A black umbilicus; what is your diagnosis?

Clindamycin induced AGEP

Screening for diabetes in women with a history of gestational diabetes

Preventability and predictability of readmission

The value of extremely elevated D-dimer levels
MISSION STATEMENT

To serve the need of the physician to practice up-to-date medicine and to keep track of important issues in health care. To promote and to enhance clinical knowledge by publishing editorials, original articles, reviews, papers regarding specialty training, medical education and correspondence.

EDITORIAL INFORMATION

Editor in chief
Paul van Daele, Department of Internal Medicine and Department of Immunology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands

Editorial team
Jelmer Alsma
Mark Eijgelsheim
Femme Harinck
Maarten Limper
Sanne Lugthart
Jorie Versmissen

Associate editors
Hannelore Bax
Ingrid Boere
Virgil Dalm
Teun van Gelder
Laura de Graaff
Wouter de Herder
Dennis Hesselink
Mandy van Hoek
Janneke Langendonk
Mirjam Langeveld
Frank Leebeek
Rob de Man
Stephanie Klein Nagelvoort
Christian Oudshoorn
Roos Padmos

Robin Peeters
Marijn Vis
Bob Zietse
Carola Zillikens

Junior associate editors
Karin Blijdorp
Mark Claassen
Gerard Jansen
Pim Mutsaers

Editorial board
G. Agnelli, Perugia, Italy
J.T. van Dissel, Leiden, the Netherlands
R.O.B. Gans, Groningen, the Netherlands
A.R.J. Girbes, Amsterdam, the Netherlands
D.E. Grobbee, Utrecht, the Netherlands
E.de Jonge, Leiden, the Netherlands
D.L. Kastner, Bethesda, USA
M.H. Kramer, Amsterdam, the Netherlands
E.J. Kuipers, Rotterdam, the Netherlands
Ph. Mackowiak, Baltimore, USA
J.W.M. van der Meer, Nijmegen, the Netherlands
B. Lipsky, Seattle, USA
B. Lowenberg, Rotterdam, the Netherlands

G. Parati, Milan, Italy
A.J. Rabelink, Leiden, the Netherlands
D.J. Rader, Philadelphia, USA
J.L.C.M. van Saase, Rotterdam, the Netherlands
M.M.E. Schneider, Utrecht, the Netherlands
J. Smit, Nijmegen, the Netherlands
Y. Smulders, Amsterdam, the Netherlands
C.D.A. Stehouwer, Maastricht, the Netherlands
J.L. Vincent, Brussels, Belgium
R.G.J. Westendorp, Leiden, the Netherlands

Editorial office
Erasmus MC, University Medical Center Rotterdam
Department of Internal Medicine
’s-Gravendijkwal 230
3015 CE Rotterdam
The Netherlands
Tel.: +31 (0)10-703 59 54
Fax: +31 (0)10-703 32 68
E-mail: p.l.a.vandaele@erasusmc.nl
http://mc.manuscriptcentral.com/nethjmed

CITED IN

Biosis database; embase/excerpta medica; index medicus (medline) science citation index, science citation index expanded, isi alerting services, medical documentation services, current contents/clinical medicine, PubMed.
Contents

EDITORIAL

Screening for complications after pregnancy-related disorders; don’t restrict to gestational diabetes
P.L.A. van Daele

419

REVIEW

Clindamycin-induced acute generalised exanthematous pustulosis: five cases and a review of the literature
T.J.L. Smeets, N. Jessurun, L. Härmark, S.H. Kardaun

421

ORIGINAL ARTICLES

Investigating screening for diabetes in women with a history of gestational diabetes
H.S. Brink, M. Alkemade, A.J. van der Lely, J. van der Linden

429

Physician consensus on preventability and predictability of readmissions based on standard case scenarios

434

Never ignore extremely elevated D-dimer levels: they are specific for serious illness
T. Schutte, A. Thijs, Y.M. Smulders

443

CASE REPORTS

Ganciclovir-induced ataxia and encephalopathy
M.C. Möhlmann, J. Stiksma, M.H.H. Kramer

449

Actinomycosis of the abdominal wall after cholecystectomy: transferral theory
E.-J. Kooi, P.J. de Vries, A.W.W. van Geloven, H.V. Stel, P.J. Kingma

451

A novel mutation in mitochondrial DNA in a patient with diabetes, deafness and proteinuria
A.Y. Adema, M.C.H. Janssen, J.W. van der Heijden

455

PHOTO QUIZ

A black umbilicus in a patient with a decompensated liver cirrhosis
J.H. Smalberg, T.R. Hendrikz, P. Honkoop

458
Screening for complications after pregnancy-related disorders; don’t restrict to gestational diabetes

P.L.A. van Daele

Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands, tel.: +31 (0)10-7040704, email: p.l.a.vandaele@erasmusmc.nl

In the current issue of the journal, Brink et al. report the low adherence to screening recommendations after pregnancies complicated by gestational diabetes. Only one-third of women were routinely screened. By increasing awareness under general practitioners screening rates went up to over 60%. Almost 20% of screened patients were shown to have diabetes five years after delivery. Data on the number of patients who were diagnosed only after the primary care physician was requested to recommence screening are not mentioned, so we do not know how many patients are missed by non-adherence. Non-adherence to screening recommendations is not a problem restricted to the Netherlands as was recently reported by Eggleston et al. They reported that 75% of patients did not receive screening in the first year after delivery. The population under study is small but other studies show a similar high prevalence of diabetes in this group of women with gestational diabetes. Screening in this high-risk population is therefore important especially because long-time unawareness of the diagnosis may lead to significant complications.

And increased diabetes risk is not the only complication threatening women with reproductive and pregnancy-related disorders. Goueslard et al. showed that women with gestational diabetes had a 25% increased risk of developing cardiovascular disease within seven years' post-partum. Hypertension, angina pectoris and myocardial infarction were all significantly more prevalent. And not only women with gestational diabetes, but also women with hypertensive disorders in pregnancy such as preeclampsia and eclampsia are at increased risk of developing cardiovascular disease in the future. The risk of post-partum hypertension is already higher the first year after pregnancy. But it is not restricted to hypertension. There is also a small but significantly increased risk for cardiomyopathy and even more important a more than 50% increased risk for cardiovascular mortality. In light of the substantially increased risk and given that timely intervention may prevent significant cardiovascular disease, the Dutch Society of Obstetrics and Gynaecology has recently initiated a multidisciplinary working group to develop a guideline for cardiovascular risk management after reproductive and pregnancy-related disorders.

Although gestational diabetes and hypertensive disorders in pregnancy may appear to be the most important ones regarding late severe sequela, other diseases that associate with pregnancy may also cause substantial morbidity post-partum. Despite the lack of published data, it seems prudent to assume that gestational thyroidal disease may also precede late thyroidal dysfunction. The presence of anti-TPO antibodies is associated with an increased risk of developing hypothyroidism during pregnancy due to the fact that the thyroid fails to adapt its function to the increased hormone requirement during pregnancy. Hormone requirement returns to normal after delivery but patients probably still have an increased risk of developing overt hypothyroidism later in life. Despite the substantial risk of late sequelae following complicated pregnancy and the availability of adequate screening methods only a minority of women at risk will in fact receive screening. Luckily, as Brink et al. have shown, increasing awareness under physicians may reduce this problem.

REFERENCES


Clindamycin-induced acute generalised exanthematous pustulosis: five cases and a review of the literature

T.J.L. Smeets¹, N. Jessurun¹, L. Härmark¹, S.H. Kardaun²*

¹Netherlands Pharmacovigilance Centre Lareb, ’s-Hertogenbosch, the Netherlands, ²Department of Dermatology, Reference Center for Cutaneous Adverse Reactions, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands, *corresponding author: tel.: +31 (0)50-3612520, email: s.h.kardaun@gmail.com

ABSTRACT

Acute generalised exanthematous pustulosis (AGEP) is a rare but serious cutaneous adverse drug reaction, often related to antibiotics such as beta-lactams or macrolides. However, it is rarely associated with clindamycin which belongs to the lincosamide antibiotics. The Netherlands Pharmacovigilance Centre Lareb received five reports of AGEP associated with the use of clindamycin. We present these five cases and provide support for this association from the Lareb database, the database of the WHO Collaborating Centre for International Drug Monitoring (Vigibase™), the database of the European Medicine Agency (Eudravigilance), and from a mini review of the literature.

KEYWORDS

Clindamycin, adverse drug reaction, acute generalised exanthematous pustulosis (AGEP), spontaneous reporting system, reporting odds ratio

INTRODUCTION

Besides lincomycin, clindamycin is the only marketed antibiotic of the lincosamide group. Primarily, it has a bacteriostatic action against Gram-positive aerobic and a wide range of anaerobic bacteria. It binds to the 50S rRNA subunit of the bacterial ribosome, similarly to macrolides such as erythromycin, and inhibits the early stages of protein synthesis. However, it is not chemically related to the macrolides. The adverse drug reaction (ADR) profile of clindamycin is similar to that of most antibiotic drugs regarding frequently occurring diarrhoea, nausea/vomiting and rash.

Acute generalised exanthematous pustulosis (AGEP) is a rare but serious acute pustular reaction pattern characterised by pin-point, sterile, non-follicular pustules on a bright erythematous, oedematous background and a distinctive histopathology (figures 1 and 2). Mild, non-erosive mucous membrane involvement (mostly oral) may occur in about 20% of cases. Other skin symptoms, such as marked oedema of the face, purpura, ‘atypical target-like lesions’ and blisters have been described but are not typical for AGEP. In most cases, the course of AGEP is characterised by fever (≥ 38 °C) and peripheral neutrophilia (≥ 7.0 x 10⁹/l); mild eosinophilia may be present in about one-third of the patients. Visceral internal organ involvement may occur and is generally restricted to mild and transient liver and/or kidney involvement. After withdrawal of the culprit, pustules resolve spontaneously within a few days, typically followed by post-pustular desquamation, while total recovery is usually within 15 days. The overall prognosis in AGEP is good although high fever and superinfection of skin lesions can sometimes lead to life-threatening situations in patients of old age or in a poor general condition. The reported mortality is 1-5%. More than 90% of cases of AGEP are drug-induced, with antibiotics being the most frequent triggers. A high proportion of these cases have been attributed to beta-lactams or macrolides, but interestingly not to sulphonamides which have a high potential for causing serious cutaneous ADRs. AGEP has also been ascribed to a wide variety of other drugs, including antimycotics, calcium channel blockers, carbamazepine and acetaminophen. In a minority of cases other causes, in particular viral infections, have been suspected to trigger AGEP.
Clindamycin has been associated with serious cutaneous ADRs such as Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms. Notwithstanding emerging evidence of a link between clindamycin and AGEP, knowledge about this association is, however, still limited.6-14 The five case reports received by the Netherlands Pharmacovigilance Centre Lareb add to the current knowledge on this relationship. Additionally, to strengthen this association we summarise the cases in the database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (Vigibase™), and the database of the European Medicine Agency (Eudravigilance). Furthermore, we performed a literature review of the cases of AGEP, associated with clindamycin.

**METHODS AND MATERIALS**

Lareb maintains the spontaneous ADR reporting system in the Netherlands. The reports associated with clindamycin and AGEP submitted to Lareb until October 2015 are described. Extensive narratives with additional clinical information for the cases of interest were obtained from the reporters. The reports from Vigibase™ and Eudravigilance until September 2015 and 26 October 2015, respectively, are summarised. Subsequently, the reports submitted by Lareb, Vigibase™ and Eudravigilance are analysed for disproportional reporting. ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA®; version 17.0) and the suspected drugs are classified according to the WHO Anatomical Therapeutic Chemical classification system. Cases were defined as reports mentioning the MedDRA® Preferred Term acute generalised exanthematous pustulosis associated with clindamycin. The control group consisted of all other reports in the databases.

The strength of the association between AGEP and the use of clindamycin is calculated using the reporting odds ratio (ROR), with corresponding 95% confidence intervals (CI), as a measure of disproportionality. In instances where the ROR is statistically significant, AGEP is more frequently reported than could be expected. In order to compare the data of Lareb and Vigibase™ more easily, the measure of disproportionality of Vigibase™ (Bayesian Confidence Propagation Neural Network) was converted to ROR.

Finally a PubMed search was conducted in October 2015 using the keywords “clindamycin”, “AGEP”, “acute generalised/generalised exanthematous pustulosis”. Relevant English-language case reports were included and references of retrieved publications were screened for relevant literature. Cases with a possible or lower rate of causality for clindamycin were excluded.
**RESULTS**

**Lareb reports**

Until October 2015, Lareb received 165,000 reports, including five of AGEP associated with the use of clindamycin. The details of the latter are described below. Patient A (2015), reported by a dermatologist, concerns a 32-year-old female with AGEP after seven days use of clindamycin for paronychia. Due to high fever (39.0°C), painful toes, itching pustular rash, raised C-reactive protein (CRP) and pronounced peripheral neutrophilia, the patient was hospitalised for seven days. The patient was treated with topical tetracycline, triamcinolone ointment, paracetamol and morphine. Clindamycin was withdrawn and the patient recovered 12 days later with post-pustular desquamation. The only concomitant medication was ciprofloxacin, which was started and withdrawn at the same time as clindamycin. Histology was typical for AGEP, while epicutaneous testing was positive for clindamycin and negative for ciprofloxacin.

Patient B (2015), reported by a dermatologist, concerns a 68-year-old female with AGEP with some toxic epidermal necrolysis-like features after one day of clindamycin for sepsis. A dark red pustular erythema on the abdomen, redness on the torso, blistering on the back, and a positive pseudo-Nikolsky’s sign were observed. Histopathology was compatible with AGEP. The patient experienced high fever (>38°C) and laboratory examination revealed a white blood cell count of 22.5 x 10⁹/l, neutrophilia, a raised creatinine of 138 µmol/l and normal transaminases. The lesions had almost recovered eight days after withdrawal of clindamycin and unspecified supportive treatment. Total recovery took 4-6 weeks, due to concomitant disease. The patient’s medical history indicated lactose intolerance, ulnar nerve entrapment, lung carcinoma surgery and collagenous colitis.

Patient C (2013), reported by a dermatologist, concerns a 58-year-old female with a history of hypothyroidism, hypertension and depression, for which she used levothyroxine sodium, enalapril, temazepam, omeprazole, and sertraline, all long term and without adverse reaction. Several years previously, she had experienced a macular rash after penicillin; two days after a clindamycin infusion, followed by oral clindamycin for tonsillitis she was hospitalised for a pustular rash and fever, treated with prednisone, antihistamines, and triamcinolone cream. Twelve days after withdrawal of clindamycin, the patient had recovered with post-pustular desquamation. Three months later, the patient had a positive skin patch test for clindamycin.

Patient D (2012), reported by a physician of internal medicine, concerns a 65-year-old-female with a history of hypertension, polycythaemia vera, myelofibrosis, arteritis temporalis, aneurysm of the abdominal aorta, and percutaneous transluminal coronary angioplasty. Two days after the start of clindamycin for a jaw abscess she experienced AGEP with haemodynamic instability, fever, increased INR, and ventricular tachycardia. The diagnosis of AGEP was confirmed by a dermatologist. The patient was admitted to the hospital and recovered after withdrawal of clindamycin, and treatment with clemastine, prednisolone, intravenous fluids, intravenous metronidazole/ciprofloxacin, topical hydrocortisone acetate, ketoconazole, dalteparin, esomeprazole and paracetamol. Concomitant medications at the time of the event, all used long term and without adverse reaction, were furosemide, atorvastatin, tramadol, omeprazole, diltiazem, perindopril, prednisolone, loperamide, calcium carbonate, acenocoumarol and diclofenac.

Patient E (2009) was reported by a 53-year-old male consumer who was a health professional himself and had a history of mastocytosis. The patient experienced AGEP, 12 hours after starting clindamycin because of sinusitis. The diagnosis of AGEP was confirmed by a dermatologist. He recovered quickly after withdrawal of the clindamycin and treatment with corticosteroids. Concomitant medication was not reported.

**Disproportionality analysis**

On 1 October 2015, the Lareb database contained 165,000 reports, including 235 reports of ADRs associated with clindamycin, among which five reports associated with AGEP as described above. Vigibase™ contained a total of 11.8 million reports of ADRs, including 25,659 cases associated with clindamycin. Among these cases, 91 cases concerned AGEP, including 26 males, 62 females and three cases of unknown gender. Ages varied from 2 to over 75 years. Positive dechallenge and rechallenge were reported in 54 cases and 1 case, respectively. On 26 October 2015, Eudravigilance contained 4.2 million reports, including 5518 reports of ADRs associated with clindamycin among which 81 reports of AGEP. As shown in table 1, the association of clindamycin with AGEP was significant in all databases.

**Literature review**

Up until now, nine reports with ten cases of AGEP, probably induced by clindamycin, have been published in the English language literature. These cases concerned seven females (age 72, 38, 49, 82, 56, 70, and 78 years) and three males (age 69, 76 and 83 years). The latency time between the start of clindamycin and onset of the symptoms of AGEP in most cases was within a few days. Only in the cases from Deng et al. and Navarini et al. was time to onset longer: 7 and 13 days, respectively. All cases
showed resolution of the pustules in less than 15 days; in three the relation between AGEP and clindamycin was supported by a patch test.\(^7\)\(^\text{42}\) Histopathological findings were concordant with AGEP. Clinical findings including patient details, laboratory features, time of onset, treatment and recovery of AGEP are summarised in \(\text{Table 2.}\)

**DISCUSSION**

AGEP is a rare, most often drug-induced, serious pustular reaction pattern, characterised by an acute onset and typical clinical picture and course. In 2001, a standardised validation score system was proposed, taking into account the morphology of the lesions, the course of the disease, and laboratory and histopathological features.\(^8\) AGEP is considered to be a subtype of a delayed hypersensitivity type IV reaction with a role for both CD4+ (helper) and CD8+ (cytotoxic) T cells.\(^9\)\(^\text{10}\) The latency period between the administration of drugs and onset of AGEP is typically short, most often within 1-3 weeks after starting the causative drug. Yet in the group of anti-infective drugs the time to onset may be as short as a few hours to three days.\(^8\) The culprit drug in AGEP can regularly be confirmed by a positive patch test and/or lymphocyte transformation test with the suspected drug.\(^7\)

We describe five further cases of clindamycin-induced AGEP. Moreover, we show that the association between clindamycin and AGEP is statistically supported by the Lareb database, Vigibase™, and Eudravigilance by a significantly raised ROR. Of note is that the cases from the Lareb database are included in Vigibase™ and Eudravigilance. A reporting disproportionality for a specific drug-ADR combination, detected by spontaneous reporting of ADRs, plays an important role in providing early signals for detecting new ADRs in the post-marketing phase. The statistical relevance of a raised ROR will be more reliable if the number of cases on which it is calculated is higher. However, the clinical relevance of these reporting systems is limited to the assumed existence of a certain association, although they can contribute to more knowledge of the nature and incidence of ADRs in daily practice. The quality of information and causality of the reported drug-ADR association of an individual report in spontaneous reporting systems can vary substantially. Disproportionality analysis is hypothesis generating and can indicate where harm might be, but to confirm and/or quantify harm, one has to rely on case reports or series or use other pharmacoepidemiological methods.

Our cases, all confirmed by a dermatologist, provide further support for the association of clindamycin with AGEP. The relatively short time to onset is consistent with drug-induced AGEP. Median latencies for the Lareb and the published cases were 2 days (0.5-7 days) and 2 days (1-13 days), respectively. In all cases the patients recovered without reported sequelae after withdrawal of clindamycin. In addition, all the described cases met the criteria for full recovery of AGEP within 15 days. Lareb case B describes a patient with AGEP associated with some toxic epidermal necrolysis-like features, with a prolonged recovery time of 4-6 weeks due to other disease. Toxic epidermal necrolysis-like features in AGEP, resulting from coalescence of pustules, sometimes accompanied by more severe visceral organ involvement and haemodynamic instability, have been reported before.\(^8\) It should be noted that patient D concomitantly used diltiazem, which is strongly associated with AGEP.\(^9\) However, since it was used long-term, causality was unlikely. Although AGEP has rarely been associated with infectious diseases, particularly of viral aetiology, it is unlikely that underlying diseases were causative in our cases. No association between mastocytosis and AGEP could be found in the literature. As the cases described by Valois et al. and Llamas-Velasco et al., Lareb case A and C were confirmed by a positive patch test. Information extracted from the Lareb cases and the published case reports in the literature shows that different kinds of treatments are being applied. However, as AGEP is a self-limited disease, the mainstay of treatment is withdrawal of the suspected culprit and supportive therapy such as topical and/or systemic corticosteroids, antihistamines and sometimes antibacterial agents. Use of systemic steroids, however, has not yet been sufficiently evidenced in the literature.

In conclusion, we report five cases of AGEP associated with the use of clindamycin. We reviewed the literature on similar case reports and performed a case/non-case analysis in Vigibase™, the Eudravigilance database and the Lareb database. AGEP should be considered a rare, but possible, serious cutaneous adverse drug reaction of clindamycin.
Table 2. Summary of case reports with AGEP associated with clindamycin

<table>
<thead>
<tr>
<th>Source</th>
<th>Sex, age</th>
<th>Clinical and laboratory features</th>
<th>Time to onset</th>
<th>Co-medication</th>
<th>Indication; medical history</th>
<th>Histopathology</th>
<th>Treatment</th>
<th>Time to recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwab</td>
<td>Female 72</td>
<td>Erythematous, oedematous, pruritic plaques on the chest, back, groin, arms and legs with numerous non-follicular pinhead sized pustules</td>
<td>1 day</td>
<td>Oestrogen, long-term</td>
<td>Pre-operative prophylactic antibiotic; penicillin allergy;</td>
<td>Subcorneal and intraepidermal pustules with neutrophils, eosinophils and focal spongiosis. Dermal interstitial infiltrates with numerous eosinophils and neutrophils</td>
<td>Clindamycin withdrawn; unspecified systemic corticosteroids</td>
<td>1 week</td>
</tr>
<tr>
<td>Valois</td>
<td>Male 69</td>
<td>Pruritic exanthema on trunk, spreading distally</td>
<td>Day 3 after 300 mg qid</td>
<td>Mouth abscess</td>
<td>Spongiosis, exocytosis of lymphocytes and some neutrophils. Dermal oedema, interstitial mixed infiltrates, including neutrophils and eosinophils</td>
<td>Withdrawal of clindamycin</td>
<td>2 weeks</td>
<td></td>
</tr>
<tr>
<td>Valois</td>
<td>Male 76</td>
<td>Mildly pruritic, generalised erythematous rash</td>
<td>36 hours after 300 mg qid</td>
<td>Levofoxacin, started simultaneously</td>
<td>Necrotic finger ulcer</td>
<td>All antibiotics withdrawn</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>Kapoor</td>
<td>Female 38</td>
<td>Widespread, painful, pruritic, erythematous macules and papules (80% BSA), studded with tiny flaccid pustules, evolving to desquamation</td>
<td>Day 4 after 300 mg tid</td>
<td>Prednisone, methotrexate, fluvoxetine, valacyclovir, alendronate, atenolol, losartan, hydroxychloroquine, clonidine, amlodipine, furosemide, insulin; all long-term</td>
<td>Suspected intravenous site infection; SLE, hypertension, diabetes mellitus, depression</td>
<td>Withdrawal of clindamycin methylprednisolone iv, hydroxyzine, diphenhydramine, hydromorphone and topical lidocaine</td>
<td>14 days</td>
<td></td>
</tr>
<tr>
<td>Meiss</td>
<td>Female 49</td>
<td>AGEP with TEN-like features</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>Withdrawal of clindamycin</td>
<td>Unspecified systemic corticosteroids, infliximab</td>
<td>6-14 days</td>
</tr>
</tbody>
</table>

Smeets et al. Clindamycin-induced acute generalised exanthematous pustulosis.
<table>
<thead>
<tr>
<th>Source</th>
<th>Sex, age</th>
<th>Clinical and laboratory features</th>
<th>Time to onset</th>
<th>Co-medication</th>
<th>Indication; medical history</th>
<th>Histopathology</th>
<th>Treatment</th>
<th>Time to recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulewski10</td>
<td>Female 82</td>
<td>Extending erythematous diffuse papular, pruritic eruption, on the face, trunk and extremities. Numerous, scattered, non-follicular pustules. Unspecified fever and malaise. Butterfly-shaped erythema of the face and sheets of desquamation on the back</td>
<td>Day 2</td>
<td>Potassium supplements, losartan, escitalopram, occasionally ibuprofen or aspirin for pain, all long-term use</td>
<td>Prophylaxis for dental procedure; fibromyalgia, idiopathic peripheral polyneuropathy, osteoarthritis, obesity, hypertension, peripheral vascular disease, and bilateral lower extremity lymphedema. Stevens-Johnson syndrome (levofloxacin)</td>
<td>Spongiform subcorneal pustules, perivascular and diffuse dermal infiltrates of lymphocytes and eosinophils</td>
<td>Clindamycin already withdrawn. Methylprednisolone iv, doxepin, hydroxyzine, acetaminophen; hydrocortisone cream 1%</td>
<td>12 days</td>
</tr>
<tr>
<td>Makrisa</td>
<td>Female 56</td>
<td>Erythematous, burning, pruritic and partly oedematous eruption, starting in the gluteus area bilaterally, expanding to the trunk, arms and femurs with dozens of small, pinhead sized, non-follicular pustules; mainly in the folds</td>
<td>Day 2 after 600 mg bid</td>
<td>Cefuroxime 750 mg tid</td>
<td>Skin lesions due to a spider bite (Loxosceles rufescens)</td>
<td>Subcorneal and intraepithelial pustules, papillary dermal oedema and diffuse perivascular infiltrates</td>
<td>Antihistamines and emollients</td>
<td>14 days</td>
</tr>
<tr>
<td>Denga</td>
<td>Female 70</td>
<td>Erythroderma (BSA 80%) with hundreds of non-follicular pustules, fused into large bullae, involving the intertriginous as well as the extensor areas</td>
<td>7 days</td>
<td>NK</td>
<td>Skin symptoms not specified; Hailey-Hailey disease</td>
<td>Subcorneal/ intraepidermal pustules. Mild spongiosis, confluent acantholysis, mild exocytosis. Superficial perivascular and interstitial infiltrates</td>
<td>Withdrawal of clindamycin</td>
<td>4 days</td>
</tr>
<tr>
<td>Llamas-Velasco3</td>
<td>Female 78</td>
<td>Diffuse erythematous oedematous plaques on trunk and extremities, studded with large numbers of non-follicular, pinhead-sized pustules. Erythema and oedema of the face, with honey-coloured crusts, pustules, and pinpoint desquamation</td>
<td>1 day</td>
<td>Levofoxacin</td>
<td>Prophylaxis hip replacement procedure; hypertension, haemochromatosis, osteoporosis and bilateral hip replacement</td>
<td>Subcorneal pustules and diffuse perivascular dermal infiltrates of atypical mononuclear cells with large nuclei, prominent nucleoli, and mitotic figures, positive for CD3 and CD30</td>
<td>All antibiotics withdrawn</td>
<td>1 week</td>
</tr>
<tr>
<td>Source</td>
<td>Sex, age</td>
<td>Clinical and laboratory features</td>
<td>Time to onset</td>
<td>Co-medication</td>
<td>Indication; medical history</td>
<td>Histopathology</td>
<td>Treatment</td>
<td>Time to recovery</td>
</tr>
<tr>
<td>----------</td>
<td>----------</td>
<td>----------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-----------------------------</td>
<td>----------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Navarini*</td>
<td>Male</td>
<td>83</td>
<td></td>
<td>13 days</td>
<td>Rifampicin</td>
<td>NK</td>
<td>Infection of osteosynthesis</td>
<td>NK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-follicular pustules (8% BSA) on widespread erythema</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever (39.4°C), WBC 22.2 x10^9/l and heterozygous IL36RN mutation (c.338C&gt;T)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient A</td>
<td>Female</td>
<td>32</td>
<td>7 days</td>
<td>Ciprofloxacin, started concomitantly</td>
<td>Paronychia; obesity; muscle growth</td>
<td>NK</td>
<td>Histology compatible with AGEP</td>
<td>All antibiotics withdrawn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Itching pustular rash, post-pustular desquamation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever (39.0°C), Pronounced peripheral neutrophilia, raised CRP.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patch test clindamycin positive, ciprofloxacin negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient B</td>
<td>Female</td>
<td>68</td>
<td>1 day</td>
<td>Sepsis; lactose intolerance, ulcer, joint, peripheral ulceration, surgery lung carcinoma, collagenous colitis</td>
<td>Histology compatible with AGEP</td>
<td>NK</td>
<td>Clindamycin withdrawn</td>
<td>Unspecified supportive treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dark red pustular erythema on abdomen, redness on torso and blistering, Positive pseudo-Nikolsky’s sign</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever (&gt;38.0°C) WBC 22.5 x 10^9/l, neutrophils &gt;7x10^9/l , creatinine 138 µmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient C</td>
<td>Female</td>
<td>58</td>
<td>2 days</td>
<td>Levothyroxine sodium, enalapril, temazepam, omeprazole, sertraline: all long-term use</td>
<td>Tonsillitis; depression, hypertension and hypothyroidism, macular rash after penicillin</td>
<td>NK</td>
<td>Clindamycin withdrawn</td>
<td>Prednisone, antihistamines, Triamcinolone cream</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pustular rash, recovering with post-pustular desquamation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever</td>
<td>Patch test clindamycin positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient D</td>
<td>Female</td>
<td>65</td>
<td>2 days</td>
<td>Furosemide, atorvastatin, tramadol, omeprazole, diltiazem, perindopril, prednisolone, loperamide, calcium carbonate, acenocoumarol, and diclofenac: all long-term use</td>
<td>Jaw abscess; hypertension, polycythemia vera, myelofibrosis, arteritis temporalis, aneurysm of the abdominal aorta, and percutaneous transluminal coronary angioplasty</td>
<td>NK</td>
<td>Clindamycin withdrawn</td>
<td>Clemastine, prednisolone, ketoconazole, dalteparin, esomeprazole, acetaminophen, i.v. fluids, metronidazole/ ciprofloxacin; topical hydrocortisone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AGEP according to dermatologist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever, haemodynamic instability, increased INR, and ventricular tachycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient E</td>
<td>Male</td>
<td>53</td>
<td>0.5 day</td>
<td>NK</td>
<td>Sinusitis</td>
<td>NK</td>
<td>Clindamycin withdrawn</td>
<td>Unspecified corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AGEP according to dermatologist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NK = not known; WBC = white blood cell count; SLE = systemic lupus erythematosus; BSA = body surface area; CRP = C-reactive protein; iv = intravenous.
DISCLOSURES

All authors declare that they have no conflict of interest. No financial support was received for the conduct of this study or preparation of this manuscript.

REFERENCES


Smeets et al. Clindamycin-induced acute generalised exanthematous pustulosis.
Investigating screening for diabetes in women with a history of gestational diabetes

H.S. Brink*#, M. Alkemade†, A.J. van der Lely‡, J. van der Linden*

*Both authors contributed equally to this work

1Department of Endocrinology, Maasstad Hospital, Rotterdam, the Netherlands, 2Department of Internal Medicine, Erasmus University MC, Rotterdam, the Netherlands, *corresponding author: tel.: +31 (0)10-2912889, fax: +31 (0)10-2913361, email: BrinkH@maasstadziekenhuis.nl

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is encountered more frequently in women with a history of gestational diabetes (GD). Screening for T2DM after pregnancy is, therefore, recommended every ≥ 1-3 years in this population. Early detection could allow for timely intervention strategies, especially in women of childbearing age. Data on adherence to diabetes screening recommendations and the prevalence of T2DM in this population are not available in the Dutch population.

Aim: To investigate the T2DM screening rate and evaluate the risk of T2DM in the five-year period following GD pregnancy.

Methods: Single-centre survey in 85 women diagnosed with GD in 2010, using electronic medical records. Primary care physicians were asked to complete a survey regarding the screening frequency and the onset of T2DM in the five-year period following the GD pregnancy.

Results: On average 33% underwent yearly screening. The screening rate, however, went up to 61.2% after primary care physicians were requested to screen this population in 2015. Of the women who were screened, 10 (19.2%) developed T2DM within five years after GD.

Conclusion: Current screening recommendations are poorly met, leading to missed, or delayed diagnosis of T2DM in our population. T2DM is a frequently occurring long-term complication in those who were screened in the five-year period after delivery. Optimising awareness amongst health care professionals of GD as a risk factor for T2DM is warranted and strategies to improve surveillance are necessary.

KEYWORDS

Follow-up studies; gestational diabetes; risk factors; type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health problem of epidemic proportions. The increasing incidence of T2DM is attributed to a global rise in obesity, growing elderly population and improved screening methods. In 2030 an estimated 66.5 million people will be diagnosed with diabetes in Europe alone. Identifying high-risk populations is essential for the initiation of screening and prevention in daily practice. Gestational diabetes (GD) is associated with a sevenfold increased risk for T2DM when compared with non-diabetic pregnancies. Furthermore, their offspring are at increased risk of developing obesity and T2DM later in life. Therefore, long-term screening is justified in this population. Without appropriate screening, T2DM often remains undiagnosed with asymptomatic progression. This is a concern, especially in young women of childbearing age, as undetected hyperglycaemia may cause early foetal loss or congenital malformations in a subsequent pregnancy. Evidence shows that interventions with lifestyle adjustments and diet are cost-effective and may prevent or delay the onset of diabetes. Nonetheless, 6-12 weeks postpartum screening rates are low; 20-45% of women with a GD pregnancy return for screening. Little is known about adherence to long-term yearly screening recommendations. In the Netherlands, yearly T2DM screening is recommended in the first five years after delivery. No data on adherence to these screening recommendations are available. The aim of this study was
to investigate the T2DM screening rate and determine the long-term risk of T2DM in the five years following the GD pregnancy.

METHODS

We retrospectively analysed 85 women diagnosed with GD at the Maasstad Hospital, Rotterdam, the Netherlands in 2010. GD was defined as meeting one or more of the following criteria: fasting plasma glucose ≥ 7.0 mmol/l or 2-hour plasma glucose ≥ 7.8 mmol/l (75 gram oral glucose tolerance test). Patient baseline characteristics were obtained from electronic medical records (tables 1 and 2). BMI (kg/m²) was determined in early pregnancy at the first visit to the obstetrics & gynaecology outpatient clinic. Insulin therapy was initiated when dietary and lifestyle adjustments did not result in treatment targets (fasting glucose < 5.3 mmol/l and 2 hours after meals < 6.7 mmol/l). In the Netherlands, primary care physicians are responsible for yearly T2DM screening in women with a history of GD. According to the Dutch College of General Practitioners, yearly screening (fasting glucose) is advocated for the five-year period directly following the GD pregnancy and every three years thereafter. In accordance with these recommendations, we conducted a survey in 2015 among the primary care physicians of the 2010 cohort of 85 women with GD. They were asked to answer two questions: 1) Did yearly T2DM screening (fasting glucose) take place during the five years following the GD pregnancy? 2) Was the patient diagnosed with T2DM in the five years following the GD pregnancy? Diagnosis of T2DM was defined as: fasting glucose ≥ 7.0 mmol/l on two separate days, or fasting glucose ≥ 7.0 mmol/l or a random glucose ≥ 11.0 mmol/l in combination with symptoms associated with hyperglycaemia. If patients had not been screened in 2015, the primary care physicians received a request to recommence T2DM screening. The percentage of T2DM in the five-year follow-up period was determined in those patients who were screened every year (2010-2015) or in those who were only screened in 2015.

RESULTS

In total 85 women diagnosed with GD in 2010 were analysed. Maternal characteristics are shown in table 1. The median age was 33 years with a range from 28-37. The majority of women (76.5%) had a BMI > 25 in early pregnancy. The population is diverse in terms of ethnicity: about one-third are Caucasian, while one out of four women were of north-African descent. Insulin therapy was required in n = 39 (45.9%) of cases. Diabetes mellitus in a first-degree family member (58.8%) appeared to be a prevalent risk factor in our population. Patient characteristics during the pregnancy of the women who developed T2DM are shown in table 2. In the first four years of follow-up, 33% of the population were screened yearly. In 2015, when the primary care physicians were requested to recommence screening, the rate increased to 61.2% (n = 52). In the population of women who were screened in the five-year follow-up period, 10 (19.2%)...
Table 2. Patient characteristics during pregnancy of women who developed T2DM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T2DM (n = 10)</th>
<th>No T2DM (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33±10</td>
<td>33±9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.1±9</td>
<td>28.5±6</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>3 (10)</td>
<td>17 (40.5)</td>
</tr>
<tr>
<td>Negroid</td>
<td>1 (10)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (10)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Hindu</td>
<td>1 (10)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>North-African</td>
<td>2 (20)</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>Turkish</td>
<td>1 (10)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Middle East</td>
<td>1 (10)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>First trimester random glucose (mmol/l)</td>
<td>5.05±0.75</td>
<td>5.5±1.2</td>
</tr>
</tbody>
</table>

BMI = body mass index. Data are presented as proportion n (%), median [IQR] or mean ± SD.

dveloped T2DM and 42 did not. In the group that were not screened (n = 33), 11 women did not respond to the screening invitation and 22 moved away, or changed primary care doctors or were lost to follow-up.

**Discussion**

To our knowledge this is the first study to investigate adherence to long-term diabetes screening recommendations in women with a history of GD in the Netherlands. Our study shows that the mandatory screening of women with GD for the development of overt T2DM is suboptimal at best. Furthermore, T2DM was a frequent complication in those who were screened. Similar low screening rates have been reported before. Sending a reminder to the primary care physicians seems to have a significant effect on the screening rate, suggesting that reminders could help to accomplish higher screening rates. There are a number of explanations as to why long-term screening recommendations are not met. Post-partum screening studies have shown that women fail to return for screening (20-45% attendance) shortly after delivery. Reported barriers for postpartum screening included: limited time and other priorities such as childcare. However, when GD women do not attend post-partum screening programs, they appear to remain out of sight of screening in the subsequent years after pregnancy.

Furthermore, the transition of care from the endocrinologist and obstetrician during pregnancy to the primary care setting after delivery remains a pitfall in accomplishing proper screening. Thirdly, conflicting screening programs on long-term follow-up frequency do exist, promoting ambivalence towards systematic screening. The American Diabetes Association recommends diabetes screening 6-12 weeks postpartum using OGTT and every 1-3 years thereafter. Women should be screened every three years if the results are normal; however, if impaired glucose tolerance or impaired fasting glucose is detected, screening should be done annually. The American College of Obstetrics and Gynaecology recommends screening six weeks postpartum, but does not provide recommendations after this period. The Dutch Obstetrics and Gynaecology Association recommends screening six weeks postpartum and yearly screening thereafter, but no statement is made about the duration of follow-up.

Finally, recognition and awareness of GD as a risk factor for diabetes is not widespread among patients and health care providers. In a long-term follow-up study more than half of the women with a history of GD reported that they had not been informed about their risk of T2DM. In a survey among women 3-5 years after their GD pregnancy, less than half believed that it was ‘highly possible’ or ‘very possible’ that they would develop T2DM. Another survey showed that although almost all women with a history of GD were aware of the risk for diabetes, only 16% believed that they were at risk as an individual.

Improving screening rates is important for a number of reasons. First, early detection could allow timely intervention. Additionally, considering the childbearing age of this population, it is important to aim for glycaemic control before future pregnancies. Furthermore, in women with a history of GD, compared with placebo, lifestyle intervention and metformin reduced progression to T2DM by 35% and 40%, respectively. The number of screened women was relatively small, the risk of T2DM found in our population should be interpreted with caution. Although T2DM is a frequent long-term complication in women with GD, the percentage of T2DM in our population appeared to be lower than previously reported. However, our estimates are in line with more recent data from a systematic review showing a risk between 9.5% and 37% (3.5-11.5 years follow-up).

In our study, the risk of T2DM was determined in women with a history of GD, compared with placebo, lifestyle intervention and metformin reduced progression to T2DM by 35% and 40%, respectively. Since the number of screened women was relatively small, the risk of T2DM found in our population should be interpreted with caution. Although T2DM is a frequent long-term complication in women with GD, the percentage of T2DM in our population appeared to be lower than previously reported. However, our estimates are in line with more recent data from a systematic review showing a risk between 9.5% and 37% (3.5-11.5 years follow-up).

In our study, the risk of T2DM was determined in those women with a complete five-year follow-up or with T2DM screening in 2015. Theoretically, women with pre-gestational diabetes could have been included; however, since the first trimester screening showed normal random glucose levels this is less likely. The need for insulin therapy was higher in our population than previously described. This could be attributed
to strict multidisciplinary management policy. Insulin therapy was initiated if glycaemic targets were not met on two consecutive days. Furthermore, obesity was highly prevalent in our population. Other limitations of this study include the retrospective design, and the fact that data on BMI before pregnancy were not available.

**Potential strategies to improve surveillance**

As education regarding the risk of T2DM during pregnancy will probably result in improved awareness and self-management after pregnancy, counselling women about long-term screening and raising awareness is clearly needed. Correspondence with clear screening recommendations from the gynaecologist or endocrinologist to the primary care physician is a vital step in the transfer of care. Subsequent registration of the GD diagnosis in primary care medical record systems is important for the identification of women who should be screened for T2DM after delivery. As long as GD is not classified in the international disease codes (International Classification of Primary Care – ICPC), no automatic yearly screening invitations will be generated and yearly screening will likely not be performed. This is particularly worrisome in those patients who do not initiate screening themselves. Through ICPC registration in electronic medical records, screening could be implemented on a large scale by means of automatic yearly reminders. Furthermore, uniformity in international long-term screening guidelines should be met for the implementation of systematic screening. Several types of reminding systems have been investigated. Women prefer SMS reminders according to a questionnaire in an Australian cohort. Postal and voice calls were the least preferred types. A systematic review investigated the effect of reminder systems for postpartum screening. Results showed that direct telephone calls strengthened the reminding effect on the women. Surprisingly, reminding both the primary care physician as well as the patient has not proven to be effective. A recent study showed that introducing a regional central coordinator to remind women both in writing and verbally improved post-partum screening rates to 75%. Furthermore, identifying those women who are at greatest risk of developing diabetes postpartum would allow better individual education during pregnancy. Maternal age, obesity, insulin therapy, highest fasting glucose level (4th quartile vs. 1st quartile range), severity of glucose intolerance and a previous GD pregnancy have been reported to be predictive factors for the development of T2DM.

In summary, current screening recommendations appear to be largely unsuccessful, leading to missed diagnoses of T2DM in women of childbearing age. T2DM is a frequent long-term complication in those women who were screened. Optimising awareness amongst health care professionals of GD as a risk factor for T2DM is warranted and strategies such as systematic reminder systems are necessary to improve surveillance.

**DISCLOSURES**

The authors declare no conflicts of interest.

**REFERENCES**


Physician consensus on preventability and predictability of readmissions based on standard case scenarios

L.S. van Galen¹, T. Cooksley², H. Merten³, M. Brabrand⁴, C.B. Terwee¹, C.H. Nickel¹, C.P. Subbe⁵, R. Kidney⁷, J. Soong⁸, L. Vaughan⁹, I. Weichert¹⁰, M.H.H. Kramer¹, P.W.B. Nanayakkara*¹

¹Department of Internal Medicine, VU University Medical Centre, Amsterdam, the Netherlands, ²Department of Acute Medicine, University Hospital of South Manchester, Manchester, UK, ³Department of Public and Occupational Health, EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, the Netherlands, ⁴Department of Emergency Medicine, Hospital of South West Jutland, Denmark, ⁵Department of Emergency Medicine, University Hospital Basel, Switzerland, ⁶Department of Acute Medicine, Ysbyty Gwynedd Hospital, Wales, ⁷Department of Internal Medicine, St. James Hospital, Dublin, Ireland, ⁸Department of Acute Medicine, Imperial College London, UK, ⁹Department of Medicine and Therapeutics, Chelsea and Westminster Hospital, London, ¹⁰Department of Internal Medicine, The Ipswich Hospital NHS Trust, Ipswich, United Kingdom, *corresponding author: tel.: +31(0)20-4444444 ext. 6791, email: p.nanayakkara@vumc.nl

ABSTRACT

Background: Policy makers struggle with unplanned readmissions as a quality indicator since integrating preventability in such indicators is difficult. Most studies on the preventability of readmissions questioned physicians whether they consider a given readmission to be preventable, from which conclusions on factors predicting preventable readmissions were derived. There is no literature on the interobserver agreement of physician judgement.

Aim: To assess the degree of agreement among physicians regarding predictability and preventability of medical readmissions.

Design: An online survey based on eight real-life case scenarios was distributed to European physicians.

Methods: Physicians were requested to rate from the first four (index admission) scenarios whether they expected these patients to be readmitted within 30 days (the predictability). The remaining four cases, describing a readmission, were used to assess the preventability. The main outcome was the degree of agreement among physicians determined using the intra class correlation coefficient (ICC).

Results: 526 European medical physicians completed the survey. Most physicians had internal medicine as primary specialism. The median years of clinical experience was 11. ICC for predictability of readmission was 0.67 (moderate to good) and ICC for preventability of readmission was 0.13 (poor).

Conclusion: There was moderate to good agreement among physicians on the predictability of readmissions while agreement on preventability was poor. This study indicates that assessing preventability of readmissions based solely on the judgement of physicians is far from perfect. Current literature on the preventability of readmissions and conclusions derived on the basis of physician opinion should be interpreted with caution.

KEYWORDS

Patient safety, quality improvement, readmissions

INTRODUCTION

Hospital readmissions within 30 days are of interest to many policy makers internationally. They are used as a quality and safety indicator with financial penalties levied in many countries including the United
States and United Kingdom. The main problem in using readmissions as a quality indicator is that the preventability of these readmissions is not properly defined and integrated in this indicator making it difficult to use as a genuine measure of quality of care. By not distinguishing between preventable and non-preventable readmissions this indicator might therefore result in distorted evaluation of hospital care. Furthermore, there is increasing evidence that the causes of mostly medical readmissions are often multifactorial and usually the result of natural disease progression, underlying comorbidity or socio-environmental factors beyond the control of the hospital and not solely caused by inadequate hospital care. The use of readmissions as a quality indicator necessitates that they reflect poor care, are preventable and that a consensus definition for these two aspects is agreed. Previous research has not yet been able to determine uniform factors related to preventable readmissions. To date, consensus definition of preventability has not been established. Many studies use the opinion of physicians as the gold standard to determine if readmissions are preventable, and derive factors that would predict preventable readmissions from these findings. However, to our knowledge, no study has yet been performed to examine the interobserver reliability of the physicians’ judgement on preventability. Therefore, we performed an international study to assess if there is any consensus between physicians regarding the predictability and preventability of medical readmissions.

**MATERIAL AND METHODS**

This study is an initiative of the safer@home consortium, an international group founded in 2013 consisting of 13 acute medical physicians, emergency physicians and epidemiologists from Europe that focus on readmissions and safer discharge processes. During the 3-month study period (1 September to 1 December 2015) a survey on eight cases based on common clinical scenarios (see appendix) was distributed to physicians throughout Europe.

**Survey**

The survey consisted of eight case-based medical scenarios (table 1 shows a summary of the case vignettes). The scenarios were generated using a Delphi-type methodology, whereby multiple scenarios were generated and then represented to the safer@home consortium in two rounds. In the first round underlying assumptions and information leading to different judgements was explored using current readmission literature. This round took place in a face-to-face half-yearly consortium meeting with all 13 members. After this, seven clinically active medical physicians in the group were asked to provide examples from their daily work in order to compose cases. In the second round, these cases were discussed in a conference call during which the cases that would be representative for all countries were selected through consensus. In addition we assessed if, in our ‘expert’ opinion, the cases could potentially be used to fulfil the purpose of our research question. Subsequently, a pilot was performed on a small group of physicians from all countries to ensure cases were understandable and varied sufficiently. Final case selection ensured that: a) the cases would be representative of patients requiring unselected medical admission in northern Europe; b) the scenarios covered the range of factors suggested by the literature to impact on readmissions; c) cases were not traceable to real-life patients.

The online survey consisted of two parts: 1) Physicians were asked about their opinion on predictability of medical readmissions; from four cases describing an index admission, physicians were asked to rate the chance of readmission within 30 days. 2) Physicians were asked to assess the preventability of four described medical readmission cases.

From the physicians’ assessment of predictability and preventability, the degree of consensus could be derived. For both parts of the survey a five-point Likert Scale was used as an answering model (part 1: Definitely not predictable (1) – Definitely predictable (5); part 2: Definitely not preventable (1) - Definitely preventable (5)).

Data on the country and primary specialty of the responding physician filling out the survey and the number of years of clinical experience were collected in order to explore agreement within these subgroups. The survey was anonymised to ensure the researchers could not trace which physician filled out which survey. Finally, general comments concerning readmission could be made after completing the survey.

**Distribution**

The survey was distributed among physicians throughout Europe; they all worked solely in a medical specialty and not in any surgical specialty. Invitations were sent to the members of the Society for Acute Medicine in the UK, the Dutch Acute Medicine Society, the Danish Society for Emergency Medicine, physicians from Switzerland and Ireland using a common web-based platform SurveyMonkey. In order to calculate an accurate response rate, each physician communicated the number of requests sent to one research member (LG), who was responsible for data processing and statistical analysis. The ethics committee of the VU University Medical Center, Amsterdam approved the study. No funding was received for this study.
Descriptive characteristics and frequencies were calculated in SPSS version 22.0. Ratings of physicians are presented as frequencies and percentages. Using the intraclass correlation (ICC, a reliability coefficient) we assessed agreement among physicians regarding the predictability and subsequently, the preventability of the assessed medical readmissions. This coefficient (ICC) is used to assess the agreement of ratings made by multiple observers (in our study ‘physicians’) measuring the same outcome (in our study ‘the predictability and preventability of readmissions both based on four real-life readmission scenarios’). The ICC is a ratio ranging in value between 0 (representing no agreement) and 1 (implying agreement).

**Table 1. Summary of the case vignettes.** A. Predictability: Please assess on a scale from 1-5 if you think the following four admissions are followed by a readmission within 30 days: Definitely not (1) - Definitely (5). B. Preventability: Please assess on a scale from 1 to 5 if you think the following four readmissions within 30 days are: Definitely not preventable (1) - Definitely preventable (5)

### A

<table>
<thead>
<tr>
<th>Case 1.1</th>
<th>Demographics</th>
<th>Presenting complaint</th>
<th>Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>83-year-old female</td>
<td>Collapse</td>
<td>Atrial fibrillation, hypertension, urinary tract infection</td>
<td>Raised inflammatory markers, Positive urine culture</td>
<td>Antibiotics, Aspirin</td>
<td>Cardioversion with sepsis treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case 1.2</th>
<th>Demographics</th>
<th>Presenting complaint</th>
<th>Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-year-old female</td>
<td>Headache</td>
<td>Migraine</td>
<td>CT brain: normal, Lumbar puncture: normal</td>
<td>Intravenous fluids, Paracetamol, NSAID</td>
<td>Use of home nebulisers</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case 1.3</th>
<th>Demographics</th>
<th>Presenting complaint</th>
<th>Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-year-old female</td>
<td>Dyspnoea</td>
<td>Productive cough</td>
<td>Infective exacerbation of COPD</td>
<td>Sputum culture negative, Oxygen, Bronchodilators, Steroids, Antibiotics</td>
<td>Use of home nebulisers</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case 1.4</th>
<th>Demographics</th>
<th>Presenting complaint</th>
<th>Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>94-year-old female</td>
<td>Dyspnoea</td>
<td>Pneumonia</td>
<td>Persistently raised inflammatory markers two days before discharge</td>
<td>Antibiotics</td>
<td>Chest pain, dyspnoea and vomiting prior to discharge</td>
<td></td>
</tr>
</tbody>
</table>

### B

<table>
<thead>
<tr>
<th>Case 2.1</th>
<th>Demographics</th>
<th>Presenting complaint</th>
<th>Diagnosis</th>
<th>Investigation</th>
<th>Management</th>
<th>Readmission diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>63-year-old lady</td>
<td>Fever</td>
<td>Gemcitabine-induced fever</td>
<td>None of note</td>
<td>Supportive treatment</td>
<td>Neutropenic sepsis 10 days later</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case 2.2</th>
<th>Demographics</th>
<th>Presenting complaint</th>
<th>Diagnosis</th>
<th>Investigation</th>
<th>Management</th>
<th>Readmission diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-year-old male</td>
<td>Ascites</td>
<td>Childs B cirrhosis Alcohol dependency</td>
<td>None of note</td>
<td>Abdominal paracentesis, Diuretics, vitamins, lactulose, Alcohol support declined</td>
<td>Upper gastrointestinal bleed 3 weeks later</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case 2.3</th>
<th>Demographics</th>
<th>Presenting complaint</th>
<th>Diagnosis</th>
<th>Investigation</th>
<th>Management</th>
<th>Readmission diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-year-old male</td>
<td>Chest pain</td>
<td>Anterior ST-elevation myocardial infarction</td>
<td>Angiogram, Echocardiogram with moderate LV dysfunction</td>
<td>Angioplasty of the LAD, Secondary prevention</td>
<td>Pulmonary oedema 3 weeks later</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case 2.4</th>
<th>Demographics</th>
<th>Presenting complaint</th>
<th>Diagnosis</th>
<th>Investigation</th>
<th>Management</th>
<th>Readmission diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>32-year-old female</td>
<td>Loin pain</td>
<td>Pyelonephritis Hydronephrosis due to ureter stenosis</td>
<td>Ultrasound abdomen Urine culture</td>
<td>Intravenous antibiotics as outpatient</td>
<td>Pyelonephritis one month later</td>
<td></td>
</tr>
</tbody>
</table>

LAD = left anterior descending artery; LV = left ventricular; NSAID = non-steroidal anti-inflammatory drug.

**Statistics**

Descriptive characteristics and frequencies were calculated in SPSS version 22.0. Ratings of physicians are presented as frequencies and percentages. Using the intraclass correlation (ICC, a reliability coefficient) we assessed agreement among physicians regarding the predictability and subsequently, the preventability of the assessed medical readmissions. This coefficient (ICC) is used to assess the agreement of ratings made by multiple observers (in our study ‘physicians’) measuring the same outcome (in our study ‘the predictability and preventability of readmissions both based on four real-life readmission scenarios’). The ICC is a ratio ranging in value between 0 (representing no agreement) and 1 (implying agreement).
Calculating the variance components we constructed the ICC formulas from which the ICC could be calculated. For dependent variables we used the outcome ‘Likert scores’ and for random factors ‘physicians’ and ‘case numbers (1.1, 1.2, 1.3, 1.4 and 2.1, 2.2, 2.3, 2.4)’ were used. The variance among cases (case numbers 1.1, 1.2, 1.3, 1.4 and 2.1, 2.2, 2.3, 2.4) was analysed separately, among physicians, and the random error were calculated in SPSS using the VARCOMP procedure. From the variance components we calculated the ICC for absolute agreement as the variance among cases divided by the total variance of the cases, physicians and random error.

RESULTS

Physician characteristics

During the three-month study period (1 September to 1 December 2015) the survey was distributed to physicians in Europe. In total 526 medical physicians filled out the survey. The overall response rate was 24.2%. Seventy-seven (14.6%) physicians did not complete all the questions in the survey. Table 2 shows physician characteristics. Dutch physicians were the largest group of respondents (46.2%), followed by Danish (25.1%) and physicians from the United Kingdom (23.6%). Most physicians had internal medicine (33.3%) as their primary specialty followed by acute medicine (24.5%) and geriatrics (12.5%). The median years of clinical experience was 10.75 (interquartile range: 5-20).

Agreement on predictability of readmission

For the first part of the survey physicians were asked if they could predict a readmission based on the four case descriptions of medical index admissions. Responses are shown in figure 1. The results show that there was substantial variation in the degree of predictability between the physicians’ judgements in all four cases. The cases were assessed with different degrees of predictability. To illustrate, for case number 1.2, about half of the physicians assessed the likelihood of readmission as ‘definitely not’ (score 1), while in case number 2.1 over 60% of the physicians predicted that the patient will definitely be readmitted (score 5).

The ICC for agreement of predictability was 0.67 (Var(Casenumber) 1,444, Var(Observer) 0.054, Var(error) 0.649) which indicates a moderate to strong interobserver agreement between the raters (physicians). These findings suggest that the surveyed doctors had a moderate to good degree of agreement about the patients that were prone to come back, they predicted the same patients as having a higher chance of a readmission occurring.

Agreement on preventability of readmission

In the second part of the survey the respondents were asked to rate the preventability of four medical readmission cases. The results in figure 2 show the distribution of answers by the physicians. It shows that the physicians rated the cases differently; there was a wide variety in assessment. In all four cases no clear majority seemed to rate the same readmissions with similar scores. These findings were also reflected in the ICC for this part of the survey.

The ICC was calculated at 0.13 (Var(Casenumber) 0.194, Var(Observer) 0.168, Var(error) 1.076), which implies poor agreement. Doctors do not seem to agree on the preventability of readmissions. However, one must note that the variance among case numbers was relatively low which may indicate that the cases assessed were not sufficiently distinct enough to obtain a high reliability coefficient.

Subgroup analysis

To assess if there was any difference in agreement between subgroups of physicians we subdivided the doctors into years of clinical experience. They were grouped based on clinical experience up to 5 years (n = 151, 28.7%), from 5-15 years (n = 208, 39.5%), and 15 years and higher (n = 167, 31.7%).
**Figure 1.** Part I: The predictability of readmission

![Graph showing the predictability of readmissions](image1)

Spread of Likert scores (Definitely not predictable (1) – Definitely predictable (5)) given per case (1.1, 1.2, 1.3, 1.4) by 526 physicians (in percentage)

**Figure 2.** Part II: The preventability of readmission

![Graph showing the preventability of readmissions](image2)

Spread of Likert scores (Definitely not preventable (1) – Definitely preventable (5)) given per case (2.1, 2.2, 2.3, 2.4) by 526 physicians (in percentage)
Results suggest that medical physicians with less clinical experience had a trend towards greater agreement than those with more clinical experience as to the likelihood of readmission but these differences are minimal (ICC 0.70, 0.69, 0.63, respectively). Physicians with more clinical experience seemed to have more agreement about the preventability of a readmission compared with those with less clinical experience (ICC 0.08, 0.01, 0.19, respectively).

DISCUSSION

In this survey among 526 European physicians there was moderate agreement as to the predictability of medical readmissions but poor agreement about their preventability. These results suggest that doctors agree on the patients who have a higher risk of being readmitted, but the physicians differ on how preventable these readmissions are. To our knowledge, the current study is the first to investigate interobserver reliability on the evaluation of unplanned readmissions in such a large group of observers.

Unplanned readmissions are a complex phenomenon, which are influenced not only by medical factors but also by a range of social and political issues. Readmission risk is difficult to define and is less predictable than mortality. Nevertheless, there are a number of risk factors which are recognised as increasing the risk of readmission and multiple predictive scoring systems based on these factors have been designed.

Although the risk factors for predominantly medical readmission are increasingly well recognised, the dynamic of how they interact and whether they can be influenced remains controversial. The poor consensus among physicians found in our study as to whether the readmissions were preventable underlines this issue. A US study of 17 hospitalists reviewing 300 consecutive readmissions also found a wide variation in their scoring of preventability; however, comparability might be limited since these were real-life readmissions. We can concur their findings of interobserver variability in a European setting.

The above findings illustrate the problem faced by policy makers trying to integrate preventability in the readmission indicator since doctors, who are supposed to be experts in the field, cannot even agree on the readmissions that are potentially preventable. Current literature, however, often uses the opinion of one or more physicians as the gold standard to gain insight into preventability and draw conclusions on factors predicting preventability. The results in this study, however, demonstrate that the assumptions derived from these studies might lead to misperception since physicians do not share similar ideas on the potential preventability of readmissions. Hence, it can be questioned whether conclusions drawn from these studies might not provide reliable conclusions to create an appropriate quality indicator.

Readmitted medical patients are a heterogeneous group; there is a wide variation in the age, comorbidities and social support of these patients. It remains unclear as to whether the factors which drive unplanned readmission, including medical, social, cultural and environmental, are modifiable. This is reflected by an increasing body of evidence that suggests readmissions do not always reflect poor care and preventability of these readmissions is poorly defined. More research studying ‘the preventability’ in a structured manner might help to improve the difficult task in creating a reliable indicator.

We used adapted real-life case scenarios in our study, which may be a limitation. This was also reflected in the comments section, where physicians mentioned they were missing information that would allow them to thoroughly assess the case, for example more details on the patients’ social situation. It would, however, be difficult to incorporate all the potentially relevant social and environmental factors into scenarios particularly in a pan-European study where there is a wide variety of political and health policies that influence readmissions. Furthermore, in calculating the ICC for the preventability part of the survey one could suggest that there was little variation in the preventability of the cases. This may reflect either that there was insufficient variation with regards to preventability within the scenarios, potentially caused by balancing between uniformity in the cases in a way they could be representative for all countries participating in the study and enough variation in the cases in order to create different opinions per case. It may also reflect an uncertainty among physicians regarding what comprises a preventable admission.

On a final note, our respondents were of high seniority with a median of 11 years of clinical experience. If clinicians with this level of experience cannot agree on the predictability of readmission, is it wise to use it as a marker of quality of care?

CONCLUSION

This study demonstrates that there is moderate agreement among experienced medical physicians about the predictability of readmissions but poor agreement about their preventability. Therefore, the conclusions derived from earlier studies on preventability, on the basis of physician consensus as the gold standard, are questionable. Hence, a good way of defining and integrating preventability into this quality indicator remains elusive.

## DISCLOSURES

The authors have nothing to disclose.

## REFERENCES


## APPENDIX

**Physician**

Years of clinical experience:

Country:

Rationale and aims of this research project:

Hospital readmissions within 30 days are highly prevalent and costly.14 Readmission rates are already commonly used as a quantity and safety measure to rate and reimburse units across hospitals internationally.14 As of 2016, the Dutch National Health Care Program readmission rates are also an official new indicator to assess quality in hospitals. The problem in using readmission as such a quality indicator is that this approach does not focus on readmissions that are preventable. This is noteworthy since it seems to be logical that penalties should only be attached to those readmissions that could have been prevented.

Current literature, however, has not been able to find reliable percentages of readmissions deemed preventable. More importantly, the definition of preventability has not yet been defined uniformly.1 The above mentioned leads to difficulties faced by the health inspection services globally in finding an integral way to get accurate ‘preventable’ data from electronic databases. Previous research performed on preventable readmissions is often based on some physicians randomly determining if readmissions are preventable.6 However, no study has ever been performed to look into the interobserver reliability of these observations.
Therefore the main aim of this study is to assess if there is any consensus between physicians internationally regarding the occurrence and preventability of readmissions. This study is effectuated by a survey based on real-life cases and spread over clinicians internationally. It is the initiative of the international group that focuses on readmission (‘safer@homeconsortium’).

References

Part I
Please assess on a scale from 1-5 if you think the following four admissions are followed by a readmission within 30 days:
Definitely not (1) - Definitely (5) (choose 1,2,3,4,5)

1. An 83-year-old female is admitted to the acute medical unit with a collapse secondary to atrial fibrillation (160 bpm) due to a urinary tract infection – she did not have any other complaints before collapsing. Blood counts show moderately elevated CRP and leucocytes, urine testing shows leukocytes and nitrite. Her medical history includes hypertension and severe epistaxis. She is a widow and lives alone with some additional help from her daughter when needed. She takes lisinopril 5 mg, but she does not use any blood thinners or other medication. Because of her epistaxis, treating doctors decide not to start oral anticoagulation or rhythm control but only aspirin as prophylaxis for her heart rhythm disorders. During admission she receives antibiotic treatment, and her heart rate returns to sinus rhythm without extra intervention. At discharge she has no complaints.

2. A 20-year-female presents with acute onset of occipital headache suggestive of a subarachnoid haemorrhage. She is investigated with a CT brain, which is normal and subsequently undergoes a lumbar puncture, which is also entirely normal. She is treated with IV fluids, paracetamol and NSAIDs. Her headache settles and following investigations she is discharged.

3. A 60-year-old lady with severe COPD on home oxygen and nebulisers is admitted with increasing dyspnoea and a productive cough. She is diagnosed as having an infective exacerbation of COPD and is treated with steroids and antibiotics alongside her usual nebulisers, inhalers and oxygen. She makes steady progress, her sputum culture is negative and she is discharged three days later.

4. A 94-year-old woman was initially admitted with pneumonia. She was treated with ceftriaxone 2g once a day, azithromycin 500 mg once a day and discharged on doxycycline 100 mg once a day. According to the patient file, the patient was clinically doing better. However, the night before discharge the patient experienced chest pain, dyspnoea and vomiting. Last measured CRP and leucocytes were 60 (< 8 mg/l) and 22.4(4-10 x 10⁹/l) 2 days before discharge.

General comments:

Part II
Please assess on a scale from 1 to 5 if you think the following four readmissions within 30 days are:
Definitely not preventable (1) - Definitely preventable (5) (choose 1,2,3,4,5)

1. A 63-year-old lady with locally advanced pancreatic cancer presents with an episode of fever 12 hours after receiving her dose of gemcitabine. She has no other systemic symptoms and feels well in herself. Investigations are unremarkable. She is diagnosed with gemcitabine-induced fever and is discharged. Ten days later she presents with fever and diarrhoea. She is diagnosed with neutropenic sepsis.

2. A 40-year-old male with alcohol dependence presents with ascites. He consumes one bottle of whisky a day. At presentation he has Childs B cirrhosis. His undergoes abdominal paracentesis. He is commenced on diuretics, vitamin supplements and lactulose. He is offered support to reduce his alcohol intake but declines this. Three weeks later he is readmitted with haematemesis and melaena.
3. A 55-year-old male presents with an anterior STEMI. He is transferred straight to the cardiac catheter theatre and undergoes angioplasty to his LAD. He makes a good recovery. He is started on standard and appropriate secondary prevention treatment. His echo shows moderate LV dysfunction. Follow-up in the cardiac rehabilitation clinic is arranged. Three weeks later he is readmitted with dyspnoea. Clinical and radiological findings are consistent with pulmonary oedema.

4. A 32-year-old woman was admitted to the internal medicine ward under the suspicion of pyelonephritis. Her medical history mentioned an atonic bladder and hydronephrosis with ureter stenosis causing recurring pyelonephritis. The pyelonephritis was treated with iv antibiotics according to urine culture and antibiogram. Because the patient wanted to be discharged so badly and was fairly mobile it was decided to administer the iv antibiotics daily at the outpatient clinic according to the treatment plan as discussed with the nephrologist and the microbiologist. A little less than a month later the patient presented again with pyelonephritis. In between admissions the patient had been free of any UTI symptoms. Patient was treated in the same way as during the index admission and was once again discharged with a course of daily iv antibiotics at the outpatient clinic.

Thank you very much for filling out this survey!

This survey was performed as a research project from the safer@home consortium. We are an international group that focuses on readmissions. In January 2016 we will start the first prospective multicentre study on readmission:

The CURIOUS@ study (CaptUring Readmission InternatiOnally to prevent Readmission by Safer@home consortium)

In this study the main aims are: 1) to inventarise (preventable) risk factors for readmission, and 2) to verify the opinions of patients, their informal carers, nurses and physicians about the preventability of their readmissions. We are still looking for centres to join! Your participation is much appreciated. Are you or do you know anyone that is interested? Please contact us at saferathomeconsortium@gmail.com or at lo.vangalen@vumc.nl.

On behalf of the safer@home consortium:
Mikkel Brabrand, Denmark
Tim Cooksley, United Kingdom
Kristien Fluitman, the Netherlands
Louise van Galen, the Netherlands
John Kellet, Ireland
Rachel Kidney, Ireland
Hanneke Merten, the Netherlands
Prabath Nanayakkara, the Netherlands
Christian Nickel, Switzerland
John Soong, United Kingdom
Christian Subbe, Wales
Louella Vaughan, United Kingdom
Immo Weichert, United Kingdom
Never ignore extremely elevated D-dimer levels: they are specific for serious illness

T. Schutte*, A. Thijs, Y.M. Smulders

Department of Internal Medicine, VU University Medical Center, Amsterdam, the Netherlands,
*corresponding author: tel.: +31 (0)20-4448090, email: t.schutte@vumc.nl

ABSTRACT

Background: D-dimer is routinely measured as part of the clinical diagnosis algorithms for venous thromboembolism (VTE). In these algorithms, low D-dimer cut-off values are used to generate a dichotomous test result that is sensitive, but very non-specific for VTE. A consequence of any test dichotomisation is loss of information that is hidden in the continuous spectrum of results. For D-dimer, the information conveyed by extremely elevated results may be particularly relevant. Our aim was to assess the differential diagnosis of extremely elevated D-dimer levels in a hospital setting.

Methods: Retrospective cohort study of patients > 18 years with an extremely elevated (> 5000 µg/l; > 10x cut-off to exclude VTE) D-dimer test result. Electronic medical records were reviewed for diagnoses.

Results: A total of 759 extremely elevated D-dimer results were identified. After exclusion of 120 duplicate cases, 53 patients undergoing cardiopulmonary resuscitation, and 5 cases without diagnostic information, 581 cases were analysed. Their D-dimer ranged between 5030 and 239,000 µg/l, with a mean of 17,598 µg/l (SD 22,972 µg/l). Altogether, 89% of these patients had a diagnosis of VTE, sepsis and/or cancer. The prevalence was highest for pulmonary embolism (183 patients; 32%), followed by cancer (168 patients; 29%), sepsis (142 patients; 24%), trauma/surgery (142 patients; 24%), and deep vein thrombosis (73 patients; 13%).

Conclusion: Although D-dimer testing has a reputation for being very non-specific, an extremely elevated D-dimer is uniquely associated with severe disease, mainly including VTE, sepsis and/or cancer. These results suggest that, even if sharply elevated D-dimers are a seemingly solitary finding, clinical suspicion of severe underlying disease should be maintained.

KEYWORDS

VTE, D-dimer, pulmonary embolism, cancer

INTRODUCTION

D-dimer is a degradation product of cross-linked fibrin and is routinely used in diagnostic algorithms for venous thromboembolism (VTE). Since in such algorithms, the D-dimer is exclusively used as part of a rule-out strategy, a low cut-off value has been chosen to generate a highly sensitive dichotomous test for diagnosing VTE. Indeed, in both deep vein thrombosis (DVT) and pulmonary embolism, the commonly used cut-off value (500 µg/l) is associated with a high sensitivity which, combined with a low probability of VTE based on a clinical decision rule (such as the Wells Score), effectively rules out clinically significant VTE. This strategy is now firmly established in national and international guidelines and routine practice. Among clinicians, a positive D-dimer test has a reputation of being very non-specific for VTE or in fact for any other disease. It is important, though, to acknowledge that tests that generate results on a continuous scale have no intrinsic sensitivity or specificity: only results above or below a chosen threshold have such properties. In general terms, and as illustrated by receiver operating characteristic curves, the more abnormal a test result becomes, the higher its specificity. Previous studies on the magnitude of D-dimer elevation mainly focused on the positive predictive value for diagnosing VTE. Limited data from such studies indeed suggest that with higher D-dimer values, VTE becomes more likely. However, which conditions other than VTE may cause sharply elevated D-dimer levels is less well established. It is also unknown how often sharply elevated D-dimer levels occur without evidence of underlying disease. The latter is particularly relevant when no diagnosis is as yet apparent, and discharge or outpatient follow-up may be considered. Knowing that D-dimers reflect fibrinolysis, we hypothesised that extremely elevated D-dimers are almost universally associated with either VTE or with other conditions known to be associated with activation of coagulation, such as sepsis or cancer. Hence, we
anticipated that in the vast majority of cases of sharply elevated D-dimer levels, there is an associated clinical condition that requires further investigation or (urgent) medical treatment.

METHODS

Study design and patient selection
We performed a retrospective cohort study of patients with an extremely elevated D-dimer, which we arbitrarily defined as more than 10 times the commonly used cut-off value of 500 µg/l. All D-dimer results > 5000 µg/l, between 1 January 2004 and 31 December 2012, were obtained from the laboratory database of our hospital, which is a large secondary and tertiary care facility. Patients ≥ 18 years were eligible regardless of whether they were outpatients, admitted patients, or patients presenting via the emergency department. In our hospital, the routine indication for ordering D-dimer is to rule out VTE (at a fixed cut-off of 500 µg/l), but in daily practice, many physicians do not order D-dimer measurement as part of a formal VTE diagnostic strategy. D-dimer values were determined using a standardised immune-turbidimetry assay (Modular P800, Roche diagnostics). Besides D-dimer, concomitant leucocyte, platelet, coagulation and C-reactive protein results were retrieved, if available. Patients who underwent cardiopulmonary resuscitation (CPR patients) were excluded. The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines were followed where possible.

Data collection and analysis
Electronic medical records were reviewed for the primary diagnosis. If multiple diagnoses were recorded, all were included in the database. Furthermore, pregnancy and known cancer were registered. If imaging modalities were used following D-dimer testing, the results were registered. All diagnoses were categorised into predefined major disease groups (table 1). One-way ANOVA was used to compare coagulation parameters in tertiles of D-dimer levels. A p-value of ≤ 0.05 was considered to indicate statistical significance.

Ethical considerations
Formal ethical approval of the VU University Medical Center ethics review board was not necessary, as this study does not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO).

RESULTS

Patient characteristics
A total of 759 extremely elevated D-dimer values (> 5000 µg/l) were identified. An inclusion flow diagram is shown in figure 1. After exclusion of 120 duplicate cases, 53 CPR patients, and 5 patients without clinical information in the medical records, 581 cases (295 male, 286 female, mean age 62 years, SD 19) were included. The D-dimer range of included patients was 5030 µg/l to 239,000 µg/l, with a mean of 17,597 µg/l (SD 22,972 µg/l). Pulmonary CT angiography was performed in 299 patients (51.5%), in 28 (4.8%) ventilation-perfusion scintigraphy was performed, and in 95 patients (16.4%) leg compression ultrasonography was done.

Venous thromboembolism, cancer and sepsis account for the majority of diagnoses
In 577 patients (99.3%) a primary diagnosis was registered, and in 252 patients (43.3%) one or more secondary diagnoses were also established. No diagnosis was
registered in only four cases. The most frequent diagnoses are displayed in table 1. Almost one-third of all patients were diagnosed with pulmonary embolism. Combined with the DVT cases (12.6%) they were categorised as VTE, which accounted for just over 40% of all patients; 168 patients (28.9%) were diagnosed with cancer, which was the second most common diagnosis. Severe infection/sepsis was the third most frequently encountered diagnosis, established in 142 patients (24.4%). Trauma or surgery was the prime diagnosis in 142 patients, but was frequently complicated by a second diagnosis, as 15.5%, 15.5% and 14.8% of them additionally had VTE, cancer or sepsis/infection, respectively. A total of 79 patients with sharply elevated D-dimers had surgery/trauma as a single diagnosis.

In the 233 patients diagnosed with VTE (DVT or pulmonary embolism), 69 (29.6%) had a concurrent diagnosis of cancer. We observed more malignancies in the VTE cases with a D-dimer ≥ 20,000 µg/l (n = 15/30, 50.0%) compared with VTE patients with a D-dimer between 5000 and 20,000 µg/l (n = 54/203 26.6%), (chi-square, p = 0.009).

Other diagnoses
In 11.5% of cases, no VTE, sepsis, cancer and/or trauma/surgery was diagnosed. Among these, the most frequent diagnoses were aortic dissection/aneurysm (6.0%), and stroke (2.6%). All other clinical diagnoses were less frequent than 2.5% (table 1). The 5.2% of diagnoses classified as ‘other’ in table 1 occurred in two patients or less and included, among others, liver failure, childbirth, childbirth,

### Table 1. Diagnoses on discharge of patients with an extremely elevated D-dimer

<table>
<thead>
<tr>
<th>Diagnosis (multiple diagnoses possible in a single case)</th>
<th>Total</th>
<th>5000 - &lt;20,000 µg/l</th>
<th>&gt;20,000 µg/l</th>
<th>Mean D-dimer µg/l (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td></td>
<td>n = 581</td>
<td>n = 459</td>
<td>n = 122</td>
</tr>
<tr>
<td>Disorders known to cause diffuse intravascular coagulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>168</td>
<td>28.9% (119)</td>
<td>40.2% (49)</td>
<td>22,987 (30,331)</td>
</tr>
<tr>
<td>Infection</td>
<td>142</td>
<td>24.4% (110)</td>
<td>26.2% (32)</td>
<td>18,648 (25,392)</td>
</tr>
<tr>
<td>Total</td>
<td>272</td>
<td>46.8%</td>
<td>59.0% (70)</td>
<td>20,370 (25,889)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>183</td>
<td>31.5%</td>
<td>16.4% (20)</td>
<td>12,434 (9971)</td>
</tr>
<tr>
<td>DVT</td>
<td>73</td>
<td>12.6%</td>
<td>11.5% (14)</td>
<td>15,721 (13,865)</td>
</tr>
<tr>
<td>Total</td>
<td>256</td>
<td>40.1%</td>
<td>24.6% (30)</td>
<td>13,335 (11,419)</td>
</tr>
<tr>
<td>Trauma/surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>87</td>
<td>15.0%</td>
<td>24.6% (30)</td>
<td>24,218 (33,444)</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>58</td>
<td>10.0%</td>
<td>10.7% (13)</td>
<td>17,399 (27,730)</td>
</tr>
<tr>
<td>Total</td>
<td>142</td>
<td>24.4%</td>
<td>22.0% (101)</td>
<td>20,188 (27,358)</td>
</tr>
<tr>
<td>Dissection / aneurysm</td>
<td>35</td>
<td>6.0%</td>
<td>7.4% (9)</td>
<td>19,793 (19,516)</td>
</tr>
<tr>
<td>Thrombotic microangiopathies</td>
<td>15</td>
<td>2.6%</td>
<td>4.9% (6)</td>
<td>24,826 (21,238)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3</td>
<td>0.5%</td>
<td>-</td>
<td>6230 (1841)</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>2.6%</td>
<td>6.6% (8)</td>
<td>25,544 (2331)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14</td>
<td>2.4%</td>
<td>3.1% (14)</td>
<td>9610 (1823)</td>
</tr>
<tr>
<td>Auto-immune diseases</td>
<td>14</td>
<td>2.4%</td>
<td>4.9% (6)</td>
<td>16,812 (13,687)</td>
</tr>
<tr>
<td>Auto-immune diseases</td>
<td>11</td>
<td>1.9%</td>
<td>2.4% (11)</td>
<td>10,975 (4820)</td>
</tr>
<tr>
<td>Arterial thrombus</td>
<td>8</td>
<td>1.4%</td>
<td>1.7% (8)</td>
<td>9720 (4577)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>4</td>
<td>0.7%</td>
<td>0.3% (4)</td>
<td>12445 (7548)</td>
</tr>
<tr>
<td>Other**</td>
<td>30</td>
<td>5.2%</td>
<td>4.9% (6)</td>
<td>13,880 (12,559)</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>4</td>
<td>0.7%</td>
<td>0.8% (1)</td>
<td>22,270 (28,419)</td>
</tr>
</tbody>
</table>

*The diagnosis 'Infection' was registered for patients with a diagnosis of an infectious disease together with a systemic inflammatory response.

**Other included severe liver failure, childbirth, bleeding or haematoma (e.g. subdural haematoma), allergic (anaphylactic) reaction and multiorgan failure (not otherwise specified).
bleeding or haematoma (e.g. subdural haematoma), allergic (anaphylactic) reaction and multiorgan failure (not further specified). Pregnancy, a condition known to contribute to elevated D-dimer levels, was present in 25 cases (4.3%). In all pregnant patients a second diagnosis was noted, being pregnancy related (i.e. pre-eclampsia, HELLP, or childbirth) or with another diagnosis in the table. Fourteen patients were diagnosed with heart failure, which we believe is unlikely to contribute significantly to such a D-dimer elevation in cases that are otherwise uncomplicated.

Many patients with sharply elevated D-dimers have additional signs of activated coagulation. Table 2 shows the results of haemostatic variables. Over one-third of the studied patients had concurrent thrombocytopenia (thrombocyte count $< 150 \times 10^9$) and over half of the patients had a prolonged coagulation time (prothrombin time $> 1.20$ INR, or activated partial thromboplastin time; aPTT $> 40$ sec). Haemostatic variables were generally more indicative of diffuse intravascular coagulation (DIC) in the highest tertile of D-dimer levels.

**DISCUSSION**

The salient finding of our study is that a sharply elevated D-dimer level, arbitrarily defined as $> 5000 \mu g/l$, has a very high predictive value for serious disease, mainly including VTE, sepsis and cancer. Even in the patients with VTE, underlying cancer was more prevalent in the highest D-dimer ranges. If the cause of an extremely elevated D-dimer is not immediately apparent during initial clinical evaluation because patients may not appear seriously ill, suspicion of serious underlying disease should persist. The most common diagnoses were VTE (40.1%), sepsis (24.4%), cancer (28.9%), and complicated trauma/surgery (24.4%). In clinical practice, VTE and sepsis are unlikely to be missed if such extreme D-dimer results are found, because suspicion of VTE is commonly the clinical indication for D-dimer testing in the first place, and sepsis is usually evident on clinical grounds. However, some cases of sepsis and many cases of cancer may not be evident clinically, and extreme D-dimer levels in patients without VTE or manifest sepsis should thus alert clinicians to the possibility of these diagnoses. In addition, sharply elevated D-dimer levels more rarely point to other conditions that may be difficult to diagnose, particularly in an acute setting, such as aortic dissection. In any case, our results suggest that virtually all patients with sharply elevated D-dimer levels have one or multiple serious conditions. Clinicians may regularly encounter patients who are, for example, suspected of having pulmonary embolism, have an extremely elevated D-dimer level but negative results on CT angiography. The results of our study encourage careful evaluation of other causes of such extreme D-dimer levels, rather than disregarding them because ‘D-dimer is a non-specific test’.

Previous studies on the magnitude of D-dimer elevation mainly focussed on the positive predictive value specifically for diagnosing VTE, and also suggested that the magnitude of D-dimer elevation correlates with the likelihood of having VTE. One study found pulmonary embolism in 35.3% of 34 patients with a D-dimer of 5000 to 20,000 $\mu g/l$ and in 45.5% of only 11 patients with a D-dimer of $> 20,000 \mu g/l$. A second study concluded that infection, sepsis and cancer should be considered in patients with elevated D-dimer above the regular cut-off level of 500 $\mu g/l$. In this study the prevalence of cancer and infection/sepsis was 6.3% and 35.9%. This study, however, did not address prevalence for extremely elevated D-dimer levels, such as we present here. Mechanistically, sharply elevated D-dimer levels must reflect widespread activation of the coagulation and

<table>
<thead>
<tr>
<th>Tertiles of D-dimer levels:</th>
<th>Mean platelet count / % with thrombopenia (n)</th>
<th>PTT-INR / % INR $&gt;1.2$ (n)</th>
<th>APTT / % $&gt;40$ sec (n)</th>
<th>Fibrinogen Mean/SD (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>193/35.7% (555)</td>
<td>1.40/82.5% (457)</td>
<td>45/39.2% (459)</td>
<td>3.2/1.7 (180)</td>
</tr>
<tr>
<td>Lowest (5030 to 7380)</td>
<td>213/28.1% (178)</td>
<td>1.30/67.1% (129)</td>
<td>45/39.2% (130)</td>
<td>3.8/1.7 (37)</td>
</tr>
<tr>
<td>Middle (7610 to 14620)</td>
<td>212/32.8% (186)</td>
<td>1.36/79.2% (157)</td>
<td>42/31.2% (157)</td>
<td>3.3/1.8 (52)</td>
</tr>
<tr>
<td>Highest (14,710 to 239,000)</td>
<td>146/45.5% (191)*</td>
<td>1.50/95.3% (171)*</td>
<td>48/46.5% (172)</td>
<td>3.0/1.6 (93)*</td>
</tr>
<tr>
<td>p-value (one-way ANOVA)</td>
<td>$p &lt; 0.001$</td>
<td>$p = 0.021$</td>
<td>$p = 0.212$</td>
<td>$p = 0.019$</td>
</tr>
</tbody>
</table>

Results are presented as mean and, except for fibrinogen, percentage of patients with abnormal test results as indicated. n = total number of patients with available data. P-values are indicated for the overall one-way ANOVA test, asterisks indicate significant differences between the highest and both other tertiles; plus signs indicate significant differences only between indicated tertiles, both in the Tukey post hoc test.
Among the diagnoses that can be missed are for example pregnancy, which may be denied or unknown to patients, and the ones that are notably difficult diagnoses such as aortic dissection and thrombotic microangiopathy. Although such diagnoses are rare, even in our group with extremely elevated D-dimer levels, clinicians should consider them if no other causes are apparent. Even in pregnant patients their pregnancy was ‘just’ a contributing factor to the elevated D-dimer levels, it was always complicated by other diseases in this sharply elevated D-dimer study.

Several limitations of this study merit consideration. We retrospectively identified causes of sharply elevated D-dimer levels from the medical records. A prospective, protocolised diagnostic work-up may have yielded different diagnoses. Also, disease severity and the added value of the D-dimer result in establishing a diagnosis could not be systematically assessed retrospectively from patient files. Finally, results could be different in other types of hospitals, and almost certainly will be different in primary care facilities, where the prior likelihood of severe disease is lower.

In conclusion, an extremely elevated D-dimer is specific for serious illness and should trigger suspicion of severe disease, particularly VTE, sepsis or cancer, the last of which even in the presence of VTE. In patients not appearing seriously ill, physicians are ill-advised to ignore such results based on a presumed lack of specificity of the D-dimer test. Further studies should define the optimal diagnostic work-up of an extremely elevated D-dimer.

Acknowledgements

The authors would like to thank Monique Terwijn and the Department of Clinical Chemistry of the VU University Medical Center for providing the laboratory data and the department heads of the VU University Medical Center for giving consent to perform this study.

Disclosures

The authors declare that they have no conflict of interest.

References


CASE REPORT

Ganciclovir-induced ataxia and encephalopathy

M.C. Möhlmann*, J. Stiksma, M.H.H. Kramer

Department of Internal Medicine, VU Medical Center, Amsterdam, the Netherlands,
*corresponding author: tel.: +31 (0)20-4444307, fax: +31 (0)20-4444313, email: m.mohlmann@vumc.nl

ABSTRACT

Background: Ganciclovir can be used to treat a primary cytomegalovirus (CMV) infection, however it can cause side effects.
Case description: We describe a 60-year-old immunocompromised woman with a primary CMV infection who was treated with ganciclovir. She developed an encephalopathy which resolved after discontinuation of ganciclovir.
Conclusion: A reversible encephalopathy as a side effect of ganciclovir.

KEYWORDS
Ganciclovir, encephalopathy, side effect, ataxia

INTRODUCTION

Ganciclovir is often prescribed for both prophylactic and therapeutic purposes. The use of ganciclovir for a primary cytomegalovirus (CMV) infection is debatable; moreover, ganciclovir can also be associated with severe side effects. We present a case history of a patient with a rare side effect of ganciclovir.

CASE REPORT

We describe the case of a 60-year-old woman with Crohn’s disease, which is in remission with azathioprine 200 mg once a day; she is not on any other medication. She was admitted to another hospital because of a daily spiking fever up to 40 °C and severe fatigue which had developed over the last few weeks. A CMV infection was diagnosed with haemolytic anaemia (haemoglobin 5.7 mmol/l; haptoglobin 0.08 g/l) with cold agglutinins, thrombocytopenia (119 x 10⁹/l) and leucopenia (2.6 x 10⁹/l) and lymphopenia (0.4 x 10⁹/l). Because of the symptomatic CMV infection in an immunocompromised patient, she was treated with intravenous ganciclovir. The azathioprine was discontinued.

Ganciclovir was started at 5 mg twice a day whereupon she was afebrile within a few days. A few days after ganciclovir was started, our patient developed back pain and an unsteady gait which progressed and after a few days she was unable to walk independently. She also developed bradyphrenia with anxiety and a disorder in word retrieval and memorisation. Our patient had never experienced these symptoms before. MRI of her head showed no abnormalities. Her creatinine level remained stable during her hospitalisation (52 µmol/l). Because of the unexplained deterioration, the patient was transferred to our hospital. Encephalitis was ruled out after clinical evaluation by the neurologist and normal cerebral spinal fluid. The EEG showed slow activity which is indicative of encephalopathy. We diagnosed a ganciclovir-induced ataxia and encephalopathy whereupon we discontinued the ganciclovir. Her neurological symptoms disappeared within a few weeks. This confirmed our diagnosis of ganciclovir-induced ataxia and encephalopathy as an explanation for her symptoms.

DISCUSSION

Based on literature it is unclear if a primo CMV infection in immunocompromised patients should be treated with antiviral agents. Literature suggests discontinuing or reducing immunosuppressive agents without administering antiviral drugs in a therapeutic dosage. However, if you do choose to start treatment with antiviral drugs the effectiveness of oral compared with intravenous treatment remains a subject of discussion. As described above, our patient was treated with ganciclovir intravenously because of the severe symptoms. It is recommended to start with 5 mg/kg twice a day which is reduced to once daily after seven days.

Ganciclovir is an antiviral agent that inhibits DNA polymerase and prevents replication of the virus. More than 90% of ganciclovir is eliminated through glomerular filtration and crosses the blood-brain barrier. Known side effects of ganciclovir are bone marrow depression, gastrointestinal complaints and less frequently...
psychiatric symptoms consisting of depression, fear and confusion. These last symptoms were observed in our patient; however, this did not explain all of her problems. Ataxia and encephalopathy due to ganciclovir is not officially registered as a side effect. At the Dutch registration for side effects (Lareb), 20 cases of encephalopathy and 12 cases of ataxia were known to have been reported internationally. Five unique cases are described in literature of ganciclovir-induced ataxia and encephalopathy. These cases describe the occurrence of neurological symptoms in patients receiving ganciclovir. Neurological symptoms consisted of an unsteady gait, dysarthria, disturbed consciousness or visual hallucinations. In four of these cases a high ganciclovir concentration in the blood was found. Only three out of five cases mentioned decreased kidney function. In one case ganciclovir toxicity was treated with haemodialysis after which the blood concentration of ganciclovir decreased.

In our patient, it is striking that the nature and course of the symptoms appear to be identical. The mean time to onset of symptoms is approximately one week. In all published cases, as well as our case, the ataxia and encephalopathy appears to be reversible. Renal impairment might cause an increased risk for developing ataxia and encephalopathy since the drug is predominantly excreted through the urine. However, a therapeutic ganciclovir level does not exclude the possibility of developing side effects, even with a normal kidney function (Naranjo score 7/13, probable adverse drug event; table 1).

**CONCLUSION**

Treatment of a primary CMV infection with ganciclovir in immunocompromised patients is debatable. If a patient treated with ganciclovir develops neurological symptoms one should be aware of the possibility of a reversible ganciclovir induced ataxia and encephalopathy.

**DISCLOSURES**

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

**REFERENCES**

Actinomycosis of the abdominal wall after cholecystectomy: transferral theory

E.-J. Kooi1, P.J. de Vries1, A.W.W. van Geloven2, H.V. Stel3, P.J. Kingma4

Departments of 1Internal Medicine, 2Surgery, 3Pathology and 4Gastroenterology, Tergooi Hospital, Hilversum, the Netherlands, 5Department of Pathology, VU University Medical Center, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)20-4444016, fax: +31 (0)20-4444586, email: evertjankooi@gmail.com

ABSTRACT

Abdominal actinomycosis is a rare disease caused by Gram-positive anaerobic Actinomyces bacteria. Here, we present a patient with an intrauterine contraceptive device who developed a long lasting and unexplained recurrent, painful abdominal swelling a few months after a laparoscopic cholecystectomy.

KEYWORDS

Actinomycosis, intrauterine contraceptive device, laparoscopic cholecystectomy, painful swelling

CASE PRESENTATION

A 59-year-old female was seen at our outpatient department with abdominal swelling and pain. Four months prior to this she underwent an elective laparoscopic cholecystectomy because of symptomatic cholecystolithiasis. A few weeks after the cholecystectomy she developed tenderness in the left lower abdominal quadrant which was followed by swelling and fever. The C-reactive protein (CRP) was elevated and urinalysis indicated a urinary tract infection. This was suspected to be pyelonephritis according to the general practitioner, who began treating her with amoxicillin-clavulanic acid (500/125 mg three times a day). Eight days later, the fever had subsided but the painful swelling in her left lower abdominal quadrant persisted.

On the same day she was referred to the gastroenterologist who confirmed the presence of a firm tender palpable swelling of approximately 10 cm in diameter in the left lower abdominal quadrant. Laboratory investigation showed that there was still inflammation (erythrocyte sedimentation rate: 120 mm, CRP: 168 mg/l, leukocytes: 15.2 x 10⁹/l). Abdominal computer tomography (CT) showed thickening of the wall of the transverse colon (figure 1A) and distal descending colon wall with infiltration extending through the muscles into the subcutaneous fat (figure 1B). Thickening of some small intestinal loops was also observed, with some slightly enlarged pre-aortic lymph nodes (up to 12 mm; not shown). However, no abscess was detected. In addition, the patient had an intrauterine contraceptive device (IUD) in place. Sigmoidoscopic examination until the transverse colon, performed five days later, did not reveal any abnormalities. The clinical improvement and normal sigmoidoscopy were interpreted as signs of a favourable therapeutic response to the antibiotic treatment, and it was decided that it would be beneficial to follow the response after discontinuation of antibiotics. Repeated CT scanning three weeks later showed improvement with regards to the intra-abdominal...
abnormalities with some remaining infiltration of the descending and sigmoid colon, as well as the adjacent peritoneal fat and the abdominal wall (figure 1C).

During the following months the pain and swelling did not resolve completely and an additional course of antibiotics, which was given for suspected diverticulitis, gave some temporary improvement. Six months after the first course of treatment she again suffered from increased abdominal pain and enlargement of the swelling (figure 2A). The CRP was 11 mg/l, but further laboratory results were all normal. CT scanning showed that the intra-abdominal abnormalities had all disappeared, but that the infiltration of the abdominal wall had significantly increased and was now completely located superficial to the oblique abdominal muscles (figure 2B).

Histology of a needle biopsy of the lesion showed multiple Actinomyces microcolonies surrounded by numerous neutrophilic granulocytes (figure 2C/D). Furthermore, the bacterial culture was negative. Oral treatment with pheneticillin was then administered. After two weeks the patient had recovered, the swelling had significantly decreased to approximately 5 cm in diameter, and the plasma CRP value had normalised. Antibiotic therapy was continued for four months. In this period no relapse occurred and the swelling gradually disappeared. At present, one year after the event, there are no signs of relapse.

**DISCUSSION**

This case describes a peculiar series of events with regards to intra-abdominal actinomycosis, in which the intra-abdominal lesions gradually migrated to the exterior layers of the abdominal wall. Actinomycosis is a rare infection caused by Gram-positive anaerobic bacteria from the Actinomycetaceae family, although its name suggests a fungal infection. Members of this family are typical commensals of the human urogenital and gastrointestinal tract. The incidence of actinomycosis has not been systematically investigated. It may occur at several anatomical sites (including the central nervous system, bone and muscle tissue) with a predilection for the orocervicofacial region. The latter contributes to half of the Actinomyces infections. Abdominopelvic and thoracic locations contribute to 20% and 15-20% of all infections, respectively. Abdominopelvic actinomycosis is usually a sequela of intra-abdominal infection with intestinal perforation such as (perforated) appendicitis. Less frequently it is associated with either neoplasia or foreign bodies in the gastrointestinal or urogenital tract. Notably, several reports mentioned an association between the use of IUDs and abdominopelvic Actinomyces infection, including a few reports indicating involvement with the abdominal wall.
The presented case is remarkable because the initial site of infection seemed to be in the extra-intestinal exterior of the colon and small intestines that would gradually migrate to the abdominal wall. The resolution of the intra-abdominal infection may reflect a positive response to the two short courses of antibiotics.

Intra-intestinal focus was not confirmed despite the suggestion of colon involvement in the initial CT scan. Intra-abdominopelvic actinomycosis has been attributed to previous surgery, especially laparoscopic cholecystectomy with gallstone spillage. Actinomyces species have either been isolated from subphrenic or intra-abdominal abscesses following complicated laparoscopic cholecystectomy, but this effect has mostly been present in co-infections by other bacterial species (e.g. Klebsiella pneumoniae or Escherichia coli). Actinomyces bacteria have a low growth rate and symptomatic infections may be present many years after laparoscopic cholecystectomy.

In this case, there was some spillage of bile which was immediately removed. Spillage of biliary stones did not occur. The gallbladder was removed through the sub-umbilical insertion of the laparoscope, but the infection was located in the left abdominal quadrant. We suspect that Actinomyces bacteria or endospores were inoculated during the intra-abdominal manipulation of the lacerated gallbladder before removal, and that this caused infection between the colon and abdominal wall. Primary inoculation at the sub-umbilical insertion site, or primary inoculation at a skin abrasion by spillage after evacuation from the abdominal cavity are less likely. Of note, pathological examination revealed several small, yellow granular-shaped concrements within the gallbladder and cystic duct (up to 3 mm in diameter) but microscopic examination did not reveal significant inflammation and/or colonisation by Actinomyces. Four months after surgery the intra-abdominal infection developed without

---

**Figure 2. Abdominal swelling caused by actinomycosis.** A) A red palpable swelling was found upon physical examination (arrows). B) CT scanning revealed a superficially located abdominal mass (arrow). C) A PAS-Diastase stain revealed microcolonies of Actinomyces coated and surrounded by numerous neutrophilic granulocytes (asterisk). D) High power magnification showing the periphery of an Actinomyces colony with filamentous structures (micro-organisms) extending perpendicular to the surface and covered by neutrophils.
abscess formation, and responded well to a short course of antibiotic treatment. Eleven months post-surgery the infection in the abdominal wall persisted. This remarkable course of the initial intra-abdominal Actinomyces infection suggests that Actinomyces bacteria have a preference for multiplying in the abdominal wall. The decisive characteristics which facilitate growth in the abdominal wall and arrested growth at the intra-abdominal site are not clear. Since there was no sign of endometritis or pelvic inflammatory disease, the IUD as a source of infection was considered less probable. Therefore, we consider the lacerated gallbladder as the most likely source. However, as it was previously shown that a substantial proportion of IUDs are contaminated with Actinomyces israelii, we could not completely exclude the IUD as a source of infection. The gynaecologist proceeded to remove the IUD.

Due to its rarity, its nonspecific clinical symptoms, its non-specific radiological findings and often lacking microbiological confirmation, abdominal actinomycosis is a challenging diagnosis. Nevertheless, unexplained recurrent abdominal swellings in patients who undergo a laparoscopic cholecystectomy (even after many years) that do not respond to short-term antibiotic treatment should raise suspicion of actinomycosis.

In line with previous literature, we propose to confirm the putative diagnosis with a combination of biopsy and fluid aspiration for histological and microbiological examination, keeping in mind its limited sensitivity and specificity. Patients with Actinomyces infection should be treated with prolonged antibiotic treatment and abscesses should be drained when possible.

ACKNOWLEDGMENTS

We would like to thank our patient for granting informed consent to publish this clinical case. Anonymity and confidentiality was assured at all times. Furthermore, we would like to thank P. Robinson for critically reviewing the manuscript regarding English grammar and spelling.

DISCLOSURES

The authors declare no conflicts of interest. No funding or financial support was received.

REFERENCES

A novel mutation in mitochondrial DNA in a patient with diabetes, deafness and proteinuria

A.Y. Adema*, M.C.H. Janssen#, J.W. van der Heijden

1Department of Nephrology, VU University Medical Center, Amsterdam, the Netherlands, 2Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands, *corresponding author: tel.: +31 (0)20-4441123, fax: +31 (0)20-4442675, email: a.adema@vumc.nl

CASE REPORT

A 28-year-old Caucasian woman presented with metabolic syndrome consisting of central obesity, hypertension, hypercholesterolaemia, impaired glucose tolerance and proteinuria of 3.6 grams a day. A kidney biopsy revealed FSGS. There was no hypoalbuminaemia and therefore the FSGS was thought to be secondary. She was treated with conventional therapy including an angiotensin receptor blocker and statin. One year later bilateral sensorineural hearing loss was diagnosed and she developed overt diabetes with no detectable islet cell or glutamic acid decarboxylase (GAD) antibodies. The diabetes was treated with oral medication; however within time she required insulin. Fundus examination was normal. All these years she had abdominal symptoms with diarrhoea, fatigue and muscle cramps during exercise. Family history revealed that her mother had gestational diabetes, a benign brain tumour and died after a haemorrhagic cerebrovascular accident. Due to the combination of diabetes, deafness and kidney disease, underlying MIDD was suspected. However, the m.3243A>G mutation which causes MIDD in over 85% of the cases was not detectable. Therefore, whole mtDNA sequencing was performed with the Ion Torrent PGM method (detection level of 1% with an accuracy of 0.5%) which revealed a heteroplasmic m.09155A>G mutation (p.Gln210Arg in MT-ATP6). The percentage of heteroplasmy in urine was higher than in blood (55% vs. 28%). She achieved only 65% of the expected distance on the 6-minute walk test. A muscle biopsy of the quadriceps muscle was performed. Histology demonstrated increased fatty vacuoles as often seen in mitochondrial disease. Electron microscopic examination showed abnormal mitochondria with lipid vacuoles (figure 1). Biochemical analyses of the muscle demonstrated normal ATP production (23.6 nmol/h.mUCS, reference value: 15.4-30.2

KEYWORDS

Maternally inherited deafness and diabetes, MIDD, mitochondrial DNA mutation, 09155A>G

INTRODUCTION

Maternally inherited deafness and diabetes (MIDD) is characterised by both a defect in insulin secretion and sensorineural hearing loss. The m.3243A>G mutation is the most reported in mitochondrial DNA (mtDNA) causing MIDD, although other, rare, mtDNA point mutations have also been mentioned. We report on a 28-year-old Caucasian woman with a history of diabetes, kidney disease, deafness, diarrhoea, myopathy and fatigue. The diagnosis of mitochondrial disease was made in this patient, which resulted from a novel 09155A>G mutation in the mtDNA. As far as we know, this mutation has never been described before as causing MIDD.

ABSTRACT

Maternally inherited deafness and diabetes (MIDD) is characterised by a defect in insulin secretion and bilateral hearing impairment. The m.3243A>G mutation is the most reported in mitochondrial DNA (mtDNA) causing MIDD, although other, rare, mtDNA point mutations have also been mentioned. We report on a 28-year-old Caucasian woman with a history of diabetes, kidney disease, deafness, diarrhoea, myopathy and fatigue. The diagnosis of mitochondrial disease was made in this patient, which resulted from a novel 09155A>G mutation in the mtDNA. As far as we know, this mutation has never been described before as causing MIDD.

INTRODUCTION

Maternally inherited deafness and diabetes (MIDD) is characterised by both a defect in insulin secretion and sensorineural hearing loss. The phenotypic expression is variable; mean age of onset is between 30 and 40 years. Other abnormalities commonly associated with MIDD include macular retinal dystrophy, myopathy, cardiac disorders, renal disease (particularly focal segmental glomerular sclerosis, FSGS), short stature, and gastrointestinal disease. Over 85% of MIDD is caused by the mtDNA A to G mutation at nucleotide position 3243 in transfer RNA. In this report we describe a new mitochondrial DNA mutation causing MIDD.
nmol/h.mUCS). There were no enzyme abnormalities; complex V levels (ATPase) were normal (314 mU/UCOX, reference value: 84-365 mU/UCOX). The heteroplasmy level of the m.09155A>G mutation in muscle was 64%. Her asymptomatic half-sister, sharing the same mother, was also tested, and did not carry the mutation. Metformin and statin were discontinued because of anticipated side effects in mitochondrial disease. This resulted in less muscle cramps.

**DISCUSSION**

Over 90% of the patients with diabetes have metabolic syndrome-associated type 2 diabetes, auto-immune type 1 diabetes accounts for another 5-10% and the remainder is due to other causes including genetic defects in mitochondrial DNA. Mitochondrial diabetes generally presents as an unremarkable form of diabetes. The suspicion of mitochondrial diabetes needs to be raised by a very strong family history of diabetes and deafness in combination with the suspicion of maternal inheritance. Mitochondrial genetic studies confirm the diagnosis of mitochondrial diabetes. In the majority of patients with mitochondrial diabetes an A to G substitution at position 3243 (m.3243A>G) of the mtDNA encoding for tRNA is found. Overlapping symptoms in patients with an m.3243A>G mutation suggests a spectrum of expression ranging from hearing loss and diabetes alone, to MIDD, to mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes. MIDD is found in 0.5-2.8% of diabetic patients. In MIDD, less than 15% of the cases are caused by mitochondrial mutations other than the m.3243A>G mutation. Undetectable islet cell and GAD antibodies made the diagnosis of late-onset type 1 diabetes unlikely in our case. The positive family history and constellation of symptoms in our patients raised the suspicion of MIDD. With whole mitochondrial sequencing we found a novel mitochondrial mutation in a patient with the MIDD phenotype, the m.155A>G mutation. This mutation is not described in the mitomap database and is predicted as pathogenic by the mutation prediction software (AlignGVGD, Polyphen and SIFT). The fact that her sister does not carry the mutation and the findings from histology and electron microscopic examination of the muscle biopsy strengthens the suspicion that this is a new pathogenic mutation. Biochemical analyses were normal; however, it is known that mutations in ATP6 only cause in vitro biochemical abnormalities in higher heteroplasmy values.

The proportion of mutant mtDNA in the blood of MIDD patients may vary from 1-40%. Moreover, levels of heteroplasmy may differ between tissues from a single individual and may fall with age. Heteroplasmy probably explains the large variation in phenotype found in patients. The mother of our patient had a history of gestational diabetes. Maternal transmission may not be evident when the mutation load is below the threshold required to cause symptoms. Also, mutations in mtDNA may be sporadic. The level of mtDNA is lowest in blood leucocytes, although this test is most used by laboratories. Therefore, other diagnostically accessible tissues such as urine and mouthwash samples can be used when the level of heteroplasmy is too low to detect or too low to explain the symptoms in blood leukocytes. Our patient had a heteroplasmy level of the m.09155A>G mutation of 55% in the urine and 64% in muscle, which was significantly higher than the 28% measured in the blood leucocytes. With regard to the treatment of MIDD, there is no specific disease-modifying therapy available. In general, drugs that may interfere with the respiratory chain function should be avoided in patients with mitochondrial disorders. Mitochondrial diabetes is treated as other forms of diabetes; however, the use of metformin should be avoided due to the increased risk of lactic acidosis.

**CONCLUSION**

A family history of diabetes and deafness should prompt genetic testing for mitochondrial diabetes. The most found mutation in MIDD is m.3243A>G although 15% of cases are caused by other rare mutations. Our patient presented with symptoms associated with MIDD. Whole mitochondrial DNA sequencing showed an m.09155A>G mutation. This mutation has never been described before as being associated with MIDD.
ACKNOWLEDGEMENT

We thank Dr. Küsters, pathologist at the Radboud University Medical Center in Nijmegen, the Netherlands for providing figure 1.

DISCLOSURES

The authors have no conflicts of interest or financial disclosures to report.

REFERENCES

PHOTO QUIZ

A black umbilicus in a patient with a decompensated liver cirrhosis

J.H. Smalberg*1, T.R. Hendriksz2, P. Honkoop1

Departments of 1Gastroenterology, 2Radiology, Albert Schweitzer Hospital, Dordrecht, the Netherlands, *corresponding author: tel.: +31 78 6542343, fax: +31 78 6541544, email: j.smalberg@asz.nl

CASE REPORT

A 86-year-old man presented to the emergency department with progressive dyspnoea, peripheral oedema and a black umbilicus that had developed the week before. He had a three-year history of non-alcoholic steatohepatitis liver cirrhosis and a two-year history of multifocal, incurable hepatocellular carcinoma (HCC) for which an expectant management was chosen. Several months prior to the current presentation he underwent surgery with a mesh repair because of a strangulated umbilical hernia. Physical examination showed a moderately ill patient with jaundice but no signs of encephalopathy, decreased breath sounds at the right lung base, mild abdominal distension without shifting dullness and bilateral lower extremity pitting oedema. Furthermore, we noticed a demarcated dark discoloration without palpable abnormalities of the umbilicus (figure 1). Laboratory data showed marked progression of the liver enzymes with a bilirubin of 310 µmol/l, gamma-glutamyl transpeptidase 239 U/l, alkaline phosphatase 491 U/l, aspartate aminotransferase 72 U/l, alanine aminotransferase 79 U/l and lactate dehydrogenase 257 U/l. Albumin was 24 g/l and the prothrombin time was 12 seconds, creatinine was elevated but stable at 205 µmol/l.

WHAT IS YOUR DIAGNOSIS?

See page 459 for the answer to this photo quiz.

Figure 1. Dark discoloration of the umbilicus
**DIAGNOSIS**

A liver ultrasonography was performed, which showed progression of the HCC lesions in the right and left liver lobe. A solid structure was visible in the portal trunk and there was absence of the Doppler sign in the intrahepatic and extrahepatic part of the portal vein extending to the confluence of the superior mesenteric and splenic vein, consistent with an extensive extrahepatic and intrahepatic portal vein thrombosis. In addition, a recanalised umbilical vein was seen, which drained into the left intrahepatic branch of the portal vein. Doppler flow was absent, consistent with umbilical vein thrombosis (UVT).

In retrospect, MRI of the liver performed a year earlier in the context of his HCC had already shown recanalisation of the umbilical vein with adequate flow at that time (figure 2). Liver cirrhosis and hepatobiliary malignancies are well-known precipitating factors for portal vein thrombosis, both of which were present in our patient. In addition, three months earlier he underwent surgery with a mesh repair because of a strangulated umbilical hernia, which may have added to a local prothrombotic environment.

UVT is a rare clinical entity, which appears to be caused by the local tumour and related to portal vein thrombosis. The first case report dates from 1986. In a heavy drinker with HCC, fine needle biopsy of a thrombus in a patent umbilical vein was shown to be consistent with HCC. A more recent study demonstrated HCC tumour thrombus in a recanalised umbilical vein in a patient with liver cirrhosis, primary liver cancer and portal hypertension. Chang et al. examined 431 consecutive HCC patients for UVT by ultrasound within one week of HCC diagnosis. Nine of these patients were found to have UVT (2.1%), all of which had a combination of HCC left lobe invasion and left portal vein thrombosis, as was the case in our patient. They suggest a potential mechanism in which HCC spreads into the left lobe and subsequently infiltrates the left portal vein and disseminates into the recanalised umbilical vein causing thrombosis. None of previous case reports describe the distinctive appearance of the umbilical vein, which we hypothesise is due to necrosis as a result of venous congestion of the para-umbilical veins.

Little is known about the prognosis of UVT. Chang et al. report a median survival of 25 days, survival in the patient described by Livraghi et al. was seven weeks. This poor prognosis is not necessarily caused by the UVT itself, but may also be due the advanced stage of the liver disease. Anticoagulation would be the treatment of choice, but is not without risk in light of high risk of bleeding in patients with portal hypertension. In our patient anticoagulation was contraindicated because of a high bleeding risk based on recent intra-abdominal bleeding. He developed progressive liver failure and died six days after admission. Autopsy was not performed.

**REFERENCES**