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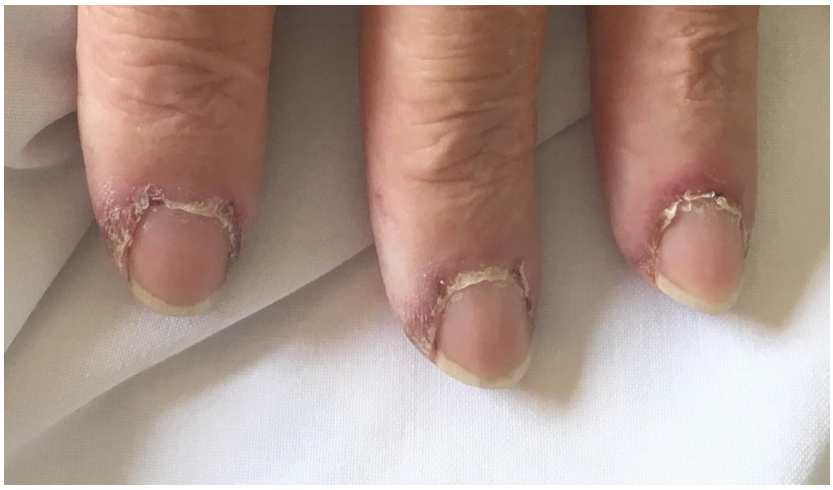

Ragged cuticles with periungual erythema: what is your diagnosis?

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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@erasmusmc.nl
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MacChain
PO Box 330
1960 AH Heemskerk
The Netherlands
Tel: +31 625056091
Email: info@macchain.nl
Web: www.macchain.nl

Contents

EDITORIAL

Adapt and adopt? The non-evidence-based implementation of evidence-based guidelines.

M. van Hoek

Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands.
Corresponding author: m.vanhoek@erasmusmc.nl

Guidelines and their revisions are usually based on an extensive amount of literature. It takes a lot of time, effort, and typically a large team of experts to formulate practical clinical advice from an abundance of data. The aim is to organize and provide the best available evidence to support clinical decision making to improve quality, patient outcomes, and cost effectiveness. It is interesting that compared to the vast amount of data new guidelines are based on, relatively little research goes into optimising dissemination, implementation, practical adherence, and monitoring of clinical results for guideline updates.

The process that takes place after a new guideline has been released is a research field of its own. At the moment, the most effective way to implement a new guideline is unclear and there is little evidence for tools to support implementation.[1,2] The most effective strategy may even differ per guideline, as the barriers to effective implementation can be personal/physician-related, guideline-related, or external.[3,4] Personal/physician-related factors comprise aspects such as lack of awareness, lack of motivation, lack of agreement, etc. These factors could be tackled by dissemination of guideline information and education of physicians. For medical guidelines, this is one of the most common strategies, where education meetings and conferences are held to update knowledge and also to explain the background and supporting evidence for the recommendations. Guideline-related factors can comprise the complexity of the guideline, its accessibility, and its layout. Most guidelines today aim for a clear set-up with intermediate outlines of the recommendations. Finally, external factors may include a lack of resources (financial or in terms of workforce) or organisational aspects.

In this edition of the *Netherlands Journal of Medicine*, Mol et al. have reviewed the implementation of an updated Dutch national guideline on peri-operative bridging of anticoagulant therapy in their hospital.[5] The study shows that the implementation of this guideline update has been successful and even took place before the local hospital protocol was updated, resulting in a large percentage of non-adherence to the local hospital protocol during the transition period. Rightly so, the authors question the usefulness of local protocols in addition to national guidelines based on these findings.

Unfortunately, this encouraging study is merely descriptive and does not discuss why this implementation has been so successful, what the implementation strategy was, and whether this success was only local or also national and international. Taking the previously presented information into account, one may speculate that this guideline update may have had few barriers in this particular hospital. Physicians may have been aware and been convinced by the evidence of the randomised controlled trial that changed the guideline. The change in the guideline was not complex and a local systematic approach to peri-operative anticoagulant therapy was already in place, posing few guideline or external barriers. This reminds me of Bram Stoker's *Dracula* statement, 'We learn from failure, not from success',[6] as there was potential for this study to teach us more about effective implementation strategies.

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ORIGINAL ARTICLE

Platelet parameters aid identification of adult-onset Still's disease from sepsis

J-P. Liu, Y-M. Wang, J. Zhou*

The first two authors contributed equally to this work

Department of Laboratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China.
*Corresponding author: zhoujun5958@163.com

ABSTRACT

Background: Adult-onset Still's disease (AOSD) is a rare, chronic, and systemic inflammatory disorder. The current study aims to evaluate the ability of platelets (PLTs), plateletcrit (PCT), mean platelet volume (MPV), platelet distribution width (PDW), and PLT to PDW ratio (PPR) in a cohort of patients with AOSD or sepsis.

Methods: Serum samples were obtained from 82 AOSD patients, 48 sepsis patients, and 76 matched healthy controls. Platelet parameters were measured by Sysmex XE 2100 analysers.

Results: PPR and ferritin in AOSD patients were significantly higher than those in sepsis patients (22.18 ± 11.12 vs. 13.80 ± 8.97, $p < 0.001$; 3972.90 ± 5134.04 μg/l vs. 518.92 ± 382.50 μg/l, $p = 0.001$, respectively) and they were independent factors to differentiate AOSD from sepsis (OR: 5.86, 95%CI 1.59-21.60, $p = 0.008$; OR: 54.06, 95%CI 9.57-305.44, $p < 0.001$; respectively). Furthermore, PPR in AOSD and sepsis was significantly higher than that in matched controls. The area under the ROC curve of PPR, ferritin, and the combination were 0.733 (95%CI 0.646-0.820), 0.887 (95%CI 0.825-0.950), and 0.931 (95%CI 0.884-0.984), respectively.

Conclusion: PPR can be used as a useful marker to differentiate AOSD from sepsis and the combined identification value of PPR and ferritin is much higher than that of any single factor.

KEYWORDS

Adult-onset Still's disease, platelets, platelet distribution width, sepsis

INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare, chronic, and systemic inflammatory disorder.[1] It was first described in 1971, but the etiopathogenesis of the disease is still unclear.[2] The incidence of AOSD can reach to 0.16-0.4 per 1,000,000 persons.[3] Fever is a main sign of patients with AOSD.[4,5] Fever is also common in sepsis.[6] Diagnosis of patients with AOSD or sepsis is exhausting, time-consuming, and costly.[7] Differentiating these two clinical diseases with a simple and easily available marker is invaluable; however, there is no objective marker to distinguish AODS from sepsis.

Several reports have suggested that platelets (PLTs) contribute to antimicrobial defence during various acute and chronic infections.[8,9] It might be beneficial when PLTs, plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW) are combined with other acute phase reactants to demarcate inflammatory diseases.[10,11] The objective of this study is to evaluate whether PLTs, PCT, MPV, PDW, and the PLT-to-PDW ratio (PPR) are reliable for distinguishing diagnosis of AOSD from sepsis.

METHODS

Patients

This retrospective cohort study was carried out in a tertiary hospital. Patients newly diagnosed with AOSD between 2010 and 2018 in The First Affiliated Hospital of Nanjing Medical University were recruited. The diagnosis of AOSD was confirmed by the Yamaguchi criteria.[12] For the present analysis, only adult patients ≥ 18 years were included, but patients who had cancer, used anticoagulants prior to admission, and had no PDW values were excluded; 82 patients were included as AOSD. Simultaneously, 48 age-

and gender-matched patients with a systemic inflammatory response syndrome accompanied by proven microbial infection were included as sepsis. Patients who met two or more of the following conditions were defined as sepsis: (1) temperature > 38°C or < 36°C; (2) heart rate > 90 beats per minute; (3) respiratory rate > 24 breaths per minute or partial pressure of carbon dioxide < 32 mm Hg; (4) white blood cell count > 12×10^9/l, < 4×10^9/l, or > 10% immature forms.[13,14] Seventy-six age- and gender-matched healthy controls were also included.

Ethical statement

The study protocol was performed to conform with the Declaration of Helsinki and was approved by the local ethics committee of the hospital. This article does not contain any studies with animals.

Data collection

Patients' age, gender, clinical features (fever, arthritis, myalgia, rash, sore throat, lymphadenopathy, pericarditis, hepatomegaly, splenomegaly, pleuritis, pneumonitis), and clinical data (organism, C-reactive protein (CRP), ferritin, whole blood counts (WBC), lymphocyte count, neutrophil count, PLTs, PCT, MPV, and PDW, which were measured from peripheral venous blood samples at admission) were collected.

WBC; neutrophil, lymphocyte, and platelet counts; and platelet parameters (PCT, MPV, and PDW) were analysed using Sysmex XE 2100 analysers (Sysmex, Hyogo, Japan). CRP level was performed by a BN II nephelometer (Dade Behring, Marburg, Germany). Ferritin analysis was performed on a Unicel DXI 800 (Beckman Coulter, Brea, CA, America). All blood samples were taken on the day of admission and measured within two hours. PPR was calculated by dividing the platelet count by the PDW.

Statistical analysis

Statistical analysis was performed using SPSS 21 software (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean and standard deviation or median and range. The Kolmogorov-Smirnoff test and Levene's test were used to assess the normality of the distribution and

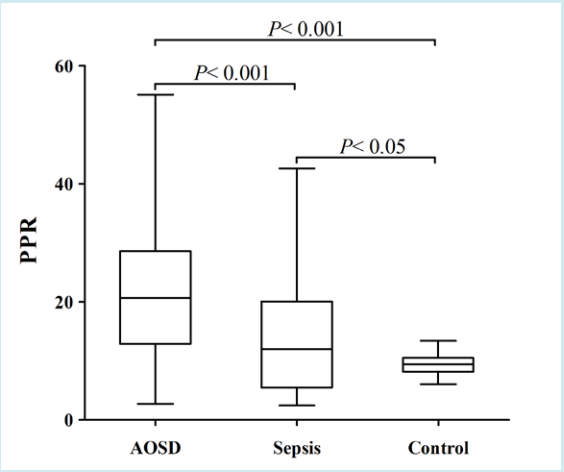
Table 1. *Demographics and characteristics of the study cohorts*

Variables	AOSD patients (n = 82)	Sepsis patients (n = 48)	Healthy control (n = 76)	p-value
Demographic variables				
Age, year	36 (18-74)	40 (18-78)	39 (18-75)	0.566
Sex, male/female	29/53	25/23	31/45	0.063
Clinical features				
Fever, n	82 (100%)	48 (100%)		1.00
Arthralgia/arthritis, n	35 (42.7%)	5 (10.4%)		< 0.001
Typical skin rash, n	41 (50.0%)	3 (6.3%)		< 0.001
Sore throat, n	37 (45.1%)	4 (8.3%)		< 0.001
Lymphadenopathy, n	8 (9.7%)	1 (2.1%)		0.011
Myalgia, n	29 (35.4%)	2 (4.2%)		< 0.001
Hepatomegaly, n	0 (0%)	2 (4.2%)		0.168
Splenomegaly, n	1 (1.2%)	1 (2.1%)		0.966
Positivity of culture studies				
Blood, n		21 (43.6%)		
Sputum, n		19 (39.6%)		
Urine, n		11 (22.9%)		
Biliary drainage, n		6 (12.5%)		
Cerebrospinal fluid, n		4 (8.3%)		
Secretion, n		2 (4.2%)		

AOSD = Adult-onset Still's disease

the homogeneity of variance. Variables were compared by the independent sample t-test or one-way ANOVA test and the nonparametric Kruskal-Wallis test, depending on distribution form. The Fisher Exact test was used for categorical variables. Spearman correlation was used when variables were normally distributed and the data of descriptive analysis were expressed as mean ± standard deviation (SD). Pearson correlation was used when variables were non-normally distributed and the data were expressed as the median, interquartile range. Non-collinear and significant variables in the univariate analyses were included in multivariate logistic regression analyses. The optimal differential diagnosis values of the laboratory variables were identified by receiver operating characteristic curves (ROC) and quantified by calculating the area under the ROC curve (AUC). A p-value < 0.05 was considered statistically significant. All p-values were from two-sided tests.

Figure 1. *Comparison of the median PLT to PDW ratio (PPR) among patient with adult-onset Still's disease (AOSD) and sepsis and healthy controls.*



AOSD = Adult-onset Still's disease; PDW = platelet distribution width; PLT = platelet; PPR = PLT to PDW ratio.

RESULTS

Demographic and clinical features of study patients

Clinical characteristics of all patients are described in table 1. Median age of AOSD patients (male/female: 29/53) was 36 (18-74) years old, that of sepsis patients (male/female: 25/23) was 40 (18-78) years old, and that of healthy controls (male/female: 31/45) was 39 (18-75) years old. There were no significant differences in the median age and gender among the three groups. The most common clinical manifestation of AOSD patients was fever (100%), followed by typical rash (50%), sore throat (45.1%), arthralgia/arthritis (42.7%), and myalgia (35.3%). The main clinical symptoms in sepsis included fever (100%), arthralgia (10.4%), skin rash (6.3%), and sore throat (8.3%). Bacteraemia was verified in 21 (43.6%) sepsis patients. Nineteen (39.6%) sepsis patients had pneumonia, 11 (22.9%) had a urinary tract infection, and 6 (12.5%) had hepatobiliary infection.

Univariate and multivariate analyses

Table 2 shows the clinical data of the patients between the two groups. The results suggest that PPR and ferritin were significantly higher in the AOSD group compared with

Table 2. *Clinical data of patients for AOSD and sepsis*

Variables	Patients with AOSD	Patients with sepsis	p-value
CRP (mg/l)	106.9 ± 69.2	72.1 ± 56.7	0.005
Ferritin (μg/l)	3972.9 ± 5134.0	518.9 ± 382.5	0.001
WBC (× 10^9/l)	15.5 ± 8.1	14.0 ± 8.2	0.341
Lymphocyte (× 10^9/l)	1.3 ± 0.6	1.1 ± 0.9	0.096
Neutrophil (× 10^9/l)	13.4 ± 8.0	12.2 ± 7.6	0.420
PLT (× 10^9/l)	255.3 ± 106.4	174.8 ± 92.9	< 0.001
PCT (%)	0.25 ± 0.1	0.2 ± 0.1	0.002
MPV (fL)	9.8 ± 1.2	11.1 ± 1.1	< 0.001
PDW (%)	12.3 ± 2.5	14.0 ± 2.9	0.001
PPR	22.2 ± 11.1	13.8 ± 9.0	< 0.001

AOSD = Adult-onset Still's disease; CRP = C-reactive protein; WBC = white blood cell; PLT = platelet; PCT = plateletcrit; MPV = mean platelet volume; PDW = platelet distribution width; PPR = PLT to PDW ratio.

Table 3. *Correlation between PLT-to-PDW ratio and other variables*

Variables	Correlation coefficient (r)	p-value
CRP (mg/l)	0.246	0.006
Ferritin (μg/l)	0.180	0.070
WBC (× 10⁹/l)	0.174	0.048
Lymphocyte (× 10⁹/l)	0.167	0.057
Neutrophil (× 10⁹/l)	0.165	0.061
PLTs (× 10⁹/l)	0.943	< 0.001
PCT (%)	0.880	< 0.001
MPV (fL)	-0.462	< 0.001
PDW (%)	-0.652	< 0.001

CRP = C-reactive protein; WBC = white blood cell; PLTs = platelets; PCT = plateletcrit; MPV = mean platelet volume; PDW = platelet distribution width.

sepsis patients (22.18 ± 11.12 vs. 13.80 ± 8.97, p < 0.001; 3972.90 ± 5134.04 μg/l vs. 518.92 ± 382.50 μg/l, p = 0.001, respectively). In addition, the median PPR in both AOSD and sepsis groups was significantly higher than that in healthy controls (figure 1). The CRP of AOSD and sepsis groups was 106.94 ± 69.22 mg/l and 72.13 ± 56.69 mg/l, respectively, and significantly higher in the AOSD group (p = 0.005). A significantly higher PCT level was observed in the AOSD group than in the sepsis group (0.25 ± 0.10 vs. 0.19 ± 0.09, respectively, p = 0.002). Both lymphocyte count and PLTs were higher in the AOSD group than in sepsis group (p =0.096, p < 0.001, respectively); MPV and PDW were lower in the AOSD group than in sepsis group (all p < 0.001).

PPR was positively correlated with CRP (r = 0.25), WBC (r = 0.17), PLTs (r = 0.94), lymphocytes (r = 0.17), neutrophils (r = 0.17), ferritin (r = 0.18), and PCT (r = 0.88), whereas it was negatively correlated with MPV (r = -0.46) and PDW (r = -0.65). PPR showed no significant correlation with lymphocytes (p = 0.057), neutrophils (p = 0.061), or ferritin (p = 0.070) (table 3).

In the multivariate analysis (which included ferritin, lymphocytes, MPV, PDW, and PPR) only PPR and ferritin remained independent factors to differentiate AOSD from sepsis (OR: 5.86, 95%CI 1.59-21.60, p = 0.008; OR: 54.06, 95%CI 9.57-305.44, p < 0.001; respectively) (table 4).

PPR could be used to distinguish AOSD from sepsis

We further evaluated the identification value of PPR and ferritin in AOSD and sepsis by constructing ROC curves (figure 1). The ROC analysis showed that the AUC of PPR and ferritin were 0.733 (95%CI 0.646-0.820, p < 0.001) and 0.887 (95%CI 0.825-0.950, p < 0.001), respectively. The best cutoff value of PPR was 16.8, with a sensitivity of 61.0% and specificity of 68.0%. With a cutoff value of 1120 μg/l, the sensitivity and specificity of ferritin were 74.7% and 88.9%, respectively. Moreover, the combination of PPR and ferritin yielded a higher AUC value at 0.931 (95%CI 0.884-0.984, sensitivity: 84.0%, specificity: 92.6%). The results indicate that PPR has individual identification value and the combined identification value of PPR and ferritin is much higher than that of any single factor.

DISCUSSION

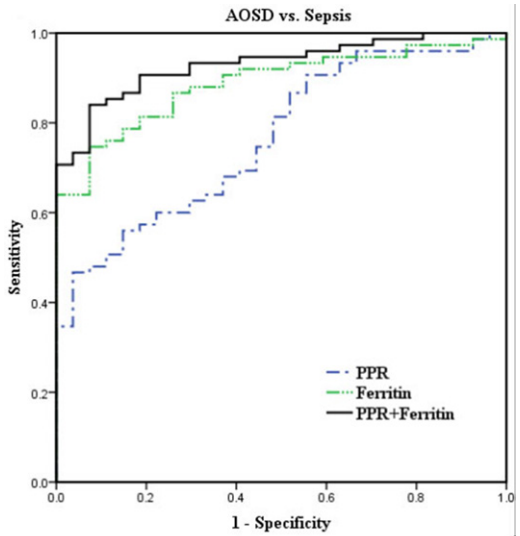
In this study, we found that PPR in both groups (AOSD and sepsis) was significantly higher than that in healthy controls and it was an independent factor for differential diagnosis of AOSD and sepsis. The value

Table 4. *Univariate and multivariate analyses of factors for differentiating AOSD from sepsis*

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-value	OR	95%CI	p-value
Ferritin	34.38	7.46-158.51	< 0.001	54.06	9.57-305.44	< 0.001
Lymphocyte	2.13	1.03-4.42	0.047			
PLTs	3.62	1.70-7.71	0.001			
PCT	2.35	1.07-5.15	0.039			
MPV	5.24	2.40-11.36	< 0.001			
PDW	2.79	1.34-5.81	0.006			
PPR	3.13	1.48-6.59	0.003	5.86	1.59-21.60	0.008

AOSD = Adult-onset Still's disease; OR = odds ratio; PLTs = platelets; PCT = plateletcrit; MPV = mean platelet volume; PDW = platelet distribution width; PPR = PLT-to-PDW ratio.

Figure 2. *Comparison of AUC between PLT-to-PDW ratio (PPR), ferritin, and the combination of them*



Variables	AUC	95%CI	Sensitivity	Specificity
Ferritin	0.887	0.825-0.950	0.747	0.889
PPR	0.733	0.646-0.820	0.610	0.680
Ferritin+PPR	0.931	0.884-0.978	0.840	0.926

AOSD = Adult-onset Still's disease; AUC = area under curve; PPR = PLT to PDW ratio; 95%CI = 95% confidence interval

of the combination of PPR and ferritin to differentiate between AOSD and sepsis was much higher than for each of them alone. Therefore, PPR and the combination of PPR and ferritin would be favourable in clinical practice for differential diagnosis of AOSD from sepsis.

Several biomarkers, such as interleukin-6, procalcitonin, and hyperferritinaemia had been investigated between AOSD and sepsis.[15-18] However, a definite biomarker had not yet been established clinically as they might emerge during inflammatory diseases.[19] Clinical manifestation could also differentiate AOSD from sepsis.[20] We compared clinical characteristics between two groups and the results showed that arthritis, skin rash, sore throat, and myalgia could distinguish them, but symptoms are nonspecific, easily ignored, and may appear at different phases of the disease. In addition, recall bias may be possible.

Therefore, a useful marker is extremely needed to discriminate AOSD from sepsis. Here, the novel marker PPR is becoming useful. In the current study, we first confirmed that PPR, ferritin, CRP, PCT, lymphocyte count, and PLTs increased in AOSD patients, and that MPV and PDW decreased in the AOSD group. Then we ascertained in the current model that PPR and ferritin were the only independent factors able to distinguish AOSD from sepsis, which indicates that ferritin and PPR are more stable than other variables, including PDW. According to the results of ROC curves, we further proved that PPR and ferritin were able to distinguish between AOSD and sepsis.

PDW is an indicator of the heterogeneity in platelet size, and may be a direct indicator of platelet demand, for example, PDW is increased with platelet anisocytosis. Gao et al. have reported a decrease in platelet count and increase in PDW amounts in patients with sepsis.[21] Another report shows the number of platelets was not significantly higher in AOSD patients than non-AOSD patients.[22] In the present study, we found that platelet count was higher and PDW lower in the AOSD group. Therefore, we suspected that there is an association between AOSD and platelet activation, and PPR (measured by platelet counts and PDW) could serve as a marker for AOSD. Our findings demonstrated that PPR could be a reliable predictive marker for AOSD, although the underlying mechanisms are still to be elucidated.

There are reports of combining biomarkers to improve the differential diagnosis accuracy of AOSD.[23,24] In our study, we also investigated whether the combination of PPR and ferritin could distinguish between AOSD and sepsis. The result showed that the AUC of the combination was 0.931 (0.884-0.984), and that the combined sensitivity and specificity of PPR and ferritin was better than that of PPR or ferritin alone. The values of sensitivity and specificity of the combined differential diagnosis of our combination (PPR and ferritin) are much higher (sensitivity: 84.0% vs. 43.2%, specificity: 92.6% vs. 88.9%) when compared with the combination of ferritin and glycosylated ferritin.[24] In addition, as part of the complete blood count test, PLTs and PDW can be measured by blood cell analysers when patients with a fever are admitted to hospital, enabling calculation of PPR. Therefore, PPR could be a helpful marker for physicians to discriminate AOSD from sepsis as objective laboratory biomarkers are lacking.

There are some limitations in our study. First, we retrospectively reviewed the clinical data and some patient data may be not available. Second, as a single centre study, there may have been selection bias. Third, due to methodological and financial reasons, we could not include potential biological markers that can differentiate AOSD from sepsis, such as interleukin-18 and serum amyloid A.[25,26] Therefore, more prospective, multi-centre, multi-population, multi-index research is needed.

In summary, both PPR and ferritin were able to independently identify AOSD from sepsis, and the combined diagnosis value of PPR and ferritin is much higher. In addition, PPR and ferritin are easy-to-obtain markers. Therefore, PPR might be useful for differentiating AOSD from sepsis as a supplementary variable to ferritin.

DISCLOSURES

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

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ORIGINAL ARTICLE

Perioperative bridging of anticoagulation: towards a more reserved approach

G.C.M. Mol[1]*, H.R. Büller[1], H.A.M. Sinnige[2], N.C.V. Péquériaux[3], M. Coppens[1]

[1]Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centre, University of Amsterdam, the Netherlands; [2]Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands; [3]Thrombosis Service of 's-Hertogenbosch, 's-Hertogenbosch, the Netherlands.
*Corresponding author: geert.mol@radboudumc.nl.

ABSTRACT

Background: Most invasive procedures require the interruption of oral anticoagulation. In 2015, an international randomised trial demonstrated that perioperative bridging caused more harm than benefit in most anticoagulated patients with atrial fibrillation, leading to a more restrictive Dutch national guideline in April 2016. The objective of the present study was to analyse the integration of the 2016 Dutch guideline for perioperative antithrombotic management from after publication until update of hospital protocols.

Methods: This is a retrospective cohort study of patients on vitamin K antagonists undergoing a surgical procedure between April 2016 and June 2017.

Results: The proportion of high-risk patients with venous thromboembolism or atrial fibrillation receiving bridging therapy decreased from 91% and 77%, respectively at the start of the study to 33% in both groups in the last months. In high-risk patients with a mechanical heart valve, the bridging rate remained stable at 70-80% for 12 months and increased to 100% in the last 3 months. Protocol adherence for high-risk patients decreased from 80% to below 43%. The 30-day incidence of major bleeding was 4.1% (15.2% in bridged patients and 0.7% in non-bridged patients) and 10.3% for clinically relevant non-major bleeding (23.9% in bridged patients and 6.0% in non-bridged patients). The incidence of thrombo-embolism was 0.5%.

Conclusion: New evidence from the Dutch national guideline on perioperative bridging was adopted by physicians before the local hospital protocol was updated. Low incidence of thromboembolism in non-bridged patients and high incidence of bleeding in bridged patients support a more restrictive bridging policy.

KEYWORDS

Bleeding, oral anticoagulation, perioperative bridging, post-procedure complications, thromboembolism

INTRODUCTION

Patients with atrial fibrillation (AF), mechanical heart valves (MHV), or venous thromboembolism (VTE) are treated with oral anticoagulation (OAC) for the prevention and treatment of thromboembolism (TE). In patients with AF, OAC reduces the risk of stroke or systemic embolism by 64% and reduces all-cause mortality by 26% compared with no OAC.[1] Before 2009, vitamin K antagonists (VKAs) were the only OAC available. Although recently introduced, direct oral anticoagulants (DOACs) are gradually replacing VKA for patients with AF and VTE. The uptake is slow and in 2016, 72% of Dutch patients receiving OAC were still treated with VKA therapy.[2]

The efficacy of VKA therapy is offset by an increased risk of bleeding. Therefore, invasive procedures including surgery usually require interruption of VKA therapy. Typically, patients are instructed to discontinue VKA treatment three to five days before surgery due to its long half-life. After surgery, adequate anticoagulation is only achieved several days after resuming VKA. This leads to a window of at least five days of subtherapeutic anticoagulation. For patients at high risk of TE, this window can be bridged by an anticoagulant with a shorter half-life, such as low molecular weight heparin (LMWH). This approach may reduce TE, but increases the risk of perioperative bleeding. In practice, perioperative LWMH bridging is used only in patients who have the highest risk of TE. Leading international guidelines on perioperative management of antithrombotic therapy, including the clinical practice guidelines of the American College of

Chest Physicians (ACCP, 9th edition, 2012), were mainly based on observational studies and expert opinions.[3] These guidelines provide practical guidance for medical professionals, however are not based on high-quality evidence.

Uncertainties regarding perioperative bridging could lead to unnecessary risks for patients and practice variation among medical professionals. In a recent Canadian cross-sectional survey, large practice variation in perioperative anticoagulation management was seen among general internists and haematologists who managed perioperative anticoagulation.[4]

Recent studies, including the international randomised controlled BRIDGE trial, provided additional evidence and demonstrated that perioperative bridging caused more harm than benefit in most anticoagulated patients with atrial fibrillation.[5,6] These studies were instrumental in a more restrictive bridging recommendation in the updated Dutch national guideline in April 2016.[7] Local hospital protocols were updated subsequently, often with a time delay.

This retrospective cohort study was performed at a regional hospital and assessed whether bridging practice was already changing after the publication of the updated national guideline, but before adaptation of the local hospital protocol 17 months later. Furthermore, protocol adherence was monitored and TE risk and bleeding risk were compared in bridged and non-bridged patients.

MATERIALS AND METHODS

Study design and patient selection

The retrospective cohort study was carried out at the Jeroen Bosch Hospital (JBH) in 's-Hertogenbosch, the Netherlands. Patients were selected from the Thrombosis Service 's-Hertogenbosch (TSH), a specialised unit of the hospital dedicated to managing VKA therapy of non-institutionalised patients and patients from regional nursing homes. At TSH, separate, temporary files are kept of patients undergoing elective surgery. TSH is actively involved in preprocedural internationalised normalized ratio (INR) management (see peri-operative protocol below). At the start of our study, files were still available from April 2016. We planned to select patients for a 15-month period.

Patients were included if they were over 18 years of age, used VKA, and had an elective surgical procedure at the JBH with a necessary interruption of their VKA treatment before surgery. Outpatient procedures and surgery at other hospitals than JBH were excluded.

Peri-operative protocol

The 'Peri-operative anticoagulation management' protocol of JBH was approved on October 15th, 2010 (first version), with a latest update in April 2014 (the 2014 protocol), which was based on the 2012 ACCP guideline.[3] Prior to surgery, the responsible surgeon indicated the bleeding

Table 1. *TE risk stratification**

	Low (< 5%)	Moderate (5-10%)	High (> 10%)[&]
The 2014 protocol			
MHV	-	Aortic valve + no risk factors[#], recurrent TIA/CVA no cardiac source of embolism	Mitral valve, recent valve (< 3 months), aortic valve + risk factors[#], intracardial thrombus
VTE	Event > 6 months ago	Event 3-6 months ago	Event 1-3 months ago, thrombophilia, recurrent VTE
AF	Isolated AF with CHADS2 score 0-1	Isolated AF with CHADS2 score 2-3	Isolated AF with CHADS2 score 4-6, AF with heart valve or CVA
The 2017 protocol			
MHV	Aortic valve + no risk factors^, recurrent TIA/CVA no cardiac source of embolism		Mitral valve, recent valve (< 3 months), aortic valve + risk factors^, intracardial thrombus
VTE	TE event > 3 months ago		Recent TE event (< 3 months ago)
AF	Isolated AF with CHA2DS2-VASc score 0-7		Isolated AF with CHA2DS2-VASc score 8-9, AF with heart valve or recent (< 6 months) CVA/TIA

MHV = mechanical heart valve; TIA = transient ischaemic attack; CVA = cerebrovascular accident; VTE = venous thromboembolism; AF = atrium fibrillation; CHADS = congestive heart failure, hypertension, age, diabetes, and stroke/TIA (CHADS2 and CHA2DS2-VASc are scores used to estimate the risk of stroke in patients with AF)
*Annual TE risk for patients who are not receiving effective anticoagulation therapy
[#]AF, left atrium dilation, reduced left ventricular ejection fraction, prior myocardial infarction
[&]Additionally, patients with caged-ball or tilting disc aortic heart valves or patients with rheumatic heart disease are also considered high risk
^AF, left ventricular ejection fraction < 35%, prior thromboembolic event

risk of the procedure, whether the VKA therapy should be interrupted (high bleeding risk) or not (low bleeding risk), and the targeted preprocedural INR (below 2.0, below 1.8, or below 1.5). The peri-operative TE risk of a patient was determined during the pre-operative screening by an anaesthesiologist based on the TE risk stratification model used by JBH (table 1). Patients with high TE risk (> 10%) undergoing a high bleeding risk procedures should receive peri-operative bridging. Patients with low (< 5%) or moderate TE risk (5-10%) should not be bridged.

Details of the individual bridging policy per patient were registered in the patient information system by TSH. The VKA therapy (acenocoumarol and phenprocoumon) should be interrupted two to four days prior to surgery depending on the target INR as determined by the responsible surgeon. Additional vitamin K was allowed in cases where phenprocoumon was used. LMWH therapy was started at the same time and stopped 24 hours before the procedure. The VKA and LMWH therapy were restarted 12 to 24 hours post-procedure, except in cases of an active bleeding, to be decided on by the responsible surgeon.

In 2017, the 2014 protocol was updated by the antithrombotic taskforce of JBH based on the Dutch national guideline of 2016[7] and resulted in an adjusted protocol in August 2017 (The 2017 protocol). Although ready to be implemented in April 2017, final board approval was delayed until August 2017 due to administrative reasons.

Differences between the 2014 protocol and the 2017 protocol in terms of TE risk stratification are presented in table 1. In both protocols, perioperative bridging was advised in patients with high TE risk (> 10%).

Reporting period

The total reporting period was divided into subperiods to facilitate analyses over time. Two equal six-month periods were selected, during which the JBH 2014 bridging protocol was in place (April-September 2016 and October 2016-March 2017). A third three-month period (April 2017-June 2017) was added to reflect the interim period between the 2014 protocol and the 2017 protocol. Although the 2017 protocol was not officially adopted until August 2017, it might have had an influence on bridging decisions and behaviour in the period from April 2017 to June 2017.

File review

A standardised electronic questionnaire was prepared to structure and to facilitate patients' file review and data analyses. Patient files were reviewed in the JBH electronic patient information system. This database-oriented computer system was introduced at JBH in June 2016. Files of the previous computer system were converted into the database. If necessary, data was completed with information from the TSH information system. Patients were stratified according to their risk of perioperative TE based on patients' clinical indication for anticoagulation and the presence of comorbidities (see table 1).

Outcome variables

In the present, study bridging was defined as the administration of a therapeutic dose of subcutaneous LMWH or intravenous unfractionated heparin (UFH) for a short period of time during interruption of VKA therapy when the international normalized ratio (INR) was below therapeutic range (INR < 2.0). This includes both full bridging (pre- and post-procedure) and post-procedural bridging only. The outcomes were the proportions of patients receiving bridging, adherence to hospital protocol, and the incidence of post-procedural TE or bleeding (major bleeding or clinically relevant non-major bleeding). TE events were defined as either arterial (ischaemic stroke or transient ischaemic attack) or venous (pulmonary embolism or deep vein thrombosis) as documented by appropriate imaging techniques. The primary bleeding outcome was the composite of major and clinically relevant non-major bleeding. Major bleeding was defined as bleeding which is fatal, occurs in a critical organ, causes a haemoglobin (Hb) drop of at least 1.25 mmol/l, or requires transfusion of two or more units of packed red blood cells. Clinically relevant non-major bleeding was defined as bleeding that did not qualify as major, but required medical intervention, advise of a physician, pharmacological intervention, were registered in the patient's file, or caused discomfort for the patient. Intraoperative bleeding or Hb drop due to dilution by intra-operative fluid administration were not qualified as bleeding. TE events and bleeding were included up till 30 days after the surgical procedure.

Statistical analyses

Categorical variables were presented as absolute numbers and proportions; and continuous variables as means and standard deviations or median and interquartile range, according to the normality of the data. All the analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY). Differences between categorical variables were evaluated by Chi square tests or similar tests. A p-value below 0.05 was considered statistically significant. In order to evaluate the impact of perioperative bridging on bleeding, the odds ratio for bleeding between patients treated with bridging and patients without bridging was calculated with a 95% confidence interval. Logistic regression analysis was performed to identify possible confounders for the association between bridging and bleeding. This regression analysis was focused on variables such as prior stroke, abdominal surgery, and

type of anticoagulation. Variables would be qualified as confounders if the impact of the odds ratio was more than 10% between LMWH bridging and bleeding.

RESULTS

Patients

From the 488 patients in the TSH files during the period of April 2016 to June 2017, 98 patients (20%) were excluded at the beginning of the study due to cancelled or postponed surgery or VKA continuation during procedures, such as percutaneous transluminal angioplasty or cataract surgery. As a result, 390 patients were available for the analysis.

Patient characteristics are shown in table 2. Mean age was 72.7 years with 64% of patients being male. The indication for VKA therapy was AF in 79% of patients, VTE in 10% of patients, MHV in 5% of patients, and 6% for other indications. The mean CHADS2 score of AF patients was 2.0. Just over 93% of patients in this study used acenocoumarol as VKA, the remainder phenprocoumon. The mean pre-procedure INR of 1.21 was well below the average targeted INR of 1.79.

Surgical procedures

Orthopaedic procedures were most prevalent (25.4%), followed by urological (19.2%) and abdominal (18.5%) surgery. Plastic and vascular surgery each comprised 11.8% of procedures. All interventions were considered high bleeding risk procedures based on the 2014 protocol. Figure 1 shows the categories of surgical procedures over the reporting period.

Bridging strategy over time

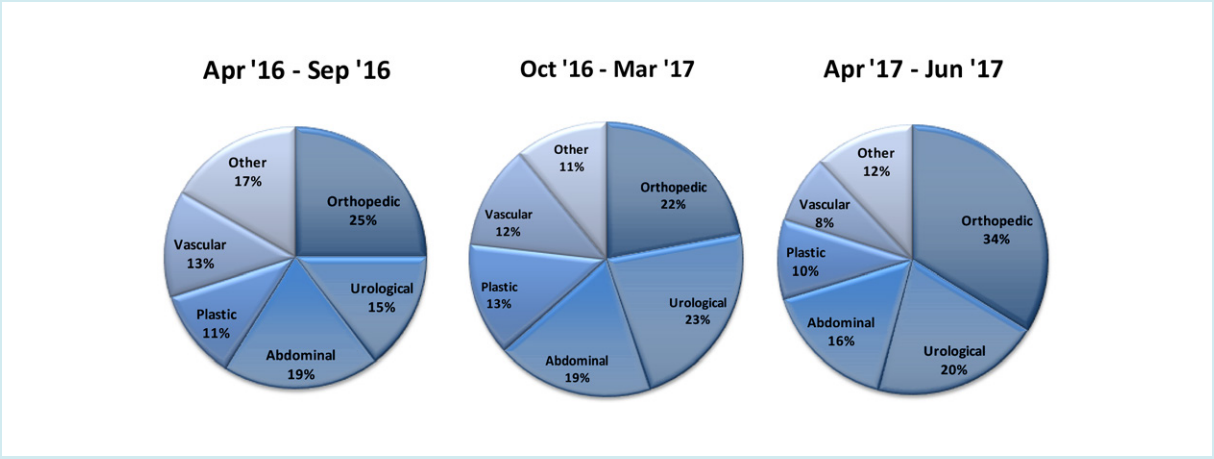
LMWH bridging was used in 24% of patients undergoing surgery. In total, 92 patients were bridged, with 61 patients (66%) receiving pre- and post-operative bridging whereas 31 patients (34%) only received post-procedural bridging. The proportion of bridged patients over the total reporting

Table 2. *Patient characteristics per reporting period and bridging strategy*

	Total cohort (n = 390)	Apr '16 – Sep '16 (n = 144)	Oct '16 – Mar '17 (n = 172)	Apr '17 – Jun '17 (n = 74)	Not bridged (n = 298)	Bridged (n = 92)
Age mean (SD)	72.7 (9.7)	71.7 (9.5)	73.0 (10.2)	73.9 (8.9)	72.9 (9.6)	71.9 (10.2)
Male (%)	63.8	61.8	65.1	64.9	64.4	62.0
High TE risk (%)						
MHV	4.9	6.9	4.1	2.7	1.3	16.3
VTE	7.7	7.6	9.3	4.1	2.3	25.0
AF CHADS2 ≥ 4	10.5	9.0	12.8	8.1	6.7	22.8
Moderate/low TE risk (%)						
MHV	0.3	0.7	0	0	0	1.1
VTE	2.6	3.5	1.7	2.7	2.3	3.3
AF CHADS2 ≤ 3	68.2	66.0	64.0	82.4	81.5	25.0
Other	5.9	6.3	8.1	0	5.7	6.5
CHADS2 score mean (SD)	2.0 (1.2)	2.0 (1.1)	2.1 (1.3)	2.0 (1.1)	1.9 (1.1)	3.0 (1.4)
CHA2DS2-VASc score mean (SD)	-	-	-	3.7 (1.4)	-	-
Comorbidity (%)						
CHF	17.7	18.1	15.1	23.0	17.8	17.4
HT	71.8	70.1	69.8	79.7	73.5	66.3
DM	21.3	20.1	20.9	24.3	21.5	20.7
Stroke/TIA	17.2	17.4	18.6	13.5	12.4	32.6
OAC (%)						
Acenocoumarol	93.3	91.7	94.2	94.6	95.6	85.9
Phenprocoumon	6.7	8.3	5.8	5.4	4.4	14.1
INR target* (SD)	1.79 (0.52)	1.96 (0.44)	1.75 (0.50)	1.54 (0.60)	1.75 (0.51)	1.90 (0.54)

SD = standard deviation; TE = thromboembolism; MHV = mechanical heart valve; VTE = venous thromboembolism; AF = atrium fibrillation; CHADS = congestive heart failure, hypertension, age, diabetes, and stroke/TIA (CHADS2 and CHA2DS2-VASc are scores used to estimate the risk of stroke in patients with AF; these scores were calculated for AF patients only); CHF = congestive heart failure; HT = hypertension; DM = diabetes mellitus; TIA = transient ischemic attack; OAC = oral anticoagulation; INR = international normalized ratio
*Weighted average of pre-procedure INR targets (< 2.0, < 1.8, and < 1.5)

Figure 1. *Proportions of surgery type over the reporting period*



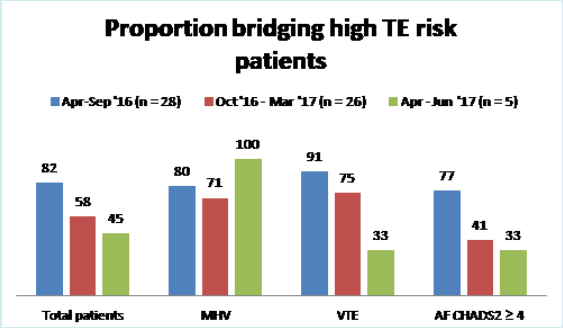
period decreased from 27% in the period April to September 2016 to 23% in the period October 2016 to March 2017, and further to 18% in the period from April to June 2017.

In high TE risk patients, the average bridging rate over the total reporting period was 66% (79% in MHV patients, 77% in VTE patients, and 51% in AF patients). The proportion of high risk TE patients with VTE or AF that received bridging therapy decreased from 91% and 77% respectively in the first period to 33% in the last period. In high risk patients with mechanical heart valves, the bridging rate remained stable at 70-80% in the first 12 months and increased to 100% at the end of the reporting period (figure 2).

In low and moderate TE risk patients, the average bridging rate was stable at 10-13% over the reporting period. In patients with MHV, VTE, and other VKA indications, the bridging rate decreased to 0% at the end of the reporting period. In patients with AF, the bridging rate increased over the reporting period from 5% to 13% due to more post-procedural bedside bridging decisions (see figure 3).

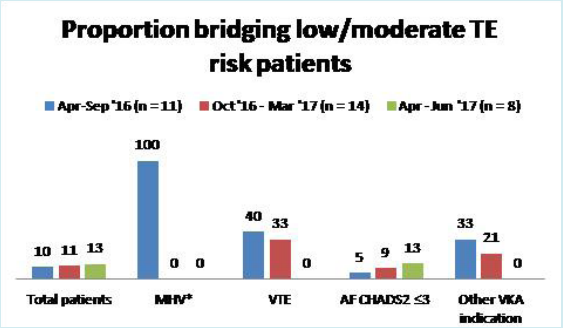
For the analyses of temporal trends in LMWH bridging, the reporting period was divided into two six-month periods and one three-month period. To evaluate whether this breakdown influenced the results, an alternative analysis was done with three periods of five months, which yielded similar results.

Figure 2. *Proportion of high TE risk patients receiving LMWH bridging*



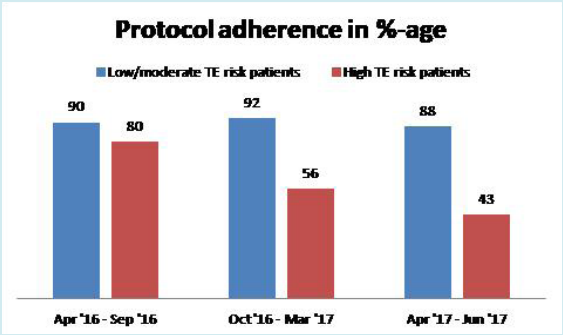
TE = thromboembolism; MHV = patient with a mechanical heart valve; VTE = patients with venous thromboembolism; AF CHADS2 ≥ 4 = patients with atrium fibrillation and a CHADS2 score equal or higher than 4.

Figure 3. *Proportion of low/moderate TE risk patients receiving LMWH bridging*



* MHV in period Apr-Sep 2016 reflects only 1 patient
TE = thromboembolism; MHV = patients with a mechanical heart valve; VTE = patients with venous thromboembolism; AF CHADS2 ≤ 3 = patients with atrium fibrillation and a CHADS2 score equal or lower than 3; other VKA indication = patient with other indications for VKA therapy.

Figure 4. *Adherence to hospital protocol*



TE = thromboembolism; low/moderate TE risk patients = patients with an annual TE risk lower than 10% (see table 1); high TE risk patients = patients with an annual TE risk equal or higher than 10% (see table 1).

Table 3. *Compliance non-bridged patients to new national guideline*

	Not bridged	Patients in compliance to new guideline	Percentage
April 2016 – September 2016	105	105	100%
October 2016 – March 2017	132	130*	98.5%
April 2017 – June 2017	61	61	100%
Total	298	296	99.3%

*For two patients it was not clear from the data whether they suffered from a vascular disease. No vascular disease was assumed, resulting in a CHADS-VASc score of 7 for both patients (low TE risk).

Adherence to protocol and the 2016 Dutch national guideline

Over the reporting period, adherence to the 2014 protocol for high TE risk patients decreased from 80% (April 2016 to September 2016) to 56% (October 2016 – March 2017) and to 43% (April 2017 – June 2017; figure 4). For low and moderate risk patients, protocol adherence was stable around 90%. Concomitantly, we observed that patients were managed according to the new national guideline published in April 2016 before the adaptation of the local hospital protocol was implemented. Adherence to this new guideline in non-bridged patients was 99.3% over the total reporting period (April-September 2016: 100%; October 2016-March 2017: 98.5%; April-June 2017: 100%) (see table 3).

TE events

Two patients developed a suspected TIA in the 30 days following the procedure (incidence 0.5%). The events occurred in patients with AF at 1 and 14 days after the procedure. Both patients were at high risk of TE based on the hospital protocol (AF, $CHADS_2$ score 4 and 5, respectively). One patient (with TE event one day post-procedure) did not receive bridging. VKA therapy was interrupted four days prior to surgery and restarted the day after the procedure. The other patient received bridging with LMWH. VKA therapy was interrupted three days prior to the procedure and restarted one day post-procedure (table 4).

Bleeding events

In total, 55 patients (14.1%) had a bleeding episode (major or clinically relevant non-major bleeding) within 30 days after the procedure. The risk was higher in patients treated with LMWH bridging than in non-bridged patients (39.1% vs 6.7%, odds ratio 8.5, 95% confidence interval 4.6-15.8).

Table 4. *Post-procedural events*

	Not bridged (n = 298)	Bridged (n = 92)	Total patients (n = 390)
TE			
Events	1	1	2
Incidence (%)	0.3	1.1	0.5
MBE + CRNMB			
Events	20	36	55*
Incidence (%)	6.7	39.1	14.1
MBE			
Events	2	14	16
Incidence (%)	0.7	15.2	4.1
CRNMB			
Events	18	22	40
Incidence (%)	6.0	23.9	10.3

TE = thromboembolism; MBE = major bleeding; CRNMB = clinically relevant non-major bleeding
*One patient developed a CRNMB first, followed by an MBE, four days later

Sixteen patients (4.1%) developed a major bleeding within 30 days after the procedure. Major bleeding occurred most often in abdominal surgery (11.1%, 8 events), followed by gynaecological surgery (10.0%, 1 event) and breast surgery (7.7%, 1 event) (table 4).

Logistic regression was performed to identify possible confounders. Unfortunately, the low number of observations of major bleeding did not allow for separate logistic regression. For this reason, regression has been extended to the impact of confounders on major and clinically relevant non-major bleeding taken together. No confounders were identified.

DISCUSSION

In recent years, practice guidelines on perioperative management of VKA therapy have recommended more restrictive use of LMWH bridging in patients who require temporary interruption for surgical procedures.[7] This change was caused by evidence from a randomised trial that confirmed previous observational studies that LMWH bridging in patients with atrial fibrillation increases the risk of post-operative bleeding without protecting against thromboembolic events.[5,8] In the present study, adherence to the hospital bridging protocol dropped from 80% to 43% in 15 months for patients at high TE risk and remained high (~ 90%) for intermediate and low TE risk procedures. This steep decline was brought on by the new Dutch national guideline on perioperative VKA therapy in April 2016. Although the hospital protocol was not changed until August 2017, clinical practice had already started to change after publication of the national guideline. This raises an important issue on the necessity of local hospital protocols on topics for which national multidisciplinary guidelines are available. If guidelines are drafted by mandated representatives of the involved specialties, local evaluation and translation into a new hospital protocol may not be necessary, which only delays implementation of recommendations to improve patient outcome. This study shows that physicians may already start to adopt new guidelines before hospital protocols are adapted. On the other hand, guidelines often offer multiple options in circumstances where evidence is less clear and guidelines usually lack details that a hospital protocol requires, such as drugs names, recommended dosage, or frequency. A hybrid approach that does not re-evaluate the evidence but does make explicit choices may reduce the time and effort needed to update local protocols. We could not compare adherence to hospital protocol at our institution with other hospitals and do not know of such available data. We speculate however, that a similar pattern would have been witnessed in other hospitals.

In this study, LMWH bridging increased the risk of bleeding and did not reduce perioperative thromboembolism in the reporting period. Although this is in agreement with previous studies, the present study was not powered to study differences in bleeding and thromboembolism in bridged versus non-bridged patients. Other limitations involve the retrospective nature of the study. Patient information was extracted by review of TSH charts, which are semi-structured and some details were unclear or may have been missing. Furthermore, due to the introduction of a new electronic record in July 2016, available information for the period April-June 2016 was limited.

CONCLUSION

In conclusion, this study indicates that in daily practice, physicians already adopt new evidence from guidelines before local hospital protocols are changed accordingly. It also confirms the rationale for a more restrictive LMWH bridging approach in patients on VKA therapy who need to interrupt oral anticoagulation for surgery.

DISCLOSURES

This study did not receive any financial support. G.C.M. Mol, H.A.M. Sinnige, and N.C.V. Péquériaux report no conflicts of interest for this study. H.R. Büller has served as a consultant to Sanofi-Aventis, Bayer, Pfizer, Glaxo-Smith-Kline, Astellas, Boehringer-Ingelheim, and Daiichi-Sankyo, outside of the submitted work. M. Coppens has received financial support for research and health innovation, as well as lecturing and consultancy fees from Bayer, Boehringer Ingelheim, Bristol Myers-Squibb, Daiichi Sankyo, Pfizer, Portola, and Sanquin Blood Supply, outside of the submitted work.

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CASE REPORT

Secondary hyperoxaluria due to pancreatic insufficiency

D.G.L. de Martines*, S. Gianotten, J. F.M. Wetzels, W.A. G. van der Meijden

Department of Nephrology, Radboud University Medical Centre, Nijmegen, the Netherlands.
*Corresponding author: Dion.deMartines@radboudumc.nl

ABSTRACT

Background: In this article, we present two cases of patients with acute renal insufficiency with a history of exocrine pancreatic insufficiency. In one case, this was caused by pancreaticoduodenectomy; in the other, by alcohol abuse. Neither patient had considerable proteinuria or haematuria. Their renal biopsies showed tubulopathy with widespread oxalate crystals, characterised by their birefringence in light microscopy. Restricting oxalate intake and prescribing oxalate binding agents reduced serum oxalate levels. Renal function partially recovered in both patients.

Oxalate nephropathy is associated with exocrine pancreatic insufficiency, gastric and pancreatic surgery, and inflammatory bowel disease. Normally, dietary calcium binds oxalate to form calcium oxalate, which is excreted in the stool. In patients with pancreatic insufficiency, fatty acids bind calcium instead, allowing oxalate to be absorbed in the colon. The resulting hyperoxaluria can cause oxalate crystal formation, tubulopathy, and renal insufficiency. Treatment relies on decreasing the amount of absorbable oxalate in the intestinal lumen, as well as lowering urinary oxalate concentrations.

Conclusion: Secondary hyperoxaluria is a common cause of renal insufficiency and should be considered in patients with a medical history of pancreatic insufficiency and progressive kidney injury.

KEYWORDS

Acute kidney injury; enteric hyperoxaluria; fat malabsorption; nephrolithiasis; oxalate nephropathy; oxalosis; secondary oxalosis

What was known on this topic?
Oxalate nephropathy is a known cause of end stage renal disease. It may be primary due to genetic defects, causing deficiencies of liver enzymes. It also has several secondary causes, which are associated with an increased absorption of oxalate in the gut, causing serum oxalate levels to rise.

What is new?
Recently, more attention has been given to oxalate nephropathy following pancreatic insufficiency. Maldigestion of free fatty acids increases the amount of calcium-free oxalate in the intestinal lumen, which facilitates its absorption. Physicians should be aware of this cause of renal insufficiency, which does not respond to corticosteroids or other immunosuppressants. Early recognition enables swift treatment, which can effectively decrease intestinal oxalate absorption and may halt further disease progression.

INTRODUCTION

Oxalate nephropathy is a rare cause of renal insufficiency. It is characterised by damage to the interstitium and tubuli of the kidneys, caused by deposition of oxalate crystals. During the past decade, oxalate nephropathy has been described several times as a complication of fat malabsorption after bariatric surgery, and in patients with short bowel syndrome, cystic fibrosis, celiac disease, and exocrine pancreatic insufficiency. Today, the diagnosis is not very rare; for example, one study identified that in a series of 611 patients referred for pre-transplantation consultation, 17 (3%) had oxalate nephropathy.[1]

We describe two patients with exocrine pancreatic insufficiency, who were evaluated in our hospital because of acute renal insufficiency of unknown origin.

Patient A

A 77-year-old male was referred to our centre with deterioration of renal function. He had a history of hypertension, hypercholesterolaemia, and a pT3N1 pancreatic head carcinoma, which had been treated by pancreaticoduodenectomy and adjuvant chemotherapy two years earlier.

There was no history of kidney stones and the family history was negative for renal diseases. Six months after the pancreaticoduodenectomy, the patient started taking pancreatic enzyme supplements (pancreatin) because of chronic diarrhoea. After surgery, his serum creatinine level was 90 µmol/l, but increased to 180 µmol/l two months later, after a brief period of heart failure due to gemcitabine. His renal function remained stable for the following five months; however, shortly before being referred to our centre, his serum creatinine level suddenly increased to over 300 µmol/l.

The patient's history revealed no clues for a prerenal cause of his renal insufficiency: the patient reported no vomiting, used no new medications or supplements, and had not used any non-steroidal anti-inflammatory drug. His diarrhoea ceased when he started taking pancreatin. There were no signs of a systemic disease and physical examination showed no abnormalities: his blood pressure was 138/75 mmHg with a heart rate of 60 beats per minute.

At the initial visit in our centre, his serum creatinine level had increased to 326 µmol/l (table 1). Further investigation showed normal anion gap metabolic acidosis (pH 7.22), normocytic anaemia (Hb 6.3 mmol/l), and hyperphosphataemia (serum phosphorus 1.76 mmol/l). Urinary examination showed some leukocytes, without erythrocytes. Twenty-four-hour urinalysis revealed a proteinuria of 0.25 grams/day. Abdominal ultrasound showed normal kidneys, measuring 10.6 and 10.1 cm. There were no signs of nephrocalcinosis. The differential diagnosis was tubulointerstitial nephritis, cholesterol-emboli, or acute tubular necrosis. A kidney biopsy was performed.

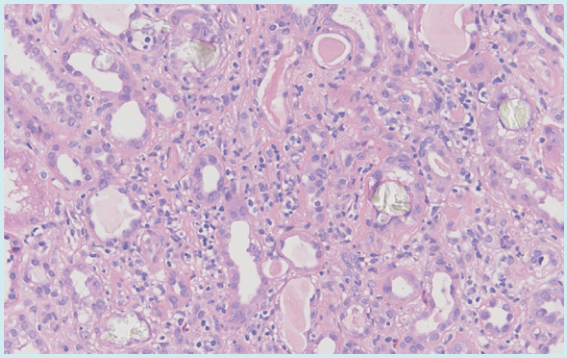
The biopsy showed pronounced tubulopathy with extensive deposits of birefringent oxalate crystals (figure 1). The glomeruli were normal and immunofluorescence revealed no immune depositions. Thus, the patient

Table 1. *Blood and urine test values for patients A and B at the time of referral*

Blood test at admission	Patient A	Patient B	Reference values
Haemoglobin	6.3	5.3	8.4-10.0 mmol/l
Mean corpuscular volume	88	91	80-100 fl
Thrombocytes	205	199	150-400 x 10^9/l
Leukocytes	5.9	9.3	4.0-11.0 x 10^9/l
Creatinine	317	742	60-110 µmol/l
Sodium	143	142	135-145 mmol/l
Potassium	3.9	4.9	3.5-4.7 mmol/l
Phosphate	1.76	2.67	1.0-1.8 mmol/l
CRP	1		< 10 mg/l
pH	7.32	7.26	7.31-7.41
Bicarbonate	18.8	14.6	22-28 mmol/l
pCO_2	5.0	4.4	5.3-6.9 kPa
Anion gap, corrected	17.4	17.9	5-11 mmol/l
Serum oxalate	55.2	116.9	< 5 µmol/l
24-hr urinary protein	0.25	0.07	< 0.3 grams/24-hr
Spot urine erythrocytes	1.40	3.20	< 5 per field of view
Spot urine leukocytes	8.25	23	5-10 per field of view
24-hr urine oxalate	0.84		< 0.5 mmol/24-hr

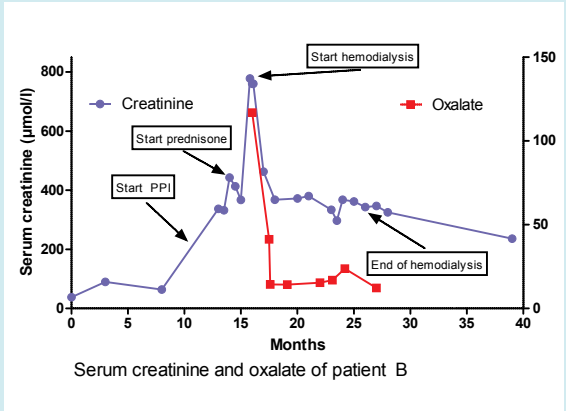
CRP = C-reactive protein; pCO_2 = partial pressue of carbon dioxide; hr = hour

Figure 1. *Light microscopy of the renal biopsy of patient A, showing tubulopathy and extensive grey-white crystal depositions: calcium oxalate crystals (HE colouring, microscopic magnification)*



HE = haemotoxylin and eosin

Figure 2. *Serum creatinine and oxalate of patient B*



PPI = proton pump inhibitor

was diagnosed with secondary hyperoxaluria due to malabsorption following exocrine pancreatic insufficiency. His serum oxalate level was 55.3 µmol/l (reference value < 5 µmol/l). Considering his age and medical history of pancreaticoduodenectomy, a primary hyperoxaluria was deemed unlikely. No mutational analysis was performed. The patient was advised to reduce dietary oxalate intake and was started on calcium supplementation before meals, together with cholestyramine. Six months later, serum oxalate levels had decreased to 30 µmol/l. Kidney function partially recovered with serum creatinine levels dropping to 244 µmol/l (estimated glomerular filtration rate (eGFR) of 21 ml/min/1.73 m²).

Patient B

A 64-year-old male with a history of diabetes mellitus type 2, depression, and an exocrine pancreatic insufficiency due to chronic alcohol abuse, was referred to our hospital for dialysis following acute on progressive renal insufficiency. Due to complaints of chronic diarrhoea, he had been prescribed pancreatin by the referring physician. No further investigations into his pancreatic insufficiency had been performed, but an earlier computed tomography scan of abdomen showed extensive calcifications and atrophy of the pancreas. The patient also used thiamine, ranitidine (H2 receptor antagonist), macrogol, furosemide (loop diuretic), alfacalcidol (1-α-OH-vitamin D3), iron, and insulin.

A proton-pump-inhibitor (PPI) was prescribed for reflux disease (figure 2). Upon his next visit, serum creatinine level had increased from 50 µmol/l to 222 µmol/l. Due to the suspicion of a medication-induced tubulointerstitial nephritis, the PPI was promptly ceased, and the patient was treated with oral prednisolone, 40 mg daily, without improvement of renal function.

When the patient was referred to our hospital for biopsy and dialysis, serum creatinine levels had increased to 742 µmol/l. His medical history and physical examination provided no further clues, except for signs of malnutrition. Family history was negative for kidney diseases and the patient had never suffered from kidney stones; his blood pressure was 130/84 mmHg.

The patient had normocytic anaemia (Hb 5.3 mmol/l), hyperphosphataemia (2.67 mmol/l), and metabolic acidosis (pH 7.26) (table 1). Serologic evaluation was negative, urinalysis revealed leukocyturia (23 leukocytes per field of view) with mild erythrocyturia. No crystals or casts were seen. Renal ultrasound showed kidneys measuring 12.9 and 11.6 cm, without hydronephrosis or nephrocalcinosis. The differential diagnosis consisted of IgG4 related disease, tubulo-interstitial disease, or oxalate nephropathy. IgG subclass quantification was normal.

A renal biopsy revealed tubulopathy and widespread oxalate crystal depositions, confirming the diagnosis of oxalate nephropathy. The serum oxalate was severely increased: 116.9 µmol/l (reference value < 5 µmol/l). No mutational analysis was performed.

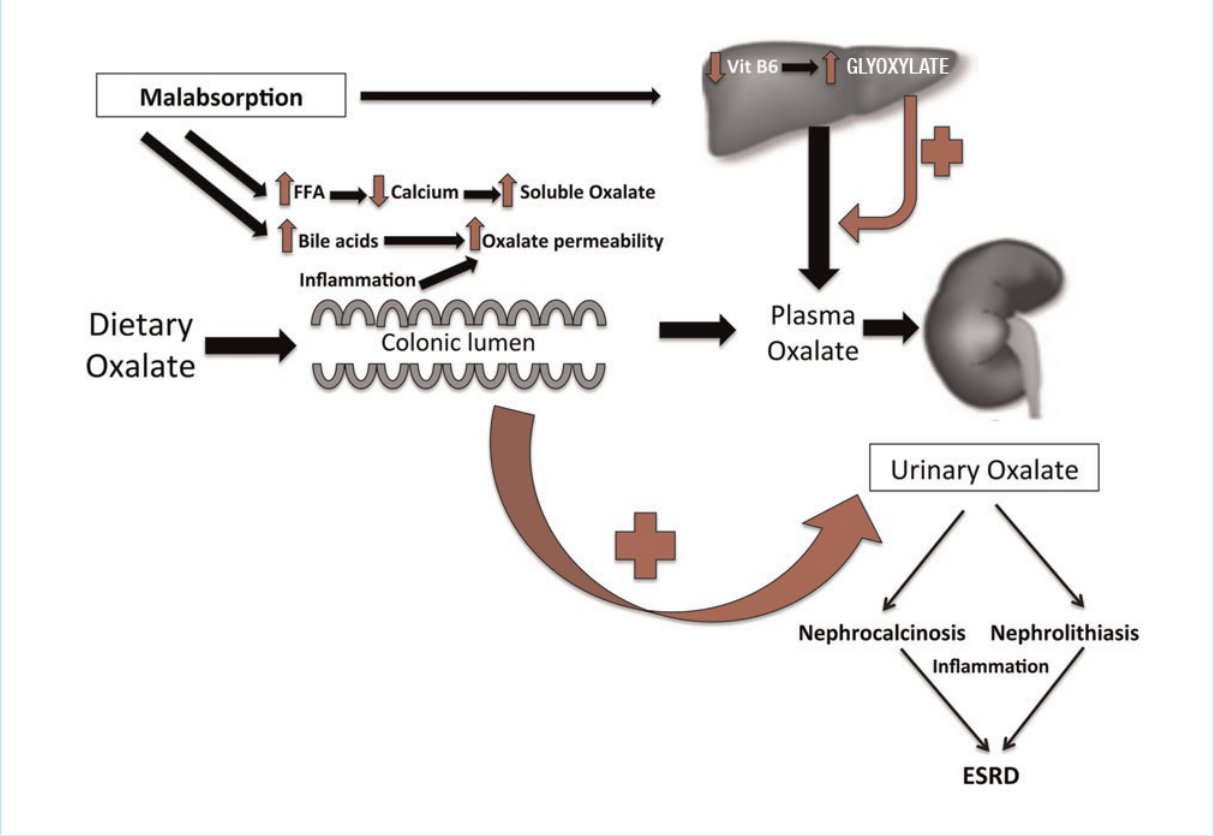
The patient started haemodialysis and was advised to adhere to an oxalate-restricted diet. In addition, the patient took calcium supplementation and cholestyramine. After 10 months of therapy, his serum oxalate levels were stable at 14 µmol/l and haemodialysis could be ceased. Renal function eventually recovered to an eGFR 24 ml/min/1.73 m² (serum creatinine level 236 µmol/l) one year after ceasing haemodialysis (figure 2).

CLINICAL LESSON

Biochemistry

Oxalic acid ($C_2H_2O_4$) is an acid with a molecular mass of 88 kDa.[2] Oxalate ($C_2O^{2-}_4$) is the ion. It is ingested through

Figure 3. *Pathophysiology of enteric oxalate nephropathy*
Oxalate is absorbed from the diet and is produced by the liver from glyoxylate. Maldigestion increases the amount of free fatty acids in the enteric lumen. These bind calcium, which leaves oxalate unbound. Free oxalate is easily absorbed by enterocytes. Secondly, unbound bile acids increase enteric permeability, which further facilitates oxalate absorption. Lastly, inflammation, such as in irritable bowel disease also increases permeability. These mechanisms increase serum oxalate levels, which may cause oxalate depositions and oxalate nephropathy.[6]



FFA = free fatty acids, ESDR = end-stage renal disease

several sources of food, notably vegetables, fruits, nuts, and grain and absorbed in the intestines, primarily in the colon. Oxalate in humans is also produced endogenously in the liver from its precursor, glyoxylate.[3] Oxalate has no known biological functions.

Pathophysiology

Two forms of hyperoxaluria can be distinguished. Primary hyperoxaluria is caused by genetic defects in the hepatic degradation of glyoxalate,[4] while secondary hyperoxaluria is caused by an increased intake of oxalate precursors such as ascorbic acid (vitamin C) or ethylene glycol (the main constituent of de-icer spray),[5] or by an increased absorption of dietary oxalate.

In healthy individuals, calcium and oxalate form calcium oxalate, which is unavailable for enteric absorption and excreted in the stool. However, in case of malabsorption, calcium will not precipitate with oxalate but bind instead with the increased levels of intraluminal free fatty acids. The unbound oxalate is then freely absorbed into the blood, mainly through passive paracellular colonic transport.[6]

Malabsorption of free fatty acids and the associated steatorrhoea are seen after Roux-en-Y bypass surgery, after pancreaticoduodenectomy, and in the setting of exocrine pancreatic insufficiency. In a study with 48 patients with chronic pancreatitis, 23% had hyperoxaluria.[7] Secondary hyperoxaluria is not described in patients after gastric sleeve surgery, since this does not cause steatorrhoea or malabsorption.[8]

Furthermore, in inflammatory bowel diseases such as morbus Crohn and celiac disease, oxalate absorption is increased due to mucosal inflammation. Elevated levels of bile acids in the intestine also seem to facilitate oxalate absorption through increased permeability.

A final cause for increased oxalate absorption is a disruption of the intestinal microbiome. Certain bacteria,

such as the anaerobic *Oxalobacter formigenes*, degrade oxalate. (Oral) treatment with antibiotics affects these bacteria and changes the amounts of oxalate excreted in the stool.[9]

Oxalate in the serum is mostly filtered by the glomerulus. Research has shown that urinary oxalate excretion increases when dietary oxalate intake increases.[10] Oxalate transporters are present in the proximal tubules of the kidney and in the gut. There is evidence for a bidirectional transport, so oxalate may be actively secreted and reabsorbed.[11] Hyperoxaluria and the resulting calciumoxalate supersaturation in the kidney can lead to formation of calcium oxalate kidney stones, nephrocalcinosis and depositions of oxalate crystals in the renal interstitium. This process is accelerated in an acidic environment, for example, in conditions such as metabolic acidosis. Dehydration promotes crystal formation due to more concentrated urine. Secretion of ADH (anti-diuretic hormone) and activation of the renin-angiotensin-aldosterone system, initiate tubular resorption of sodium and water, increasing the tubular concentration of oxalate.[12] Tubular damage due to oxalate crystals attracts lymphocytes, causing interstitial nephritis, which ultimately leads to interstitial fibrosis and permanent loss of renal function.

When renal function decreases, serum oxalate levels rise.[13] Research suggests that renal oxalate clearance decreases when GFR falls below 30-40 ml/min/1.73 m^2, causing elevated levels of oxalate and risk for further deterioration of renal function.[4] Interestingly, a recent study showed an association between urine oxalate excretion and chronic kidney disease progression.[14] Unfortunately, serum oxalate levels were not analysed. Systemic oxalosis, characterised by tissue damage in bones, skin, eyes, neurons, and heart due to deposition of oxalate crystals, may occur in patients with elevated levels of serum oxalate. Higher incidence rates of vascular events are seen in patients with systemic oxalosis, most likely explained by the toxicity of oxalate to the vascular endothelium.[14] Oxalate nephropathy can manifest as both acute and chronic renal insufficiency. Though renal function may partially recover, more than half of all patients remain dependent on dialysis.[15]

DIAGNOSTICS

In a systematic review of patients with secondary oxalate nephropathy, a mean age of 56 years was identified, with men and women being equally affected.[15]

Urinalysis may reveal leukocyturia, haematuria, and mild proteinuria. Microscopic examination of urine shows birefringent calcium oxalate crystals in the urine in roughly one in four patients.[15] Oxalate levels in both serum and urine may be elevated. Renal ultrasound may show nephrocalcinosis or nephrolithiasis, but as seen in our patients, this is not always the case. In renal biopsy, oxalate precipitations are seen in the tubular lumen, the interstitium, and the peritubulary capillaries (figure 1). Typically, the crystals are birefringent in polarized light.

TREATMENT

Treatment aims to reduce systemic oxalosis and to prevent oxalate nephropathy from developing. It relies primarily on decreasing enteric oxalate absorption by decreasing the amount of unbound oxalate in the enteric lumen. This can be achieved by reducing the amount of dietary oxalate and taking calcium supplements with meals. Foods with especially high oxalate content, such as rhubarb, spinach, purslane, Swiss chard, sorrel, and beetroot, should be avoided. Secondly, binding bile acids with cholestyramine reduces colonic permeability for oxalate, decreasing net absorption. Thirdly, supplementation of oxalate degrading bacteria such as *Oxalobacter* species, lowers intestinal oxalate levels and may decrease urinary oxalate excretion. Lastly, an ongoing trial investigates the potential of oral oxalate decarboxylase supplementation, which breaks down intestinal oxalate into carbon dioxide and formate.[16]

Fluid intake must be sufficient and dehydration should be avoided. High urine output lowers calcium oxalate supersaturation in the tubuli, decreasing the likelihood of renal crystal formation. Increasing pH of the urine by taking citrate, by correcting a metabolic acidosis, and by supplementing magnesium also reduces stone formation. Citrate also reduces calcium oxalate supersaturation by binding calcium, preventing oxalate crystal formation. Haemodialysis decreases serum oxalate levels. Patients who receive a renal transplant may also require haemodialysis in the initial days after surgery to prevent recurrence of oxalate nephropathy in the renal transplant. A living donor is preferred to minimize the chance of delayed graft function due to the injurious effects of the high oxalate burden in the transplanted kidney.[1] Following kidney transplantation, hyperoxaluria may continue for years due to prolonged release of oxalate from the tissues.[17]

In this article, we explain that fat malabsorption due to exocrine pancreatic insufficiency can cause oxalate nephropathy. Since effective management is possible, early recognition is important. In clinical practice, patients with renal insufficiency who are at risk of developing pancreatic insufficiency due to malignancy or chronic pancreatitis (often secondary to alcohol abuse, smoking, or pancreatic duct obstruction), as well as patients who have had bariatric surgery, should be evaluated for oxalate nephropathy. Presumably, this diagnosis is often missed. Considering the increasing incidence of bariatric surgery, it is likely to occur more frequently in the near future. We hope to

raise awareness for oxalate nephropathy secondary to fat malabsorption.

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CASE REPORT

Good clinical outcome in a case of *Listeria*-associated multiple liver abscesses and clinical hepatitis

S. van der Voort*, J. Branger, P. Gruteke

Flevo Hospital, Almere, the Netherlands.
*Corresponding author: svdvoort@flevoziekenhuis.nl

SUMMARY

This case report describes a patient with the rare phenomenon of multiple liver abscesses and signs of hepatitis, secondary to disseminated listeriosis. All signs and symptoms resolved with antibiotic treatment only, contradicting current literature. This suggests that the development of multiple liver abscesses following infection with *Listeria monocytogenes* does not necessarily yield a poor prognosis, even without drainage.

KEY WORDS

Hepatitis, *listeria monocytogenes*, listeriosis, liver abcesses

What was known on this topic?
Listeriosis is a potentially severe condition in which liver involvement is uncommon. Three different types of liver involvement have been reported: a solitary abscess, multiple abscesses, or diffuse hepatitis. In patients with multiple liver abscesses, signs of hepatitis (increased liver enzymes) are rarely seen. Multiple abscesses in listeriosis yield a poor prognosis, especially when abscesses are not drained.

What does this report add?
In this case report, we present a patient in which liver abscesses, hepatic inflammation, and dysfunction were secondary to disseminated listeriosis. With antibiotic treatment, our case had a good clinical outcome despite multiple liver abscesses, even without drainage. More research is required to identify the mechanisms of liver involvement in listeriosis and which factors affect prognosis.

INTRODUCTION

Listeria monocytogenes are Gram-positive bacteria that are abundantly present in the environment. Contamination of fish, meat, vegetables, and dairy products can cause potentially fatal infections. Healthy individuals who are infected with *Listeria* may develop febrile gastroenteritis which usually lasts for one or two days and in this case, is self-limiting.[1] However, in individuals of extreme age (neonates or elderly people) or in immunocompromised adults or pregnant women, listeriosis can be invasive, causing sepsis, meningoencephalitis, or infection of the pregnant uterus.[1]

In the Netherlands, listeriosis has been a compulsory notifiable disease since 2008. In 2017, 115 patients with listeriosis were registered.[2] The most frequently registered manifestations were sepsis (37 patients), meningitis (27 patients), pneumonia, and gastroenteritis. In total, 10 patients (9%) died. The majority of patients in which listeriosis occurred were immunocompromised due to underlying disease or (immunosuppressive) medications. Possible sources of infection included soft cheeses, sausages, raw and boiled hams, chicken, and fish (e.g., smoked herring, a Dutch delicacy).

Even though liver involvement has been rarely described, it can, according to Scholing et al., manifest as solitary liver abscess, multiple liver abscesses, and diffuse or granulomatous hepatitis.[3] In cases of listeriosis with multiple liver abscesses, the clinical outcome shows increased morbidity and mortality compared to presentations in which the liver is not involved.[4] In this case report, we discuss an adult patient with listeriosis

Table 1. *Laboratory results at days 0, 4, 8, and 50.*

	Reference	Day 0	Day 4	Day 8	Day 50
Leucocytes (x 10^9/l)	-10	12	9.1	7.4	3.6
CRP (mg/l)	4-10	434	339	35	0.8
Creatinine (µmol/l)	45-84	87	78	65	77
Alkaline phosphatase (IU/l)	-98	138	328	319	118
ALT (IU/l)	-40	200	380	226	35
AST (IU/l)	-31	223	270	119	22
GGT (IU/l)	-38	24	58	179	49
Total bilirubin (umol/l)	-17	9	10	6	17
PT (s)	10-12	*	13.3	11.2	11.1
APTT (s)	23.3-30.1	*	45.2	29.9	32.5

*Not determined.
CRP = C-reactive protein; ALT = alanine aminotransferase; AST = aspartate transaminase; GGT = gamma-glutamyltransferase; PT = prothrombin time; APTT = activated partial tromboplastin time.

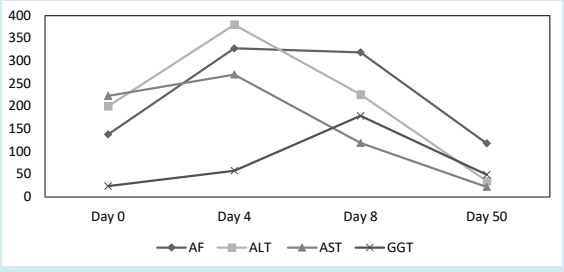
and liver involvement, who experienced a good clinical outcome.

CASE REPORT

A 73-year-old female presented to our Emergency Department with signs of sepsis. Her medical history showed hypertension and type 2 diabetes, for which she took metformin. At presentation, she had been sick for four days with a fever, headache, and drowsiness. At clinical examination, we saw a female who was visibly unwell. Her blood pressure was 120/80 mmHg with a tachycardia of 100-120 beats per minute, her rectal temperature was 39.9°C, and respiratory rate was 20 breaths per minute. The remaining physical examination revealed no other potential diagnostic clues and she did not present signs of meningitis. The laboratory results (table 1) showed increased inflammation parameters with electrolyte disturbances and kidney dysfunction most likely due to sepsis.

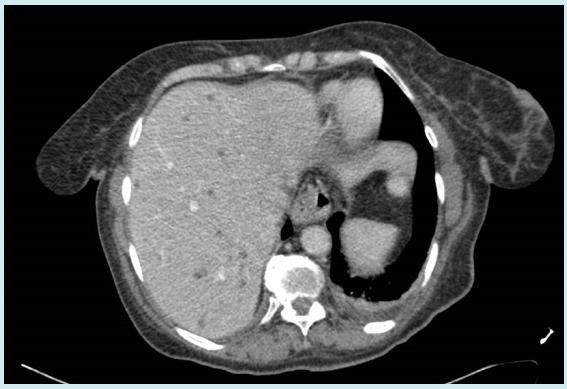
The patient's laboratory tests showed elevated liver enzymes and prolonged time of coagulation tests. A chest X-ray and urinary sediment were normal. A computed tomography (CT) scan of her thorax/abdomen showed a liver with multiple small round lesions with a density of 30-40 Hounsfield units and circular colouring, at first, appearing to be malignant metastases (figure 2).

Figure 1. *Liver enzyme levels (IU/L) at day 0, 4, 8, and 50*



AF = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate transaminase; GGT = gamma-glutamyltransferase.

Figure 2. *CT scan of the liver*



However, the scan showed no observable lymphadenopathy or any primary (malignant) tumour. The patient was admitted to the Internal Medicine ward and empirical treatment for sepsis was started, consisting of 1000/200 mg amoxicillin/clavulanate, four times a day and gentamicin 4 mg/kg, once a day, intravenously (i.v.) according to local guidelines.

Clinically, the patient recovered after two days of antibiotics. Kidney function and electrolytes were restored after fluid administration. However, liver enzymes increased with a peak level at day four (figure 1). Ultrasound investigation of the liver showed the same round lesions as seen on the CT scan with a largest diameter of 1.2 cm. Unfortunately, the lesions were too small or not well located, and we were unable to perform needle aspiration. One of two blood culture bottles (BD BACTEC) taken on admission showed growth of an apparently anaerobic Gram-negative rod after two days of incubation. However, overnight culture on solid media revealed a Gram-positive rod. This was subsequently identified as *Listeria monocytogenes* with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI TOF MS; bioMerieux, Marcy-l'Etoile, France). The antibiotic therapy was changed into i.v. amoxicillin 1000 mg, six times a day and continued for a total period of three weeks. Most liver tests improved after four days of antibiotic therapy. A second CT scan of the liver at day 15 of admission (day 19 after the onset of symptoms) showed a significant reduction in the amount and size of the lesions. The patient was discharged from our hospital after 22 days, in excellent clinical condition. Follow up at day 50 showed almost normalised laboratory results and on CT scan, a completely normal liver without any lesions.

DISCUSSION

In this case, hepatic inflammation and dysfunction was secondary to disseminated listeriosis. This was indicated by the marked improvement of liver enzymes and decrease in amount and size of the liver lesions in response to antibiotic treatment. Liver involvement in listeriosis is rarely reported in the literature, which is surprising, considering the important role attributed to the portal vein system in the pathogenesis of invasive *L. monocytogenes* disease.[5]

In a systematic literature review published in 2007, Scholing et al. compared 34 cases of *Listeria* infection with liver involvement. In 13 cases (38%), the underlying condition was type 2 diabetes, as was the case in our patient. Our case, however, differed with respect to two key characteristics: the mode of liver presentation and the outcome. Scholing et al. reported on 10 patients, each with a solitary liver abscess; 11 patients with multiple small liver abscesses; and 14 patients with diffuse (10) or granulomatous (4) hepatitis (as diagnosed by clinical presentation, biopsy, or autopsy). Interestingly, liver enzymes (alanine transaminase and aspartate aminotransferase) were grossly elevated in all patients who suffered from diffuse hepatitis, but such elevation, in general, was not a good predictor of solitary or multiple liver abscesses. Furthermore, all patients with a solitary abscess had excellent clinical outcome after drainage of the abscesses and antibiotic treatment. In the 11 patients with multiple liver abscesses, three patients were treated with abscess drainage and survived; the other patients died. However, in the 10 patients with diffuse hepatitis, the survival rate was 70%, with systemic antibiotic administration for a mean treatment period of three weeks. In our patient, we observed radiological signs of multiple small liver abscesses together with a 10-fold liver enzyme elevation. The latter could have been the direct result of the multiple abscesses, although an alternative explanation may indicate the presence of concomitant hepatitis. Elevated liver enzymes were observed in only 4 of 21 patients with solitary or multiple abscesses described in the review; however, diagnosis made by biopsy or autopsy was performed in only six of the 10 patients with laboratory tests suggesting diffuse hepatitis. In the other cases, the diagnosis 'hepatitis' was made based on clinical presentation, which included a 7-160-fold liver enzyme increase. Therefore, it is uncertain if these patients had underlying liver abscesses.

In a short review of diffuse hepatitis in listeriosis, Yu et al. described a case with clinical and laboratory findings of diffuse hepatitis, but postmortem examination revealed that the liver parenchyma was studded with firm yellowish nodules, which turned out to be miliary abscesses.[6] Ultrasound of the liver from our patient during the first week after admission showed an inhomogeneous liver with a large amount of strongly echogenic, small, round lesions, which were scattered throughout the parenchyma in a patchy pattern. Although they seemed to be metastases, as observed by CT scan, by ultrasound they appeared to be miliary abscesses because of the echo density and a sharply defined back wall. The noncancerous nature of these liver abnormalities was confirmed by the fact that after treatment with antibiotics, the liver tests had normalised, and all liver lesions had disappeared. We hypothesise that this might reflect a similar manifestation of miliary abscesses with concomitant necrosis with or without hepatitis, which could explain the observed liver enzyme elevation.

Fortunately, our patient had an excellent clinical outcome after three weeks of intravenous antibiotics, despite our inability to perform drainage of the abscesses. This is in contrast to previous literature. One reason could be

the relatively quick administration of antibiotics, which was started four days after the onset of symptoms. Also, amoxicillin-clavulanate, together with gentamycin, is the first choice of treatment in sepsis of unknown origin in our local guidelines, so our patient received adequate antibiotic therapy immediately after hospital presentation. In many Dutch hospitals, sepsis with unknown cause is initially treated with cephalosporins, which in this case, would have delayed effective treatment up to the moment the *Listeria* was diagnosed.

CONCLUSION

In this case report, we show that small liver abscesses caused by a *Listeria monocytogenes* infection can clinically mimic hepatitis, as suggested by the elevated liver enzymes. Therefore, the classification of possible liver involvement in listeriosis (a solitary abscess, multiple abscesses, or hepatitis) contains clinical conditions that are not mutually exclusive. In addition, it may be of value to add an additional classification category, for example, hepatitis mimicry due to miliary liver abscesses. It is important to keep in mind that multiple liver abscesses do not necessarily yield a poor prognosis, even in the absence of drainage. Further research is needed to identify the mechanisms of liver involvement in listeriosis and which factors affect prognosis.

DISCLOSURES

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

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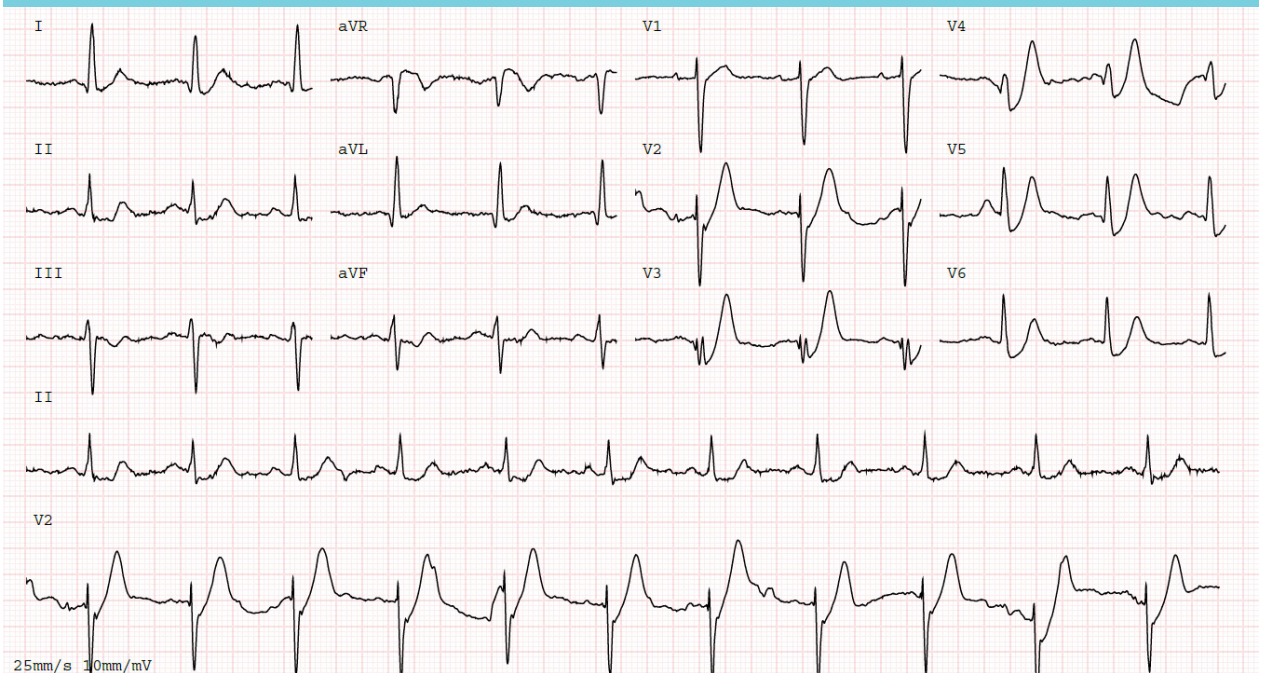
PHOTO QUIZ

A pivotal electrocardiographic presentation: reading between the lines

E.M. Vilela*, D. Caeiro, J. Primo, P. Braga

[1]Cardiology Department, Gaia Hospital Centre, Vila Nova de Gaia, Portugal.
*Corresponding author: eduardomvilela@gmail.com

Figure 1. *Admission electrocardiogram*



CASE REPORT

A 47-year-old male patient presented to the Emergency Department (ED) of our hospital due to intense and oppressive chest pain which had started about 30 minutes prior to admission. Complaints were associated with diaphoresis, and were not significantly altered by body position or breathing pattern. He had no other symptoms. The patient was a current smoker with no prior relevant medical history or medication.

On admission, he was symptomatic, haemodynamically and electrically stable, and afebrile, with no signs of pulmonary or peripheral congestion.

Given his presentation, an electrocardiogram (ECG) was performed upon arrival to the ED (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 298 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 297)

A PIVOTAL ELECTROCARDIOGRAPHIC PRESENTATION: READING BETWEEN THE LINES

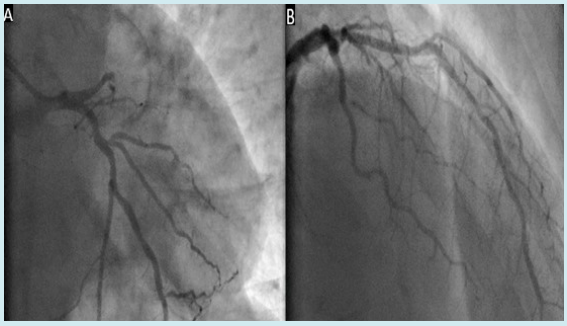
DIAGNOSIS

The patient's ECG shows sinus rhythm and ST-segment depression in leads V2 to V6 associated with tall, positive and symmetrical T waves, while there is also an approximately 1mm ST-segment elevation in lead aVR. This pattern (described as the De Winter pattern) in conjunction with the patient's presentation, is highly suggestive of an acute occlusion of the left anterior descending (LAD) artery.[1] Given these data, he was referred for emergency cardiac catheterization, which showed an occlusion of the proximal LAD artery and moderate disease of the right coronary artery (figure 2A).

The LAD artery lesion was treated with a drug-eluting stent (figure 2B) and the patient was subsequently asymptomatic. His remaining hospitalisation was uneventful, as he reached a peak high sensitivity cardiac troponin T (hs-cTnT) level of 10000 ng/l, and his echocardiogram showed a mildly reduced left ventricular systolic function.

This case highlights the paramount importance of recognizing an early and acute ECG pattern in a patient with typical chest pain. This pattern, first described by De Winter et al. in 2008, consists of ST-segment upsloping depression in the pre-cordial leads in association with tall, positive, and symmetrical T waves and in most cases, with slight ST-segment elevation in lead aVR.[1] This specific pattern was noted for being associated with an acute LAD occlusion, and whilst a recent systematic review has underlined its positive predictive value for an acute coronary artery occlusion,[2] its mechanism is still not fully ascertained.[1,3,4] Among the mechanistic explanations for this peculiar phenomenon, subendocardial ischaemia (at an hyperacute stage of the infarction, before transmural ischaemia becomes predominant) with ensuing subendocardial action potentials has presented an attractive hypothesis.[3,4,5] In the absence of significant collateral circulation (as in this case), downregulation of myocardial metabolism presents an important mechanistic pathway.[5] Interestingly, while this patient's ECG already showed the classical De Winter pattern, his hs-cTnT level at admission was only 8 ng/l (within the normal range), thus attesting to the acute nature of his presentation.

Figure 2. *Angiogram showing a significant stenosis in the proximal portion of the left anterior descending artery (A) and findings after successful implantation of a drug-eluting stent in the lesion (B)*



Additionally, albeit showing prominent T waves (one of the hallmarks of this pattern), his potassium levels were within the normal range.

In conclusion, the knowledge of the De Winter pattern is pivotal to those working with acute chest pain patients. Its identification is of interest, in order to allow for an expedite differential diagnosis among those who present with acute chest pain.

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PHOTO QUIZ

Periorbital oedema and muscle weakness

M.A. Lebbink, W.M. van der Deure*

Department of Internal Medicine, Groene Hart Hospital, Gouda, the Netherlands'.
*Corresponding author: wendy.van.der.deure@ghz.nl

Figure 1. *Periorbital erythema with oedema*

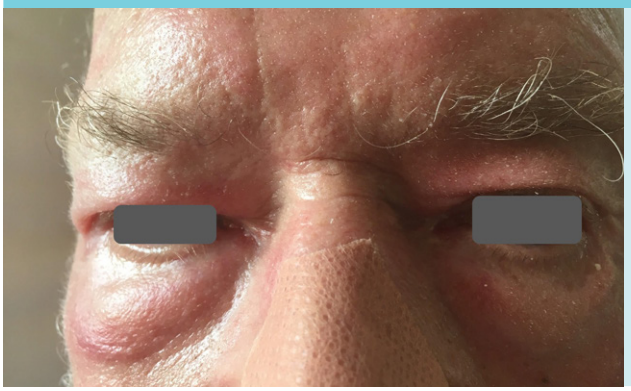
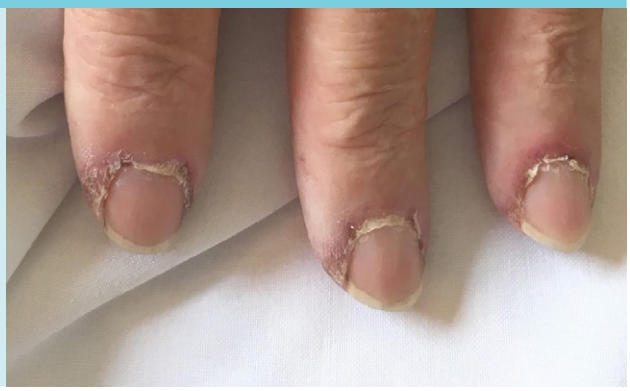


Figure 2. *Cuticles*



CASE REPORT

A 75-year-old man presented with a four-day history of periorbital erythema with oedema (figure 1) and ragged cuticles with periungual erythema (figure 2). Additionally, he developed progressive symmetric muscle weakness in the upper limbs and head-neck area, including difficulty swallowing. He had no fever. Laboratory testing revealed an elevated C-reactive protein of 39 mg/ml (normal value < 10 mg/ml), an elevated creatinine kinase of 3978 IU/l (normal value < 171 IU/l), and a lactate dehydrogenase of 511 IU/l (normal value < 248 IU/l).

WHAT IS YOUR DIAGNOSIS?

See page 300 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 299)

PERIORBITAL OEDEMA AND MUSCLE WEAKNESS

DIAGNOSIS

Based on his symptoms we suspected dermatomyositis. Diagnosis was based on skin and muscle signs and laboratory results, using Bohan and Peter's criteria (table 1).[1] Muscle weakness is the most common feature, and distribution is characteristically symmetric and proximal. The periorbital erythema with oedema is called a heliotrope rash and it is one of the hallmark features of dermatomyositis. Another hallmark feature, absent in our patient, is Gottron's sign, which refers to erythematous lesions over the hand joints. Periungual abnormalities are characteristic, although not specific, for dermatomyositis as well. Organ involvement is possible, although in our patient, a general work-up (e.g., kidney function test, urine sediment, chest X-ray) showed no signs of organ involvement.

First choice treatment for dermatomyositis is prednisone, however despite this, swallowing difficulties persisted in our patient. High-dose methylprednisolone was given and a duodenal tube for tube feeding was placed. During endoscopy, a mucosal swelling of the distal oesophagus was seen and biopsy revealed an adenocarcinoma.

The diagnosis was specified to cancer-associated-dermatomyositis. Additionally, laboratory testing revealed a positive anti-TIF1-γ-antibody, which has a strong correlation with cancer-associated dermatomyositis.[2] In dermatomyositis, the prevalence of malignant disease is 14.8% and the relative risk for an underlying malignancy is 4.66.[3] These numbers justify further diagnostics to screen for a malignancy in every patient diagnosed with dermatomyositis regardless of the presence or absence of specific autoantibodies associated with cancer.

Table 1. *Bohan and Peter's criteria*[1]

The diagnosis of dermatomyositis is considered definite, probable, and possible when skin rash is associated with 3, 2 or 1 muscular criteria, respectively*:

1. Symmetric proximal muscle weakness determined by physical examination
2. Elevation of serum skeletal muscle enzymes, including creatine kinase, aldolase, serum glutamate oxaloacetate and pyruvate transaminases, lactate dehydrogenase
3. The electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges
4. Muscle biopsy abnormalities of degeneration, regeneration, necrosis, phagocytosis, and an interstitial mononuclear infiltrate
5. Typical skin rash of dermatomyositis, including a heliotrope rash and Gottron's sign/papules

* Exclusion criteria: central or peripheral neurologic diseases, muscular dystrophies, granulomatous and infectious myositis, metabolic and endocrine myopathies, and myasthenia gravis.

Despite therapy, our patient rapidly deteriorated. He chose to stop treatment and passed away two days later.

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LETTER

A case of Syndrome of Irreversible Lithium Effectuated Neurotoxicity (SILENT)

N. Vallianou*, F. Konstantinou, V. Gennimata, P. Micha, E. Geladari, D. Kounatidis

*Corresponding author: natalia.vallianou@hotmail.com

Dear Sir,

Herein, we describe a male patient with the Syndrome of Irreversible Lithium Effectuated Neurotoxicity (SILENT), in whom some neurological deficits persisted despite removal of the drug.

A 74-year-old male patient was admitted to the hospital due to dysarthria, agitation, and confusion, which had started five days earlier. His past medical history was remarkable, including bipolar disorder, treated for 37 years with lithium, 900 mg daily; ischaemic heart disease, for which he had been taking imbesartan/hydrochlorotheiazide 300/12 mg daily, betaxolol 10 mg, triflusal 600 mg, ezetimibe/simvastatin 10/40 mg; and hypothyroidism, treated with thyroxin 50 μg daily. On clinical examination, the patient was agitated with sluggishness, coarse tremors, and myoclonus. Eleven years ago, he was admitted to the hospital with the same symptoms and toxic levels of lithium, so lithium intoxication was again suspected. Serum levels of lithium were determined and found elevated (2.03 mEq/l). Notably, the patient did not regularly measure his serum lithium levels. Lithium was immediately discontinued and vigorous hydration introduced, which resulted in subsequent normalisation of serum lithium levels two days later. However, the patient still had ataxia and memory deficits, and nystagmus was still present, together with extra-pyramidal signs. The diagnosis of SILENT was made, after the performance of two computed tomography scans of the brain, since memory deficits and extrapyramidal signs were present for a month after lithium withdrawal; scans were negative for any stroke. Notably, agitation and confusion had passed, after normalisation of serum lithium levels. The patient was discharged with the advice to stop lithium and to take quetiapine 100 mg under the strict supervision of a psychiatrist.

Lithium has a narrow therapeutic index. The therapeutic values range from 0.8 to 1.2 mEq/l. Thus, many patients on chronic lithium therapy experience at least one episode of toxicity during their lifetime.[1] The diagnosis of chronic lithium toxicity is typically made on clinical grounds and confirmed by obtaining serum lithium levels. Mild toxicity usually does not occur until serum lithium levels reache 1.5 mEq/l. Levels ≥ 2.5 mEq/l are considered a medical emergency, even in patients who appear relatively asymptomatic. Drug concentrations correlate more closely with clinical signs in patients with chronic toxicity. Clinical presentation generally involves a patient on chronic lithium therapy who, due to concurrent illness, does not drink enough free water, leading to gradual dehydration and reduced renal excretion of lithium. The initial symptoms and signs of chronic toxicity are often neurological.[1,2]

Medications that cause dehydration or renal impairment can also precipitate lithium toxicity. Examples include diuretics, angiotensin converting enzyme (ACE) inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, our patient had been on diuretics (hydrochlorothiazide), angiotensin II receptor blockers (imbesartan), and had a serum creatinine level of 1.8 mg/dl.

Indications for treatment of lithium poisoning with haemodialysis remain controversial. However, it is generally suggested that haemodialysis should be initiated in the following situations: 1) serum lithium concentration is greater than 5 mEq/l; 2) serum lithium concentration is greater than 4 mEq/l in patients with serum creatinine levels > 2.0 mg/dl); and 3) in the presence of decreased level of consciousness, seizure, or life-threatening complications, irrespective of serum lithium concentrations.[2,3]

In some cases, neurologic complications persist despite lithium removal by haemodialysis. SILENT consists of prolonged neurologic and neuropsychiatric symptoms following lithium toxicity. In typical cases, neurologic toxicity develops along with an elevated lithium concentration, but symptoms persist despite successful removal of the drug. Cerebellar dysfunction, extrapyramidal symptoms, brainstem dysfunction, and dementia can develop as part of SILENT.[3]

SILENT can continue for months and in rare cases, may persist for years. Clinicians should keep this in mind, as it is highly avoidable with regularly monitoring of serum lithium and serum creatinine levels, and with enough regular hydration; permanent discontinuation of lithium is mandatory in cases of SILENT. It is noteworthy that lithium is a very efficient drug, which needs close monitoring due to its narrow therapeutic index.

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LETTER

Treatment of flecainide intoxication with a lipid emulsion

J-T. Sohn

Department of Anesthesiology and Pain Medicine, Gyeongsang National University College of Medicine, Gyeongsang National University Hospital, Jinju-si, Gyeongsangnam-do 52727, Republic of Korea; Institute of Health Sciences, Gyeongsang National University, Jinju-si 52727, Republic of Korea.
Corresponding author: jtsohn@gnu.ac.kr

Dear Editor,

I read the article titled 'Renal failure, shock, and loss of pacemaker capture: A case of flecainide intoxication' recently published in *The Netherlands Journal of Medicine*.[1] Lipid emulsions have been widely used to treat systemic toxicity caused by local anaesthetics or other drugs with high lipid solubility.[2] Flecainide, an antiarrhythmic drug with a high lipid solubility (Log [octanol/water partition coefficient]: [3.78]) and cardiac sodium channel blocking activity similar to the local anaesthetic bupivacaine (Log [octanol/water partition coefficient]: 3.41), is used for the treatment of atrial fibrillation and supraventricular tachycardia.[3] Heldens et al. suggest lipid sink as an underlying mechanism for lipid emulsion-induced recovery from cardiogenic shock due to flecainide intoxication.[1] However, other possible mechanisms should also be considered. First, scavenging effect is another recently widely accepted mechanism, in which the lipid phase of a lipid emulsion absorbs lipid-soluble drugs such as bupivacaine from vital organs such as the heart.[2] These highly lipid-soluble drugs are then transported into adipose tissue and muscle for storage and to the liver for detoxification.[2] Second, Intralipid® attenuates the blockade of cardiac sodium channels induced by bupivacaine.[4] This may result in lipid emulsion-mediated reversal of sodium channel blockade by a toxic dose of flecainide and may contribute to recovery from flecainide intoxication. Third, flecainide has a negative inotropic effect, whereas lipid emulsion itself produces a positive inotropic effect.[3,5] Thus, I believe that lipid emulsion treatment described in this case may be effective against flecainide intoxication-induced cardiogenic shock refractory to standard treatment.

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