia.[2,5] Pathological underlying conditions are divided into three groups: intestinal wall alterations (bowel ischaemia, inflammatory bowel disease), bowel distention (bowel dilatation due to spontaneous, traumatic or iatrogenic causes) and intra-abdominal sepsis (e.g. diverticulitis, pylephlebitis). A small minority have another cause (interventional procedures, trauma, transplantation) or remain idiopathic.[4,5] Portomesenteric vein gas in combination with intramural bowel gas is very suspicious for bowel ischaemia associated portomesenteric vein gas.[4] Clinical symptoms vary but often include abdominal pain and distention eventually combined with nausea and vomiting, diarrhoea, rectal blood loss, fever and shock.[4] Urgent abdominal exploration is often needed to remove ischaemic bowel, relieve obstruction, treat bleeding ulcers or drain sepsis depending on the underlying cause. Patients with stable inflammatory bowel disease or gas due to interventional procedures, trauma or transplantation do not usually require acute surgical intervention and first need close observation combined with supportive therapy. These cases come together with a favourable prognosis.[3-5] However, in case of bowel ischaemia prognosis is poor and mortality rates range from 75% to 90% of cases.[3,4]

In this case we present a patient with bowel ischaemia associated portomesenteric vein gas. The severity of the clinical condition, the risks of surgery and the patient's performance status and medical history without curative options, made us decide to refrain from emergency surgery and start best supportive care. The patient died the same day.

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PHOTO QUIZ

What's the cause of this patient's angina?

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CASE REPORT

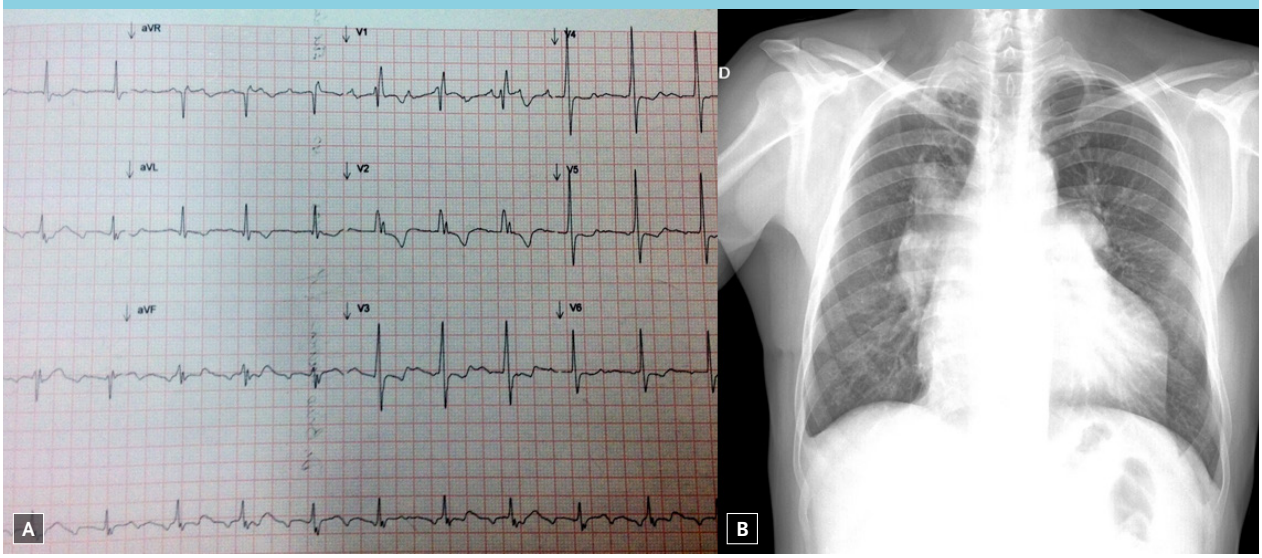
A 50-year-old male presented to our outpatient clinic after referral for a cardiac catheterisation for a three-month history of stable angina pectoris. He described his chest pain as dull, oppressive in quality and related to physical effort. His medical history was remarkable for diabetes mellitus, hypertension, and high blood cholesterol. He had also undergone thoracic surgery at the age of 12, but was unable to remember more details about it.

Cardiac examination demonstrated a laterally displaced point of maximum impulse, a left lower parasternal heave and a grade IV pulmonary systolic-diastolic murmur. ECG revealed right bundle branch block, left axis deviation, slight ST-segment elevation in aVR, and negative T waves and ST-segment depression in V3-V6 and I-aVL (*figure 1A*). A chest X-ray showed pulmonary artery and right heart enlargement (*figure 1B*).

WHAT IS YOUR DIAGNOSIS?

See page 362 for the answer to this photo quiz.

Figure 1. *A) 12-lead ECG showing right bundle branch block, left axis deviation and anterolateral ST segment depression. B) PA chest X ray showing pulmonary artery and right heart enlargement*



ANSWER TO PHOTO QUIZ (PAGE 361)

WHAT'S THE CAUSE OF THIS PATIENT'S ANGINA?

DIAGNOSIS

Transthoracic echocardiogram demonstrated severe regurgitation of a pulmonary prosthesis and a ventricular septal defect. Thoracic-vascular CT scan revealed massive enlargement of the pulmonary artery causing extrinsic compression of the left main coronary artery (*figures 2A and B*). Coronary angiogram showed critical left main coronary artery (LMCA) stenosis caused by extrinsic compression by a dilated pulmonary artery, with a slow and competitive flow through the left anterior descending coronary artery. The right coronary artery was dominant and provided collateral circulation to the left anterior descending artery.

Extrinsic coronary artery compression by a massively enlarged pulmonary artery is a rare cause of stable angina pectoris. The causes underlying pulmonary artery enlargement include primary pulmonary hypertension,[1] atrial septal defect,[2] left anomalous coronary artery origin[3] and in this case, chronic regurgitation of a dysfunctional pulmonary prosthesis. To our best understanding, this is the first case showing LMCA extrinsic compression due to massive pulmonary enlargement secondary in the context of pulmonary prosthesis dysfunction. The patient was admitted to a surgical ward and underwent pulmonary valve replacement and pulmonary artery plicature with technical difficulties due to abundant mediastinal adhesions and a prolonged extracorporeal circulation time (361 min); during the postoperative period, he presented low cardiac output syndrome and refractory cardiogenic shock, and died 72 hours later.

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Figure 2. *A) Coronary artery contrasted CT scan showing left main coronary artery extrinsic compression by a dilated pulmonary artery. B) Volume-rendered reconstruction illustrating anatomical relationship between the left main coronary artery and pulmonary artery*