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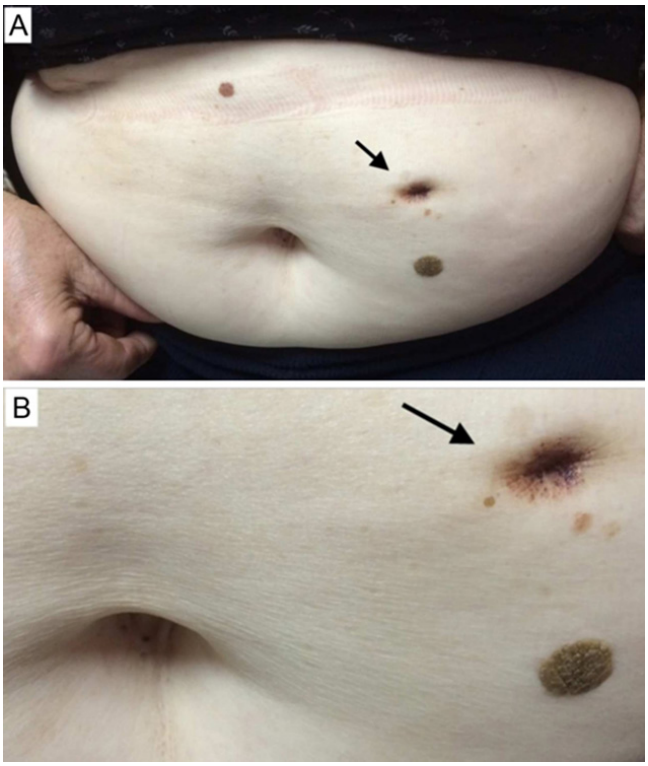

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Contents

EDITORIAL

Hypernatraemia: balancing is challenging

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As internists we like to think of ourselves as physicians with knowledge of disturbances of the milieu intérieur. Indeed, other specialities often call us for help when they are confronted with fluid and electrolyte disorders. The unrivalled number one of your electrolyte consults will undoubtedly be hyponatraemia. For example, hyponatraemia may arise in the postoperative period due to the combination of inappropriate vasopressin release and hypotonic intravenous fluids.[1] In fact, one of the first reports on acute hyponatraemia was in women undergoing elective surgery in whom the combination of postoperative vasopressin release and hypotonic fluids led to tragic neurological outcomes.[2] It is quite striking to see that the physicians at that time did not link the neurological symptoms to acute hyponatraemia. Instead of immediately infusing hypertonic saline, they pursued additional diagnostic tests such as lumbar punctures, CT and MRI scans.[2] These iatrogenic catastrophes have served as caveat that even simple infusion fluids may turn into deadly weapons when applied inappropriately. Of note, even isotonic intravenous fluids can cause hyponatraemia, for example in the syndrome of inappropriate antidiuretic hormone secretion, although this is less common.[3] Fortunately, based on cautionary tales like these, hypotonic intravenous fluids have largely been banned as maintenance fluids in adult medicine.[4] Surprisingly, however, this has not been the case in paediatrics, where caloric intake rather than tonicity has traditionally dictated the composition of maintenance fluids.[5] Maintenance intravenous fluids in sick children were therefore largely composed of glucose in half-normal saline (i.e., 5% dextrose in 0.45% NaCl). This type of intravenous fluids is hypotonic to begin with, but will become even more hypotonic when glucose is metabolised to carbon dioxide and water.[6] These physiology-based suspicions were recently confirmed by solid evidence from a randomised and blinded clinical trial.[7] Almost 700 acutely ill children who required maintenance intravenous fluids longer than six hours were randomised to receive half-normal saline or Plasma-lyte. Plasma-lyte is one of the new and commercially available balanced fluids with a sodium chloride concentration similar to plasma and the presence of buffers.[8] Hyponatraemia and epileptic seizures were significantly more common in the hypotonic arm of the trial, although the latter outcome was only borderline significant.[7] A recent review on intravenous maintenance fluids in the *New England Journal of Medicine* also focused on indications for maintenance intravenous fluids while preventing hyponatraemia.[9] According to the algorithm presented in this review, Americans, unlike Europeans, still favour glucose in their maintenance fluids, but do so in 0.9% NaCl to prevent hypotonicity. We believe that the addition of glucose to intravenous fluids will only increase the risk of hyperglycaemia without offering substantial nutritional support, although large studies are lacking.[10] Perhaps Americans prefer their intravenous fluids to resemble high-sugar soda beverages?

In contrast to hyponatraemia, hypernatraemia is less common. We expect that most of you will regard hypernatraemia as a simple clinical problem: uncompensated water loss. Treatment: just add water.[11] Indeed, we are all familiar with nursing home residents who are admitted with a serum sodium of 170 mmol/l because fever secondary to a urinary tract infection has made them somnolent and even less capable to express thirst or reach the tap. However, in the intensive care, up to half of patients actually have a positive fluid balance during the development of hypernatraemia.[12] This implies that, in these patients, hypernatraemia must be due to a positive sodium rather than a negative water balance. How can this be? Most studies that addressed this question identified factors that impair the urinary concentrating mechanisms, including acute kidney injury, loop diuretics, mannitol, hyperglycaemia, hypercalcaemia, or hypokalaemia.[13] If the excretion of hypotonic urine is subsequently matched with isotonic intravenous fluids, hypernatraemia with a positive fluid balance may ensue. The article on hypernatraemia in this issue suggests that hypernatraemia due to a positive sodium balance is also occurring on our internal

medicine wards.[14] Felizardo Lopes et al. carefully analysed the characteristics of hypernatraemia (defined as serum sodium ≥ 150 mmol/l) in a 36-bed internal medicine ward. In a 28-month observation period with close to 2000 admissions, they observed 49 patients with hypernatraemia (median serum sodium 152 mmol/l, prevalence 2.6%). As expected, hypernatraemic patients were significantly older and more often bedridden and dependent on the nurses for food and fluids. Remarkably, the patients with hypernatraemia more often had heart failure and liver cirrhosis, conditions that are normally accompanied by hyponatraemia.[15] Hypernatraemia was also associated with a much higher mortality rate (43 vs. 2%), which has been a consistent finding in previous studies,[13,16,17] but may be an epiphenomenon. However, the most striking observation in the study by Felizardo Lopes et al. was that only 39% of patients were admitted with hypernatraemia, whereas 61% developed hypernatraemia during hospitalisation. Of these patients, one third did so with a positive fluid balance. These data are comparable to the intensive care data and suggest that we as internists fail to maintain water and salt balance. The authors attribute these observations to inadequate use of intravenous fluids, which in France is managed by nurses. Recently a Dutch study found that even the use of normal saline to dissolve drugs or keep indwelling venous catheters open, contributes to hypernatraemia.[18] We believe it is the collective responsibility of both nurses and physicians to manage the patients' fluid and electrolyte balance. We argue that intravenous fluids should be regarded as drugs and therefore deserve the same precautions in prescribing.[19] This should not be limited to physicians in internal medicine but to all physicians taking care of hospitalised patients. Considering the data on iatrogenic hyponatraemia and hypernatraemia caused by intravenous fluids, the distilled message of this editorial may even be more simple: stop intravenous fluids as soon as possible!

DISCLOSURES

None.

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ORIGINAL ARTICLE

Prevalence, risk factors and prognosis of hypernatraemia during hospitalisation in internal medicine

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ABSTRACT

Introduction: Hypernatraemia in hospitalised patients is less common and less studied than hyponatraemia, although it also seems to be associated with a poor prognosis. The present study evaluates its prevalence, risk factors and prognosis in an internal medicine department.
Methods: Full hospital stays over 28 months in a 36-bed internal medicine department were analysed retrospectively. Patients with at least one plasma sodium ≥ 150 mmol/l were compared first with all other patients and then individually with sex- and age-matched normonatraemic controls.
Results: Plasma sodium ≥ 150 mmol/l was observed during 49/1945 hospitalisations (2.6%); it was acquired during hospitalisation in 30 cases (61%). Hypernatraemic patients were significantly older with no gender difference. They were comparable with their matched normonatraemic controls regarding the Charlson comorbidity index, although individual comorbidities varied. They were bedridden in 45% vs 15% for controls (p = 0.001). Nearly one-third of hypernatraemic patients had an increased extracellular fluid volume. Hypernatraemia was associated with higher in-hospital mortality (43% vs 2%, p < 0.001) and longer hospitalisation (median 21 vs 10 days, p = 0.004).
Conclusion: Hypernatraemia is more likely to occur in older and dependent patients and is associated with poor prognosis. Unlike classical teaching, it is often associated with increased extracellular fluid volume, even outside intensive care units.

KEYWORDS

Hypernatraemia, water-electrolyte imbalance, hospitalisation, prevalence, risk factors, prognosis

INTRODUCTION

Body water imbalance is common in hospitalised patients. Hyponatraemia reflects intracellular hyperhydration and occurs in up to one-third of patients; its causes and prognostic value are well established.[1,2] Hypernatraemia is less common and less studied. It is nonetheless recognised as an important clinical condition, indicating a hyperosmolar state caused by a decrease in total body water relative to the electrolyte content, leading to intracellular dehydration. During the 2003 heatwave in France, intracellular dehydration was more common than intracellular hyperhydration (10.4% vs 8.0%) in older hospitalised patients, and predicted higher in-hospital mortality (hazard ratio 1.3 for intracellular dehydration compared with normohydration vs 1.1 for intracellular hyperhydration compared with normohydration).[3] Although intracellular dehydration became less prevalent than intracellular hyperhydration (7.2% vs 9.5%) in the following years in the same settings, it was still associated with a higher risk of in-hospital death (hazard ratio 2.0 vs 1.3).
Hypernatraemia has been associated with up to 60% inpatient mortality,[4,5] but few studies describe risk factors, clinical profile and outcomes of patients with hypernatraemia in non-intensive care settings. The aim of the present study was therefore to evaluate the prevalence, risk factors and prognostic value of hypernatraemia in patients acutely hospitalised in an internal medicine department.

PATIENTS AND METHODS

Patients

Patients hospitalised in a 36-bed internal medicine department from January 2010 to May 2012 were retrospectively identified through the administrative

database. Those with at least one plasma sodium ≥ 150 mmol/l (indirect potentiometry, Architect ci8200, Abbott Diagnostics, Rungis, France) during their stay were identified through the laboratory results database. Each hypernatraemic patient was individually matched for sex and age (± 1 year) with one patient hospitalised during the same period in the same department but who always remained normonatraemic (plasma sodium between 135 and 145 mmol/l).

Data collection and definitions

Data were collected, as appropriate, through the administrative and laboratory databases or chart review. Age, sex, chronic diseases, and functional ability were recorded for each patient. The Charlson index was used as a summary measure of comorbidities.[6] We also considered the following data at admission: body temperature > 38°C, presence of oedema, systolic blood pressure (SBP), heart rate (HR), shock index (defined as the HR:SBP ratio), ongoing diuretic treatment, and estimated glomerular filtration rate (eGFR) according to the CKD-EPI equation.[7] Main diagnosis, inpatient death and length of stay were recorded at the end of the stay.

Increased extracellular fluid volume was defined by the presence of oedema. Patients were defined as bedridden if they stayed in their bed to eat, to be washed and to pass stools. Patients were defined as autonomous for meals if they were able to ask for food and beverages and to eat and drink items within their reach without help.

Statistical analysis

The study period was determined by the possibility to retrieve and match biological and administrative data from hospital databases rather than by a formal sample size calculation. We first compared the sex and age of patients with at least one plasma sodium ≥ 150 mmol/l during their stay with all other patients. We then compared characteristics at presentation and outcomes of patients with at least one plasma sodium ≥ 150 mmol/l and matched controls who remained normonatraemic during their stay.

Descriptive statistics are reported as median [interquartile range] for continuous data and number (percentage) for categorical data. Differences were tested by the Mann-Whitney and the Fisher's exact test, respectively, for unpaired comparisons, and by the Wilcoxon signed-rank or McNemar test for paired comparisons. Interaction tests were carried out with conditional logistic regression to check for a subgroup effect (pre-existing vs acquired hypernatraemia) on length of stay and in-hospital mortality. Differences were considered statistically significant if $p < 0.05$. All statistical analyses were performed with Stata 9.2 (StataCorp, College Station, Texas).

RESULTS

Plasma sodium was ≥ 150 mmol/l at least once during 49 of 1945 stays (hypernatraemia, 2.6%) and remained between 135 and 145 mmol/l during 1237 of 1945 stays (normonatraemia, 64%). Hypernatraemia was present at admission in 19 (39%) patients and was acquired during hospitalisation in 30 (61%). Median plasma sodium was 152 mmol/l at diagnosis of hypernatraemia in both subgroups.

Overall, hypernatraemic patients were significantly older than normonatraemic patients, without gender difference (*table 1*). Hypernatraemic patients and age- and sex-matched controls were similar in terms of Charlson index and vital signs at admission (*table 1*). However, they differed in the prevalence of several comorbidities included in the Charlson index, most notably heart failure and history of myocardial infarction (*table 1*).

The shock index was higher and eGFR was lower in patients with hypernatraemia than in matched controls (*table 1*). Nearly one-third of hypernatraemic patients had increased extracellular fluid volume, ascertained by the presence of oedema (*table 2*). The underlying condition was heart failure in 36%, cirrhosis in 21% and hypoalbuminaemia of various mechanisms in 29%.

Main diagnoses were heterogeneous in both groups. The most frequent diagnoses were (i) acute respiratory events, mainly pneumonia and chronic obstructive pulmonary disease exacerbation (27% in hypernatraemic and 29% in normonatraemic patients, $p = 1.00$); (ii) acute neurological events, mainly delirium and stroke (33% in hypernatraemic and 14% in normonatraemic patients, $p = 0.05$).

Hypernatraemia was associated with much higher in-hospital mortality (43% vs 2%, $p < 0.001$) and length of stays that were twice as long (*table 1*). The interaction test revealed significant heterogeneity between pre-existent (at admission) or hospital-acquired hypernatraemia regarding the association with length of stay ($p = 0.03$) but not in-hospital mortality (*table 1*).

DISCUSSION

Summary of results

About 3% of patients in a general internal medicine ward have hypernatraemia at admission or develop it during hospitalisation. They are older than other patients. Compared with sex- and age-matched normonatraemic controls, they have a similar number of significant comorbidities but of a different nature and with different functional consequences. Namely, they are more likely to have heart disease, to be bedridden and to depend on help for water intake. Hypernatraemic patients also have higher

Table 1. *Comparison of hypernatraemic and normonatraemic patients*

	Hypernatraemic patients	Normonatraemic patients	p value
Overall comparison	**N = 49**	**N = 1237**	
Age, years	81 [72, 88]	61 [30, 78]	< 0.001
Females	39%	49%	0.15
Matched comparison	**N = 49**	**N = 49**	
Patients			
Age, years	81 [72, 88]	81 [72, 88]	-
Females	39%	39%	-
Charlson index	2 [2, 4]	2 [1, 4]	0.43
Chronic heart failure	39%	10%	0.001
History of myocardial infarction	31%	10%	0.03
Liver cirrhosis	10%	0%	0.06
History of stroke	27%	14%	0.21
Diabetes mellitus	29%	33%	0.81
Dementia	43%	33%	0.35
Diuretic treatment	27%	24%	1
Bedridden	45%	10%	< 0.001
Autonomy for meals	61%	88%	0.002
At admission			
Temperature > 38°C	24%	9%	0.08
Diarrhoea	4%	4%	1
Subcutaneous oedema	29%	15%	0.14
Systolic blood pressure, mmHg	127 [106, 149]	139 [122, 157]	0.11
Heart rate, /min	90 [79, 105]	79 [68, 95]	0.04
Shock index	0.71 [0.55, 0.93]	0.60 [0.48, 0.70]	0.02
Estimated GFR, m/min/1.73 m^2	55 [33, 81]	77 [61, 86]	0.004
At discharge			
Hospital deaths	43%	2%	< 0.001
Patient with hypernatraemia at admission	53%	5%	0.001
Patients with hospital-acquired hypernatraemia	37%	0%	0.003
Hospitalisation duration, days	21 [7, 29]	10 [5, 18]	0.004
Patient with hypernatraemia at admission	27 [17, 36]	9 [5, 15]	< 0.001
Patients with hospital-acquired hypernatraemia	8 [5, 16]	11 [5, 20]	0.55

Values are presented as median [interquartile range] for quantitative variables and percentage for categorical variables. Unmatched comparisons were performed with the Mann-Whitney and Fisher's exact test, respectively. Matched comparisons were performed with the Wilcoxon signed-rank and MacNemar test, respectively. GFR = glomerular filtration rate.

Table 2. *Comparison of hypernatraemic patients with or without increased extracellular fluid volume*

	With increased ECF volume (n = 14)	Without increased ECF volume (n = 35)	p value
Patients			
Age, years	78	80	0.81
Females	43%	37%	0.75
Charlson index	3 [2, 4]	2 [1, 4]	0.51
Chronic heart failure	36%	40%	1
History of myocardial infarction	29%	31%	1
Liver cirrhosis	21%	6%	0.13
History of stroke	29%	26%	1
Diabetes mellitus	21%	31%	0,73
Dementia	29%	49%	0.34
Diuretic treatment	21%	29%	0,73
Bedridden	43%	46%	1
Autonomy for meals	64%	60%	1
At admission			
Hypernatraemia at admission	29%	43%	0,52
Temperature > 38°C	29%	23%	0.72
Diarrhoea	7%	3%	0,49
Systolic blood pressure, mmHg	120 [106, 130]	134 [106, 161]	0.16
Heart rate, beats/min	88 [84, 100]	92 [75, 107]	0.97
Shock index	0.80 [0.73, 0.86]	0.62 [0.52, 0.94]	0.12
Estimated GFR, ml/min/1.73 m^2	43 [28, 70]	61 [33, 82]	0.23
At discharge			
Hospital deaths	43%	43%	1
Hospitalisation duration, days	21 [6, 36]	22 [8, 29]	0.89

Values are presented as median [interquartile range] for quantitative variables and percentage for categorical variables. Unmatched comparisons were performed with the Mann-Whitney and Fisher's exact test, respectively. ECF = extracellular fluid; GFR =glomerular filtration rate.

in-hospital mortality and longer hospital stays, especially when hypernatraemia is already present at admission.

Comparison with previous studies and interpretation

The frequency of hypernatraemia found in our study concurs with figures reported in previous studies, ranging from < 1% to > 3%.[5,8-10] This wide variability in the frequency of hypernatraemia might be related to differences in the threshold used to define hypernatraemia, in the timing of hypernatraemia (at admission and/or hospital-acquired) or in the study population. We defined hypernatraemia by at least one plasma sodium ≥ 150 mmol/l during hospitalisation, regardless of its timing but excluding patients with moderate hypernatraemia from 145 to 150 mmol/l. Moreover, we only included patients in the internal medicine department of our hospital. Only a few studies have focused on the same population. Most of the published papers relate to ICU or emergency room patients. One study performed in an internal medicine clinic showed an overall prevalence of 1.2%: 0.5% for hypernatraemia at admission and 0.7% for hospital-acquired hyponatraemia.[5]

We saw no gender difference between hypernatraemic and normonatraemic patients. This question has been controversial, as some studies found female gender to be a risk factor[11,12] but others did not.[13,14] On the other hand, our

study confirms that age is a risk factor for hypernatraemia. One study dedicated to this question showed age as a strong independent risk factor.[13] Thirst, a very important defence mechanism against hypernatraemia, is often disturbed in elderly patients. Moreover, elderly patients may have insufficient access to free water or difficulty to express thirst.[11] This is consistent with our finding that hypernatraemic patients were more often bedridden and dependent on help for drinking. A recent study, focused on these questions, showed that patients admitted to hospital from care homes, who were more dependent or needed assistance for drinking, are frequently dehydrated and hypernatraemic at admission, and that these disorders are associated with higher in-hospital mortality.[15]

Unexpectedly, we found no significant difference in the Charlson comorbidity index between hypernatraemic and normonatraemic patients. However, a single summary score can be associated with many combinations of different comorbidities, and with different severity and functional impairment for each one. Myocardial infarction and chronic heart failure were the most frequent comorbidities found in the hypernatraemic group of our study. An association between hypernatraemia and a poorer prognosis in heart failure, independent of left ventricular ejection fraction, has been previously reported.[16] Febrile illnesses, uncontrolled diabetes and gastrointestinal losses as diarrhoea were found to be risk factors for hypernatraemia in different studies,[2,5,17-19] but we did not observe those associations in our work. Moreover, hypernatraemia is often associated with diuretic treatment, especially loop diuretics,[2,5,16-20] but this was also not the case in our study.

A high shock index and low glomerular filtration rate are consistent with a lower effective arterial blood volume (true or effective hypovolaemia) in patients with hypernatraemia. According to textbook teaching, hypernatraemia is usually due to net water loss and associated with extracellular fluid volume depletion and true hypovolaemia.[21,22] However, nearly one-third of the hypernatraemic patients in our study had oedema, indicating increased extracellular fluid volume. Still, according to textbook teaching, the few cases of hypernatraemia with increased extracellular fluid volume are due to excess intake of hyperosmolar fluids.[22] This may well be the case in ICU settings, where hypernatraemia with increased extracellular fluid has already been documented,[23,24] but not in our patients, who had classical causes of oedema such as heart failure, cirrhosis or hypoalbuminaemia. Impaired urinary concentrating mechanisms and reduced or hypertonic fluid intake compared with urine osmolarity are nonetheless necessary to generate hypernatraemia.[25] Our hypernatraemic patients with a chronically increased extracellular fluid volume had an acute condition that led to decreased water intake or increased hypotonic losses leading to hypernatraemia before normalisation of their extracellular fluid volume. A more frequent use of loop diuretics may contribute to inappropriate free water clearance in patients with increased extracellular fluid volume, although this was not apparent in our study.

The association of hypernatraemia with higher mortality has been previously reported in other populations: surgical patients,[26,27] ICU patients,[14,28-30] and heart failure patients.[16] Mortality has been more frequently associated with hospital-acquired hypernatraemia despite the fact that these patients had a lower peak plasma sodium concentration than those who were hypernatraemic at admission.[5,8-10,31] Acquired hypernatraemia in these patients may indicate less conscientious overall care, which could contribute to poorer outcomes.

However, it is important to stress that most previous studies were performed over 15 years ago and that the epidemiology and management of hypernatraemia has changed over time. Hypernatraemia is associated with serious underlying diseases, making it difficult to clarify the impact of hypernatraemia itself on the adverse outcome, especially if we consider that many hypernatraemic patients, whether at admission or acquired in hospital, were again normonatraemic before they died.[5]

Limits and strengths

Our study is limited by its retrospective and monocentric design and the small population analysed. Retrospectively collecting the clinical data of all normonatraemic patients was beyond our resources. However, matching is a powerful and hypothesis-free means to control for important confounding factors, such as age in our case. The comparison of hypernatraemic patients with or without increased extracellular fluid volume especially lacks power and we may have been unable to identify true differences between these subgroups.

Although the Charlson comorbidity index is validated and commonly used, this aggregated score masks different levels of severity for each disease and different patterns of association between them. Several substances and procedures that might influence serum electrolytes such as parenteral fluids and tube feeding were not considered. Parenteral fluids are likely to play a role in preventing hospital-acquired hypernatraemia, but we could not retrospectively retrace the data on administrated fluids, especially those used as a vehicle for parenteral medications. This study, like many others, cannot separate the contribution of hypernatraemia itself to mortality from that of the underlying frailty and acute condition.[30] The present results can therefore not predict the impact of hypernatraemia correction on outcomes.

Nevertheless, our study has several strengths. Most published evidence on hypernatraemia in hospitals is

over 10 years old and relates to intensive care units. Patients and management in our study are representative of contemporary in-patient recruitment and of current practices in a general internal medicine department. The matched design allows to control for age, the most important risk factor of hypernatraemia, and to look for independent risk factors. Comorbidities, functional status and extracellular fluid volume were taken into account.

Perspectives

The present study confirmed that elderly and dependent people are at risk to develop hypernatraemia, a condition associated with a poor prognosis. These results underscore that healthcare professionals and other caregivers need to increase their awareness and pay close attention to preventing water imbalance in home-cared and hospitalised elderly patients.[12,19] The retrospective review of our patient records showed that administrated parenteral fluids are not appropriately traced, especially those used as a vehicle for parenteral medications, which is left to the nurses' choice (in France). In many patients, these fluids add up to a large volume with possible clinical consequences in patients with or at risk of water and/or sodium imbalance. The rational choice of these fluids and their prescription by physicians is an area for practice improvement.

When it comes to the consequences for clinical research, an evaluation of interventions to lessen the risk of hypernatraemia in at-risk patients may contribute to identifying the best preventive strategies. Moreover, as referred to before, the contribution of hypernatraemia itself to mortality cannot be separated from that of the underlying frailty and acute condition. The impact of hypernatraemia correction on prognosis needs to be assessed by interventional studies.

CONCLUSION

Hypernatraemia is more likely to occur in dependent patients, but with no more comorbidities than others. Unlike classical teaching, it is often associated with increased extracellular fluid volume even in non-ICU settings, due to heart failure, liver cirrhosis or hypoalbuminaemia of various causes. Hypernatraemia is a powerful risk factor for hospital death and longer hospitalisations, especially when it is present at admission.

DISCLOSURES

The authors have no conflict of interest to disclose.

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ORIGINAL ARTICLE

Trends in practice of blood glucose control in critically ill patients in the Netherlands

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ABSTRACT

Background. Publication of the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial in 2009 and several observational studies caused a change in the recommendations for blood glucose control in intensive care patients. We evaluated local trends in blood glucose control in intensive care units in the Netherlands before and after the publication of the NICE-SUGAR trial and the revised Surviving Sepsis Campaign (SSC) guidelines in 2012.

Methods. Survey focusing on the timing of changes in thresholds in local guidelines for blood glucose control and interrupted time-series analysis of patients admitted to seven intensive care units in the Netherlands from September 2008 through July 2014. Statistical process control was used to visualise and analyse trends in metrics for blood glucose control in association with the moment changes became effective.

Results. Overall, the mean blood glucose level increased and the median percentage of blood glucose levels within the normoglycaemic range and in the hypoglycaemic range decreased, while the relative proportion of hyperglycaemic measurements increased. Changes in metrics were notable after publication of the NICE-SUGAR trial and the SSC guidelines but more frequent after changes in local guidelines; some changes seemed to appear independent of changes in local guidelines.

Conclusion. Local guidelines for blood glucose practice have changed in intensive care units in the Netherlands since the publication of the NICE-SUGAR trial and the revised SSC guidelines. Trends in the metrics for blood glucose control suggest new, higher target ranges for blood glucose control.

KEYWORDS

Blood glucose control, guideline, hyperglycaemia, hypoglycaemia, intensive care unit, normoglycaemia

INTRODUCTION

For a long time stress-induced hyperglycaemia was seen as a protective response during critical illness,[1] which was thus largely left untreated. Three single-centre randomised controlled trials showed benefit of a strategy aiming for age-adjusted normoglycaemia with intravenous insulin.[2-4] Consequently, strict blood glucose control (tight glycaemic control) was implemented in many,[5,6] but not all intensive care units (ICUs),[7] worldwide. Lack of evidence for the benefit of tight glycaemic control in successive multicentre

randomised controlled trials[8-12] abated enthusiasm for this strategy. This includes the large Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial[13] which even suggested harm from tight glycaemic control. Also the finding that even mild hypoglycaemia is associated with a worse outcome of critically ill patients[14-16] changed the opinion about tight glycaemic control, as hypoglycaemia is a frequent side effect of this strategy.[2-4,8-13] Not surprisingly, major international guidelines for the management of critically ill patients changed their recommendations for blood glucose control.[17,18]

It is uncertain how and when ICUs in the Netherlands responded to the results from the NICE-SUGAR trial[13] and the recently changed recommendations regarding blood glucose management in the Surviving Sepsis Campaign (SSC) guidelines of 2012.[17] It is even more uncertain whether eventual changes in local guidelines for blood glucose control truly affected the practice of blood glucose management. Therefore, we studied ICUs in the Netherlands for changes in their guidelines for and practice of blood glucose management, from the year before publication of the NICE-SUGAR trial until the year after publication of the latest version of the SSC guidelines. We hypothesised that both publications resulted in new, higher target ranges for blood glucose control in ICUs in the Netherlands.

MATERIALS AND METHODS

We surveyed ICUs in the Netherlands for changes in their local guidelines for blood glucose management and retrospectively calculated frequently used metrics for blood glucose control from blood glucose datasets available at the National Intensive Care Evaluation registry.[19] The employees of the National Intensive Care Evaluation registry had neither a role in the design of the survey nor in the calculation of metrics for blood glucose control from the blood glucose datasets, but extracted the blood glucose data and summarised patient demographics to guarantee complete anonymity of the participating units. According to Dutch law there is neither a need for ethical approval nor for individual patient consent to collect and analyse data from registries like the National Intensive Care Evaluation registry if patient-identifying information is excluded (Medical Ethics Review Committee of the Academic Medical Center project number W15_175).

Settings and participants

All ICUs that provide blood glucose datasets for central registration in the National Intensive Care Evaluation registry were invited to participate in the survey. For the calculation of metrics for blood glucose control we included all blood glucose data from patients admitted to the participating units. We only included critically ill adult patients. We excluded ICUs that did not respond precisely and completely to the survey and those that did not submit complete blood glucose datasets for the whole time frame. The time frame of interest was from September 2008 to July 2014, which included the publication of the NICE-SUGAR trial and the SSC guidelines.

Survey

To ensure clarity and consistency, members of our multicentre research group (DD, RB, MJS) assessed the survey for face and content validity before the final version was compounded and sent to the National Intensive Care Evaluation registry. The units received the survey through the National Intensive Care Evaluation registry via email with a link to an online questionnaire in November 2011. A reminder was sent within one month if there was no response. The survey was repeated once for the selected ICUs in May 2014, again through the registry via email, also with a reminder within one month. The survey was repeated to also include the data available after the publication of SSC guidelines.

The survey had two simple questions focusing on changes in the targeted blood glucose levels in the guideline for blood glucose management (*see Appendix*):

- Whether there had been a change in the local guideline regarding the blood glucose levels to target and if so, when this or these changes became effective, and
- The exact values of the blood glucose levels to target (i.e. the upper and lower limit of the blood glucose level), before and after any change.

Metrics for blood glucose control

A selection of units in the Netherlands submitted blood glucose datasets to the National Intensive Care Evaluation registry following strict and uniform definitions to ensure high quality of data.[20] These blood glucose datasets contained all blood glucose data generated by point-of-care devices at the bedside, or by central laboratory devices when samples are analysed centrally, and can be the level in arterial, venous, or capillary blood. The National Intensive Care Evaluation registry deleted extreme values (i.e., 0 mg/dl and > 1802 mg/dl; to convert mmol/l, multiply by 0.0555) and duplicates (41 extreme values and 7343 duplicates [0.5% of the blood glucose data]). If the data for a certain unit contained more than 5% of extreme values, that unit was deselected from participation.

We calculated the following frequently used metrics for blood glucose control[21]:

- Mean blood glucose level – the mean blood glucose level per patient summarised as median with interquartile range for the population;

- Percentage of normoglycaemic measurements – number of measurements between 80-110 mg/dl and between 110-144 mg/dl divided by the total number of blood glucose measurements x 100; and,
- Percentage of hypoglycaemic, severe hypoglycaemic, hyperglycaemic, and severe hyperglycaemic measurements – number of measurements < 80 mg/dl, < 40 mg/dl > 144 mg/dl and > 180 mg/dl, divided by the total number of blood glucose measurements x 100.

Analysis

Responses to the survey were collected through and anonymised by the National Intensive Care Evaluation registry, where the blood glucose datasets and the survey responses were labelled with meaningless codes allowing coupling of data without breaching the anonymity of the units.

Blood glucose metrics were calculated per individual ICU, and per admission category (i.e. surgical vs non-surgical patients). The main exposure variables were the dates of publication of the NICE-SUGAR trial (in March 2009) and the SSC guidelines (in January 2013). We considered these two publications to likely change clinical practice, or to trigger changes in the local guidelines for blood glucose management. Secondary exposures were changes in the local guideline for blood glucose management, revealed by the survey. Blood glucose metrics were summarised per period of exposure.

Statistical and SPC analysis

Data were reported as means (SD) or medians [IQR] where appropriate. Demographic data were summarised for all ICUs together and per unit, with each ICU having a meaningless number only used for comparisons. Descriptive analyses were performed with R (version: 3.1.1; R Foundation for Statistical Computing, Vienna, Austria), with $p < 0.05$ representing significance.

We used statistical process control (SPC) analyses to graphically describe glucose measurements and identify changes in blood glucose control.[21-23] One of the SPC tools is the control chart. A control chart is a graph of data over time with three lines: the centreline (reflecting the mean) and an upper and lower limit (± 3 sigma from the mean). When the data points are, without any special pattern, within the control limits then the process is 'in control' and stable. With control charts a differentiation could be made between common cause and special cause variation. A common cause variation is an inherent and hence expected variation of the process. A special cause variation is a variation that is not expected and is caused by an external factor (e.g. changes in the local guideline for blood glucose management). We were interested in detecting sustainable changes over time, and specifically changes that show a shift in the mean of a process. We hence used the following common rule for detecting special cause variation: a 'run' of nine consecutive points (here each point reflects a complete 'month') on one side of the centreline. There are other rules for detecting other kinds of changes, such as isolated extreme points or local trends, but our chosen rule detects significant change in the mean over time, which was of interest to us. These nine consecutive points at one side of the centreline were used to recalculate the mean and control limits, which were extrapolated to subsequent months until a new significant change or until the end of the study period.[24] Control charts were generated per ICU and per admission category group (i.e. surgical vs non-surgical patients).

RESULTS

Demographics

From 1 January 2008 to 30 June 2014, 49 ICUs sent blood glucose datasets to the National Intensive Care Evaluation registry. After excluding 32 units that could not provide the registry with a precise and complete response to the first survey, and after excluding ten units that provided blood glucose datasets that were either incomplete, or contained too many duplicate, extreme, or missing values, the final study population consisted of 44,767 patients admitted to seven ICUs (*table 1*). For the total group of patients we found that they were predominantly male, and most patients were admitted after surgery. Patient characteristics did not change over time. The units were all mixed medical-surgical units, four with a teaching affiliation. Also, the unit-level characteristics did not change over time.

Changes in local guidelines for blood glucose management

One unit reported no change in the blood glucose target levels (unit 1). One unit reported a change to a lower upper blood glucose target after publication of the SCC guidelines (unit 2), and one unit reported changes to raise the lower blood glucose targets on two occasions, once after publication of the NICE-SUGAR trial, and once after publication of the SCC guidelines (unit 6), with no change in upper blood glucose targets. In the other units, both the upper and lower blood glucose targets were changed at different time points. A detailed description of changes per unit including their timing is provided in *table 2*.

Trends over time in metrics for blood glucose control

An interrupted time-series analysis, with the publication of the NICE-SUGAR trial and the SSC guidelines as exposures, showed that the mean blood glucose level increased from 132 [121-146] mg/dl before publication of the NICE-SUGAR trial to 143 [129-159] mg/dl after publication of the SCC guidelines (*figure 1, upper panel*).

Table 1. *ICU and patient characteristics*

	ICUs			
ICU characteristics	**N = 7**			
Number of beds, median [IQR]	9 [7–21]			
Hospital, no (%)				
– Academic	1 (14)			
– Non-academic	3 (43)			
– Non-academic non-training	3 (43)			
Percentage of admission type, median [IQR]				
– Elective surgery	41 [31–56]			
– Emergency surgery	15 [11–24]			
– Non-surgical	36 [32–42]			
	All patients	**Before publication of the NICE-SUGAR trial***	**From publication of NICE-SUGAR trial to publication of the SSC guidelines****	**After publication of the SSC guidelines*****
Patients characteristics	N = 44,353	N = 6506	N = 27,723	N = 10,124
Age – years, median [IQR]	66 [57–75]	66 [57–75]	66 [57–74]	66 [57–75]
Male gender	63%	64%	63%	64%
Admission diagnosis				
– Elective surgical	53%	51%	53%	52%
– Emergency surgery	12%	13%	13%	11%
– Non-surgical	35%	36%	34%	37%
APACHE IV scores, median [IQR]	52 [38–72]	58 [43-78]	51 [37-71]	39 [39-70]
Outcome				
– ICU LOS – days, median [IQR]	1.5 [0.9–3.7]	1.9 [0.9–4.0]	1.3 [0.9–3.6]	1.6 [0.9–3.7]
– Hospital LOS – days, median [IQR]	11 [6–20]	11 [7–23]	11 [7–20]	10 [6–19]
– ICU mortality	8.2%	8.9%	8.1%	7.9%
– Hospital mortality	12%	13%	12%	11%

ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; SSC = Surviving Sepsis Campaign. *January 2008 until end of March 2009; **April 2009 until end of January 2013, ***February 2013 until end of June 2014.

Furthermore, the relative proportions of hypoglycaemic and severe hypoglycaemic measurements decreased over time, while the relative proportion of hyperglycaemic and severe hyperglycaemic measurements increased. There were notable differences between ICUs: in some units no, or only modest changes were noted, while in other units large changes were seen in almost all metrics (*figure 1, upper panel*). In one unit the metrics moved in a direction other than expected based on the changes in the local guideline for blood glucose management (unit 6). An interrupted time-series analysis with changes in the local guideline as the exposures showed similar patterns (*figure 1, lower panel*); trends were not different for non-surgical and surgical patients (data not shown).

Date of change in local guideline for blood glucose management in relation to trends in metrics for blood glucose control

The SPC charts showed an increase in hyperglycaemic measurements and a decrease in hypoglycaemic measurements in almost all ICUs (figure 2). The charts showed special cause variation shortly after the publications of the NICE-SUGAR trial and the SSC guidelines in some of the units (i.e. unit 4 and unit 5), and

Table 2. *Overview of survey results*

Unit	Date of change	Blood glucose target (mg/dl)	
		Lower target	Upper target
1		90	144
2		90	144
	Nov 2013	90	141
3		72	126
	May 2013	90	180
4		72	126
	May 2009	90	162
	Dec 2012	108	162
5		80	110
	Jul 2009	72	144
	May 2011	108	144
6		72	144
	Jan 2010	90	144
	Jan 2011	108	144
7			<123
	Oct 2011	81	162
	Jan 2013	81	144

also close to the moment a change was made in the local guideline for blood glucose management (i.e. in unit 4 and unit 5). In some units, a change in the local guideline was not followed by a special cause variation (i.e. unit 6), and some cases of special cause variation appeared spontaneously (i.e. seemed not to be related in time to the publications or changes in local guidelines (e.g. unit 1)). The SPC charts of non-surgical and surgical patients showed similar trends in metrics for blood glucose control (data not shown).

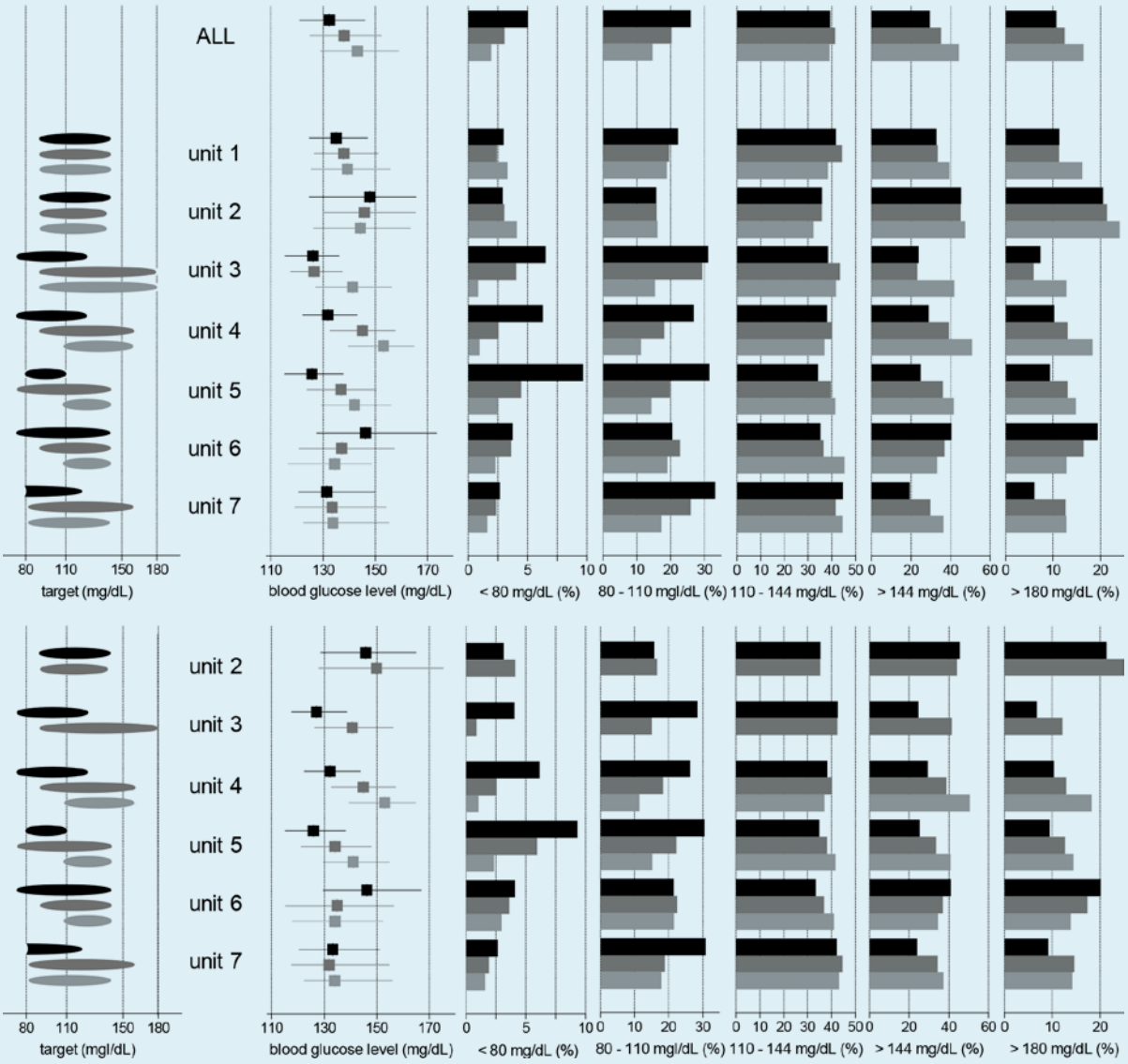
DISCUSSION

In this study, we found that six out of seven ICUs in the Netherlands changed their local guideline for blood glucose management after publications of the NICE-SUGAR trial in 2009,[13] and the SSC guidelines in 2012.[17] In five out of the six units that changed their guideline, the targeted upper and/or lower blood glucose levels were higher after these two publications, with notable differences between units. Changes in the local guidelines were associated with trends in metrics of blood glucose control: in general, the mean blood glucose levels modestly increased, and the relative proportions of hypoglycaemic and severe hypoglycaemic measurements decreased while the relative proportion of hyperglycaemic and severe hyperglycaemic measurements increased. There were differences between the units, but trends were comparable for surgical and non-surgical patients within units. To our knowledge, this is one of the first studies to investigate whether tight glycaemic control has been adopted, as recently suggested.[25] Our study provides useful insights into the way Dutch ICUs responded to new evidence, and how the practice of blood glucose control responds to changes in local guidelines. The findings of our study could also be important for those who plan intervention studies of blood glucose practice.

Studies reporting on trends in practice of blood glucose control in ICUs are scarce. In 2010, we ourselves found that tight glycaemic control was practised in nearly half of the ICUs in the Netherlands.[5] In New Zealand and Australia, however, only 10% of the units practised tight glycaemic control before publication of the NICE-SUGAR trial, and the practice of blood glucose control hardly changed after publication of that trial.[7] Of note, many ICUs in New Zealand and Australia were involved in the NICE-SUGAR trial. Recently, trends in practice of blood glucose control in 113 units in the USA were reported.[6] That analysis, covering the years 2001 to 2012 and thus the time frames between and after the publication of all major trials of tight glucose control, showed a slow adoption of tight glucose control after the initial trial, but little to no adaptation after the last trial. The results of the present analysis are, at least in part, in line with these previous investigations. Although the local guidelines changed with regard to the upper and lower targets, the changes in several metrics of blood glucose control were modest, suggesting that there is no complete adaptation of this strategy in the Netherlands.

Our study differs from the previous studies on trends in practice of blood glucose in several ways. First, in contrast to the two studies from New Zealand and Australia[7] and the USA[6] in which only the highest and lowest blood glucose levels in the first 24 hours after admission to the ICU were used, we used all blood glucose data per patient to calculate the reported metrics for blood glucose control, which we think is more accurate.[26] Second, we report the results per unit, which not only allows comparisons between units, but also the trends in blood glucose management after a change in local guidelines. Third, we collected data until July 2014 and were thus able to determine the effects of publication of the SSC guidelines on local guidelines and the practice of blood glucose control. And finally, we used SPC charts that allow a principled approach to detection of changes and a better interpretation of how changes in the local guidelines affected the practice of blood glucose control. All this allows caregivers a better insight into what affects

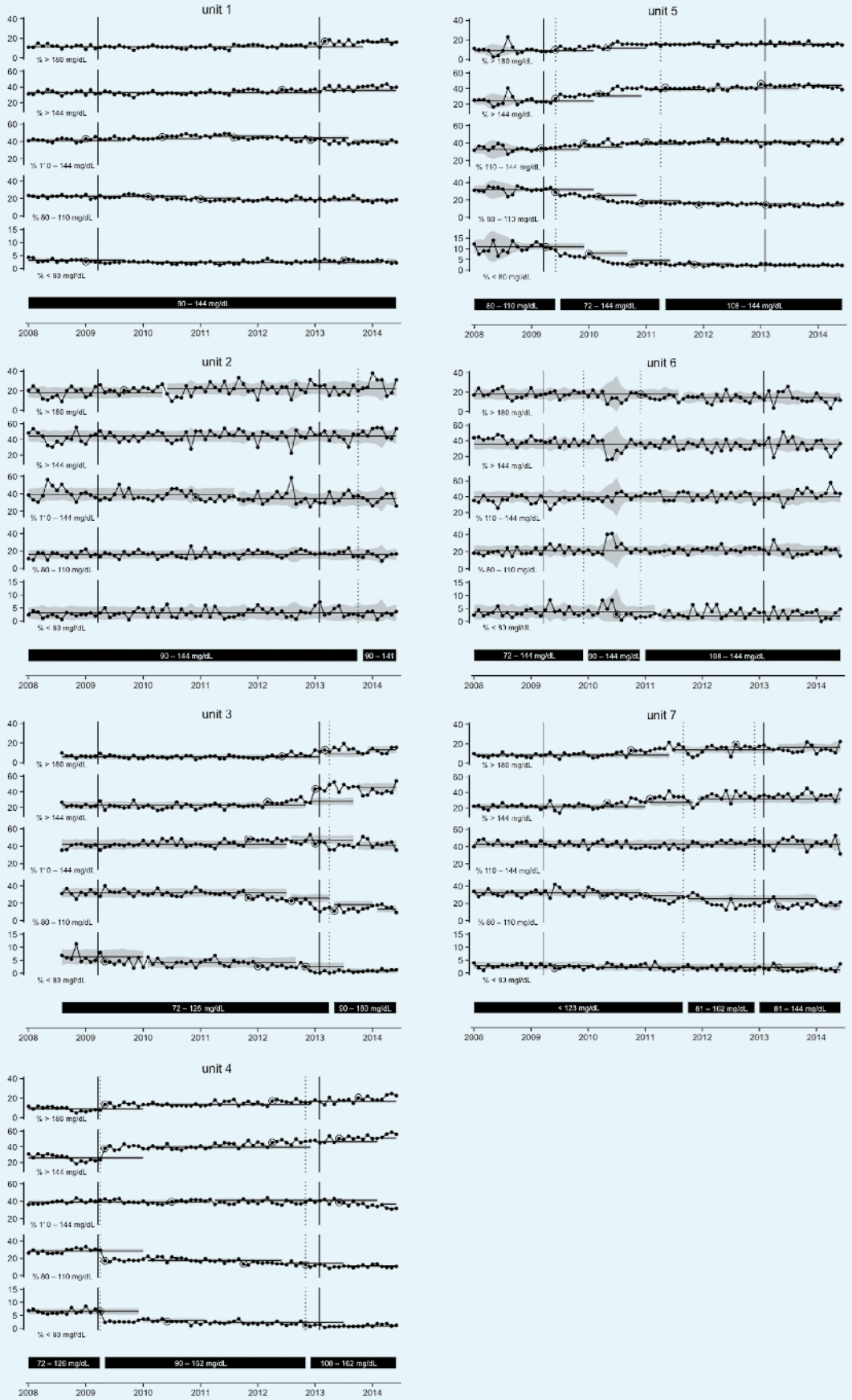
Figure 1. *The upper panel shows metrics for blood glucose summarised per fixed period for all ICUs together and per unit. The fixed periods are before publication of the NICE-SUGAR trial (in black), from publication of NICE-SUGAR trial to publication of the Surviving Sepsis Campaign guidelines (in dark grey) and after publication of the Surviving Sepsis Campaign guidelines (in light grey)*
The lower panel shows metrics for blood glucose control per individual unit summarised per local guideline for blood glucose control. When a ICU changed its guideline a new period started. Per individual unit, for blood glucose control before (in black) and after successive changes in the local guideline for blood glucose control (in dark and light grey). Unit 1 did not change its guideline and is therefore not displayed in the lower panel



the practice of blood glucose control, and when to check whether changes are truly effective.

One finding was that there were clear trends in metrics for blood glucose control that seemed independent of any change in the local guidelines for blood glucose; some trends even happened without a change in the guideline. This certainly means that practice of blood glucose control responds to other factors, such as other publications in the literature, or changes in practice not reported in the survey, e.g. changes in nursing or medical staff and measurement techniques, use of computer-assisted algorithms, et cetera. It is also important to notice that ICUs in the Netherlands remain relatively tight in their practice of blood glucose management. Indeed, at the end of our study the median blood glucose levels in units in the Netherlands were still

Figure 2. *SPC analysis per unit, solid lines represent the moment of publication of the NICE-SUGAR trial and the moment of publication of the latest version of the Surviving Sepsis Campaign guidelines, dotted lines represent a change in the local guideline for blood glucose levels. Targets of the blood glucose levels of the local guidelines are presented in the bars below*



Van Hooijdonk et al. Trends in practice of glucose control in the ICU.

lower than those reported in Australia and New Zealand[7] and the USA.[6]

While meta-analyses suggest that surgical patients could benefit more from tight glycaemic control than non-surgical patients,[18,27,28] our study shows that blood glucose control is not different between these subgroups of patients in the ICUs in the Netherlands. This is in line with the abovementioned study from Australia and New Zealand.[7] The literature also suggests that patients with a history of diabetes could benefit from blood glucose practice targeting higher blood glucose levels.[16,29,30] Unfortunately, we were not able to study data regarding the diabetic status of patients.

This study has several limitations. First, since we were interested in changes in the local guidelines and the association in time with trends in metrics of blood glucose control, we had to exclude many ICUs. This could have led to bias, as units that did not respond to the survey could have guidelines for blood glucose management that markedly differ from those that responded to the survey. Second, this is a retrospective study with data collected for quality enhancement purposes. Finally, we were not able to determine whether a blood glucose level came from an arterial or venous sample, and some measurements may have involved capillary blood, or which technique was used to measure the blood glucose level.

CONCLUSIONS

Local guidelines for blood glucose practice have changed in ICUs in the Netherlands since the publication of the NICE-SUGAR trial and the new SSC guidelines. Trends in the metrics for blood glucose control, however, suggest only modest adoption of tight glycaemic control.

DISCLOSURES

Roosmarijn T.M. van Hooijdonk reports consulting work for Medtronic Inc., GlySure Ltd and research support from Medtronic Inc and Optiscan Biomedical – all fees and financial supports were paid to the institution.

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The other authors do not report any relevant disclosures.

The NICE Foundation pays the Department of Medical Informatics to maintain, process and analyse data from the NICE registry. Ameen Abu-Hanna is head of the department of Medical Informatics. Nicolette F. de Keizer, Ferishta Bakhshi-Raiez, and Saeid Eslami are employees of the department of Medical Informatics and work on the NICE registry.

Dave A. Dongelmans, Rob J. Bosman, Ingrid van Dijk and Nicolette F. de Keizer are members of the board of the NICE Foundation.

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APPENDIX

Survey (translated from Dutch)

1. Do you have a guideline for blood glucose management in your unit?
   □ Yes → go to question 2
   □ No → go to question 4

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2. Has there been a change in the blood glucose targets of the guideline for blood glucose management after 2007?
   □ Yes → go to question 3
   □ No → go to questions 4

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3. You have indicated that the blood glucose targets in the guideline for blood glucose management changed after 2007. Please provide blood glucose targets before the first change, and the new targets with *any* new changes in the table below.

Date of change in the guideline for blood glucose management	Is this the exact date the change became effective?	Blood glucose targets	
		Lower target	Upper target
dd/mm/yyyy	Yes No	... mmol/l	... mmol/l
dd/mm/yyyy	Yes No	... mmol/l	... mmol/l
dd/mm/yyyy	Yes No	... mmol/l	... mmol/l
dd/mm/yyyy	Yes No	... mmol/l	... mmol/l
dd/mm/yyyy	Yes No	... mmol/l	... mmol/l
dd/mm/yyyy	Yes No	... mmol/l	... mmol/l

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4. You have indicated that the blood glucose targets in the guideline for blood glucose management did not change after 2007, please confirm:
   □ Yes, the blood glucose targets in the guideline for blood glucose control did not change.

Thank you for participating our survey.

ORIGINAL ARTICLE

Suspected leptospiral meningitis in adults: report of four cases and review of the literature

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ABSTRACT

Background: Leptospirosis is a widespread zoonotic disease characterised by headache and fever. These symptoms are often suggestive of meningitis, but only a proportion of patients have leptospiral meningitis.

Methods: We report episodes of leptospiral meningitis in patients admitted to a tertiary referral centre in the Netherlands, in whom lumbar puncture was performed, and conducted a literature search of adult cases of leptospiral meningitis to describe clinical characteristics and outcome.

Results: Between 2011 and 2014, 19 patients with leptospirosis were identified. Seven underwent a lumbar puncture for suspected meningitis (37%), of which six had been in contact with fresh water in a tropical area. Four patients with suspected meningitis (57%) had cerebrospinal fluid pleocytosis indicative of leptospiral meningitis and presented with headache, fever and neck stiffness. In a review of the literature we identified 366 patients with leptospiral meningitis with a median age of 33 years (range 17-77). Risk factors for leptospirosis were identified in 32 of 33 patients. Typical cerebrospinal fluid abnormalities consisted of a mildly elevated leukocyte count (median 206 leukocytes/mm^3, range 6-2072) with a lymphocytic predominance (median 95%). Outcome was generally favourable, with a mortality rate of 3% and neurological sequelae in 5% of the survivors.

Conclusion: Leptospirosis in the Netherlands has a low incidence. In the case of suspected meningitis and a history of visiting tropical areas or direct or indirect contact with animal urine, leptospiral meningitis should be considered. Cerebrospinal fluid examination is vital for the differential diagnosis of leptospirosis. Outcome is generally favourable in patients with leptospiral meningitis treated with antibiotics.

KEYWORDS

Leptospirosis, meningitis, tropical disease, zoonosis

INTRODUCTION

Leptospirosis (infection with *Leptospira* spp) is a widespread zoonotic disease. Although the majority of the case load is seen in tropical areas,[1,2] it also occurs in Europe with a reported incidence of 0.13 per 100,000 individuals.[3] Leptospirosis is caused by the transmission of a spirochete of the *Leptospira* genus through direct contact with infected animals or through indirect contact with a contaminated environment, e.g. fresh water.[4] A wide variety of mammalian hosts, both feral and domestic/semi-domestic, serve as infection reservoirs and can excrete *Leptospira* spp in the urine.[4]

Leptospira infection may cause a variety of clinical syndromes. The most severe form is Weil's disease, which has a high mortality and is characterised by high fever, bleeding, icterus and renal insufficiency.[2,5] Leptospiral infection may also present with neurological symptoms, such as meningitis, bilateral facial palsy or opsoclonus-myoclonus syndrome.[4,6-8] Many patients with leptospiral infection present with headache, fever and neck stiffness

and therefore bacterial, tuberculous or viral meningitis may often be suspected prior to the eventual diagnosis of leptospirosis.[9-11] Symptoms of meningitis due to leptospirosis occur with and without cerebrospinal fluid (CSF) abnormalities.[12]

In the Netherlands, approximately 30-40 cases of leptospirosis are reported per year.[11] We reviewed the cases of leptospirosis with suspected meningitis identified in a tertiary referral hospital in the Netherlands and performed a review of the literature on leptospiral meningitis.

MATERIALS AND METHODS

We identified all adult patients (≥ 16 years of age) with confirmed leptospirosis in the Netherlands between January 2011 and December 2014. Cases were defined as patients with a positive serology (microscopic agglutination test (MAT), enzyme-linked immunosorbent assay (ELISA)), positive polymerase chain reaction (PCR) and/or a positive culture for *Leptospira* species. These tests were performed by the World Health Organisation, Food and Agriculture Organisation of the United Nations, World Organisation for Animal Health, and the National Collaborating Centre for Reference and Research on Leptospirosis (NRL) at KIT Biomedical Research, the Royal Tropical Institute in the Netherlands. NRL confirms approximately 99% of the suspected cases of leptospirosis in the Netherlands, and thus could provide the authors with nationwide epidemiological data for this article.

From this dataset we selected patients with leptospirosis admitted at the Academic Medical Centre, Amsterdam, a tertiary referral hospital in the Netherlands, to study clinical characteristics, treatment and outcome. We analysed whether symptoms consistent with bacterial meningitis (neck stiffness, fever and headache) were associated with CSF abnormalities. All patients with abnormal CSF (defined as CSF white blood cell count > 5/mm^3, total protein > 0.6 g/l or CSF to blood glucose ratio < 0.6) were considered to have leptospiral meningitis.[13] We retrospectively collected clinical characteristics, data on ancillary investigations and outcome. The data were processed anonymously. Oral and written informed consent was obtained from all patients with leptospiral meningitis.

REVIEW OF THE LITERATURE

Subsequently, we performed a literature search for leptospiral meningitis on PubMed, using the search terms "leptospir* AND meningitis", and ""Neurologic Manifestations"[MeSH] AND leptospir*". We also searched for cohort studies and reviews about leptospirosis using the search term "leptospir*". The search was updated until 20 March 2015.

Articles reporting children or animals, duplicate articles and articles in which no specific data were given for leptospiral meningitis patients were excluded. Leptospiral meningeal involvement was defined as a combination of 1) fever with one of the following signs: neck stiffness, altered consciousness or other meningeal signs,[12] and 2) detection of *Leptospira* species in blood and/or CSF by PCR or culture, and/or detection of leptospiral antibodies by serology (MAT and/or ELISA). When CSF was abnormal (see Methods section), the diagnosis of meningitis was established. In an analysis of clinical data we systematically scored baseline and presenting characteristics, clinical course and outcome.

Differences between groups were calculated by means of Fisher's exact test. Articles with neither an abstract nor access to the full text were excluded. Studies written in English, German, French, Dutch, Spanish, Italian and Portuguese were included.

RESULTS

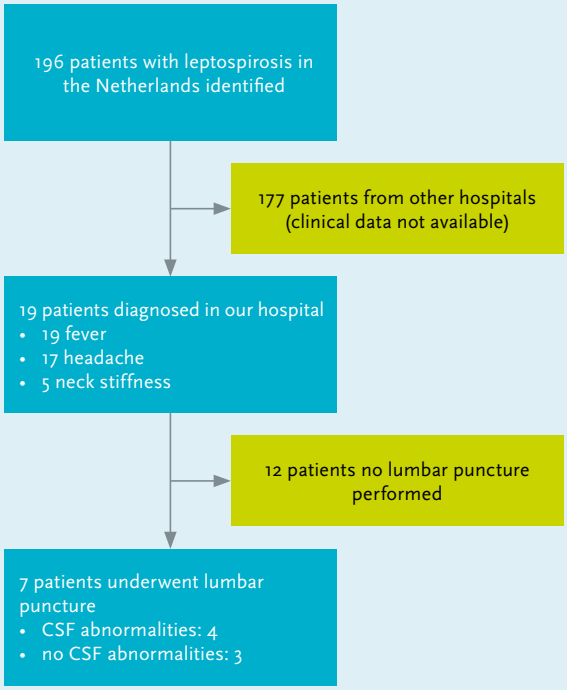
Between January 2011 and December 2014, 196 cases of leptospiral infection were identified at the NRL in the Netherlands, of which 104 contracted leptospirosis abroad (53%) and 92 contracted leptospirosis in the Netherlands (47%) (*figure 1*). The mean calculated annual incidence from 2011 to 2014 was 0.30 per 100,000 inhabitants.

Within this period we observed a threefold increased incidence in 2014 (0.57 per 100,000) compared with 2011-2013 (average 0.21 per 100,000). Furthermore, in 2014, leptospirosis was contracted in the Netherlands in 62% of the cases, compared with an average of 33% in 2011-2013.

In our hospital, 19 adult cases of leptospirosis (10%) were identified based on a positive serology and/or PCR and/or culture. All 19 patients presented with fever, 17 (89%) presented with headache and five (26%) with neck stiffness. The median age was 27 years (range 17-61 years) and 15 patients were male (79%). Eighteen patients contracted leptospirosis abroad (95%) and one patient contracted leptospirosis in the Netherlands (5%).

In seven patients (37%) there was a clinical suspicion of meningitis, for which a lumbar puncture was performed. Four patients with CSF abnormalities were diagnosed with leptospiral meningitis. Three patients had no CSF abnormalities (*figure 1*), of which one patient had not been abroad and had not been in contact with animals. The incidence of meningitis in leptospirosis in our hospital was 21% (4 out of 19 patients). The patients with leptospiral meningitis are described below.

Figure 1. *Flowchart of patients with leptospirosis in the Netherlands*



Case 1

A 27-year-old Dutch patient was admitted to the hospital in Laos with fever, myalgia, shivers and vomiting. He had been travelling through Vietnam, Laos, Cambodia and Thailand, where he had been swimming. He was treated with antibiotics but no source of infection was found. When he returned to the Netherlands a few days later, he presented with recurrent fever (temperature 38.5°C) and progressive headache. Physical examination showed conjunctivitis and neck stiffness. Laboratory examinations showed the following: creatinine 62 µmol/l, leukocytes 6.4 x 10^9/l, C-reactive protein (CRP) 3.6 mg/l, serum glutamic oxaloacetic transaminase (SGOT) 23 U/l, serum glutamic pyruvic transaminase (SGPT) 15 U/l, and bilirubin 5 µmol/l. Lumbar puncture showed turbid CSF with 734 leukocytes/mm^3 (75% polymorphonuclear leukocytes), protein level of 0.63 g/l, and CSF to blood glucose ratio of 0.45. The IgM ELISA for leptospirosis was positive. The patient was treated with 1 million IU penicillin intravenously four times a day for seven days. He was discharged in a good clinical condition without sequelae.

Case 2

A 45-year-old Dutch patient presented with fever, headache, nausea and diarrhoea. He had been travelling through Singapore, Thailand and Indonesia two weeks prior to admission, where he had suffered from gastroenteritis after he fell off a boat during rafting and ingested fresh water. Physical examination showed bilateral conjunctivitis but no other abnormalities. Laboratory examination showed the following: erythrocyte sedimentation rate (ESR) 101 mm/h, CRP 106 mg/l, leukocytes 10.8 x 10^9/l, creatinine 413 µmol/l, SGPT 36 U/l, and bilirubin 8 µmol/l. The *Leptospira* IgM lateral flow test was positive and patient was treated with oral amoxicillin and discharged. However, the next day, he presented again with aggravated headache. Neurological examination now showed neck stiffness, for which a lumbar puncture was performed. This showed turbid CSF containing 628 leukocytes/mm^3 (86% polymorphonuclear leukocytes), protein level of 0.92 g/l and a CSF to blood glucose ratio of 0.41. The IgM ELISA and MAT were both positive, the probable infecting serogroup was *Grippotyphosa*. The patient was treated with 12 million IU penicillin intravenously daily for three days followed by oral amoxicillin (750 mg three times daily) for one week. He was discharged in a good clinical condition without sequelae.

Case 3

A 20-year-old Dutch patient presented with headache, fever, nausea and diarrhoea. The symptoms appeared a week after returning from a holiday in Borneo, where he had swum in fresh water. Physical examination showed bilateral conjunctivitis and neck stiffness. Laboratory examination showed the following: CRP 45.7 mg/l, leukocytes 6.2 x 10^9/l, SGOT 354 U/l, SGPT 305 U/l, bilirubin < 2 µmol/l, and creatinine 236 µmol/l. Lumbar puncture showed turbid CSF containing 1200 leukocytes (predominantly lymphocytes, percentage not specified), protein level of 0.89 g/l and a CSF to blood glucose ratio of 0.52. The MAT and IgM ELISA for leptospirosis were positive and showed *Leptospira* serogroup Australis. The patient was treated with 12 million IU penicillin intravenously for four days followed by oral amoxicillin (750 mg three times daily) for five days. He was discharged in a good clinical condition without sequelae.

Case 4

A 22-year-old Dutch patient presented with fever, headache, cough and nausea. The symptoms appeared a week after returning from a backpack trip in Malaysia, Borneo and Thailand for two months. She had not swum in fresh water, but had slept in rice fields in Thailand. Physical examination showed a temperature of 40.5°C and neck stiffness. Laboratory examination showed the following: leukocytes 12.9 x 10^9/l, CRP 62.3 mg/l, creatinine 93 µmol/l, SGOT 58 U/l, SGPT 18 U/l, and bilirubin 8 µmol/l. Lumbar puncture showed clear CSF with 11 leukocytes/mm^3 (100% mononuclear cells), a protein level of 0.21 g/l

and a CSF to blood glucose ratio of 0.60. The MAT, IgM ELISA and PCR for leptospirosis were positive and showed *Leptospira* serogroup Mini. Patient was treated with 100 mg doxycycline twice daily for seven days. She was discharged in a good clinical condition without sequelae.

Review of the literature for leptospiral meningitis

A total of 41 relevant articles published between 1947 and 2014 were identified, describing 366 adults with leptospiral meningitis (*figure 2*).[9,12,14-52] The number of included patients per study varied between one and 162 patients. Studies were performed in Europe (25), Asia (9) and America (7) (*figure 2*).

The median age of the patients was 33 years (range 17-77 years) and 51 of 62 (82%, 95% CI 72-92%) were male (*table 1*). Two out of 26 (8%) patients were immunocompromised (95% CI 0-16%). A known aetiology was reported in 32 of 33 patients (97%, 95% CI 91-100%); seven had been in contact with fresh water (five swimming, one fishing, and one window cleaning in an endemic area), six worked with cattle, five had been in contact with dogs, five had been in contact with rats, four were farm workers, two lived in a rural area endemic for leptospirosis, one worked in sewers, one was a horse trainer and one was a hunter. In one patient, no aetiology was found. In an article describing 162 patients with leptospiral meningitis, no aetiology per patient was reported, but the patient group mainly consisted of farmers.[47]

Headache was reported in 65 of 69 patients (94%, 95% CI 88-100%). Fever was reported in 100 of 102 patients (98%, 95% CI 93-100%), neck stiffness in 77 of 83 (93%, 95% CI 87-99%) and altered consciousness in 8 of 54 patients (15%, 95% CI 5-25%). The classic triad of fever, altered consciousness and neck stiffness[53] was present in 5 of 39 patients (13%, 95% CI 3-23%).

The median CSF leukocyte count was 206 leukocytes/mm^3 (range 6-2072). All but one of the patients in whom the

Figure 2. *Flowchart review of the literature for leptospiral meningitis*

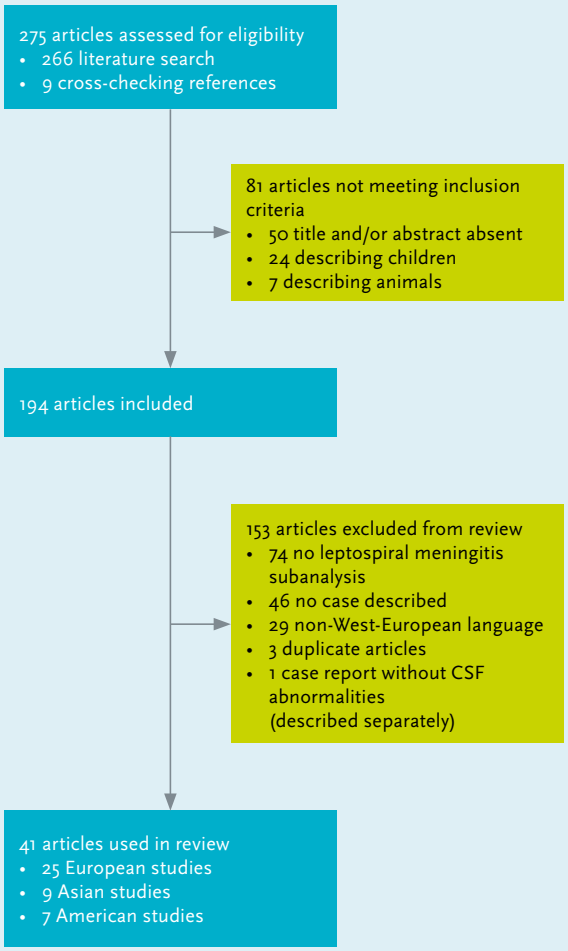


Table 1. *Clinical characteristics, aetiology, laboratory findings, treatment and clinical outcome for 366 adults with leptospiral meningitis, compared with our patients*

Characteristics	n/N	Cases
Age (median)	33	25
Male sex	51/62 (82%)	3/4 (75%)
Immunocompromised	**2/26 (8%)**	**0/4 (0%)**
Alcohol	1 (4%)	0 (0%)
Diabetes mellitus	1 (4%)	0 (0%)
Known aetiology	**32/33 (97%)**	**4/4 (100%)**
Animal contact	24 (75%)	0 (0%)
Water	8 (25%)	4 (100%)
Symptoms		
Headache	65/69 (94%)	4/4 (100%)
Fever	100/102 (98%)	4/4 (100%)
Neck stiffness	77/83 (93%)	4/4 (100%)
Altered consciousness	8/54 (15%)	0/4 (0%)
Meningitis triad	5/39 (13%)	0/4 (0%)
Cerebrospinal fluid characteristics		
Median CSF leukocytes (range)	206 (5-2072)	681 (11-1200)
Treatment		
Antibiotics	245/267 (92%)	4/4 (100%)
Outcome		
Death	8/229 (3%)	0/0 (0%)
Sequelae	3/56 (5%)	0/0 (0%)

CSF leukocyte counts were known had a leukocyte count under 2000, with a predominance of lymphocytes (95%, 95% CI 92-98%) in most patients (224 of 236; 95%, 95% CI 92-98%). The CSF protein was known in 39 patients and the CSF glucose in 27 patients. The median CSF glucose was 2.5 mmol/l, while the median CSF protein was 1.10 g/l. In 190 of 208 patients (91%, 95% CI 87-95%), CSF protein was normal, and CSF glucose was normal in 201 of 207 patients (97%, 95% CI 95-99%), while CSF leukocytes were elevated (> 5/mm^3). In all patients, antibodies to *Leptospira* were detected by blood serology (either ELISA or MAT); no *Leptospira* were detected in CSF by culture or PCR.

A total of 245 patients (91%) were treated with antibiotics (mostly penicillin and doxycycline). Twenty-three patients were not treated with antibiotics. One patient was treated with dexamethasone and received antibiotics (penicillin) as well.[4,8] Eight of 229 patients (3%, 95% CI 1-5%) died during hospital admission, of which five had received antibiotics. The cause of death was reported in two cases and consisted of respiratory insufficiency[4,6] and gastrointestinal bleeding.[27] The mortality rate in patients who were not treated with antibiotics was 13% compared with 2% in patients treated with antibiotics (Fisher's exact test, p = 0.04).

Three of 56 patients (5%) had sequelae; one patient was not able to walk until two months after discharge,[4,8] one patient had transient renal insufficiency[3,8] and one patient had neurocognitive defects which resolved after a few weeks.[22] Two articles describing two case reports of patients with meningeal symptoms but normal CSF were identified.[25,54] When combining these patients and our three patients with meningeal symptoms without CSF abnormalities, we identified five male patients with a median age of 27 years (range 20-47). Two had had animal contact, two travelled to a tropical area and one (one of our patients) worked in the municipal cleansing department. All five presented with headache and fever and two with neck stiffness. Diagnosis was established by blood tests; no leptospiral antibodies or DNA were detected in the CSF. All recovered without neurological sequelae.

DISCUSSION

We found a low incidence of leptospirosis in the Netherlands: 0.30 per 100,000 inhabitants in the period 2011-2014. In the period 2011-2013, the calculated annual incidence was 0.21 per 100,000 inhabitants, while the annual incidence in Europe in 2010 was 0.13 per 100,000 inhabitants.[3] In 2014, however, a threefold increase was observed in the incidence of leptospirosis in the Netherlands: 0.57 per 100,000 inhabitants. The contribution of travelling to leptospirosis in the Netherlands has been up to 50% since 1995[10,11,55] and was 33% in the period 2011-2013, but in 2014, the majority of patients (62%) contracted leptospirosis in the Netherlands. This increase is currently being investigated (unpublished data).

In our hospital, 18 out of 19 patients and 6 out of 7 patients with suspected meningitis contracted leptospirosis after fresh water contact while travelling in Southeast Asia, which has been reported to be the main risk factor for leptospiral infection worldwide.[5,6] The high contribution of travelling to leptospirosis in our hospital, compared with the national results, is probably caused by most patients being diagnosed at the AMC Department of Tropical and Travel Medicine. Only one patient had not been abroad, but worked at the municipal cleansing department where he could have been infected through contact with sewage water.[47]

From the 19 patients with leptospirosis identified in our hospital, all had fever (100%), 17 had headache (89%) and 5 had neck stiffness (26%). In general, headache and fever are common symptoms in leptospirosis which have been reported in 60-100%,[4] and neck stiffness is found in 10-20% of the cases,[10] which confirms our findings.

The incidence of meningitis in leptospirosis is relatively low despite the high frequency of headache and neck stiffness, although there could be an underestimation since not all patients undergo a lumbar puncture. In a cohort study of 63 cases, 12 patients (19%) were diagnosed with leptospiral meningitis,[4] which is similar to the incidence of meningitis in leptospirosis in our hospital (21%).

In our review of leptospiral meningitis, headache was seen in 94%, fever in 98% and neck stiffness in 93% of cases. When a patient presents with meningeal symptoms after fresh water contact in tropical regions or direct or indirect contact with animal urine, the diagnosis of leptospiral meningitis should be considered.

Our review showed that most patients with leptospiral meningitis have a mildly elevated CSF leukocyte count and a normal CSF glucose and protein. In a cohort study performed in 2008, CSF pleocytosis was seen ranging from 16 to 850 leukocytes/mm^3.[4] In this cohort study CSF analysis of patients with suspected leptospiral meningitis showed that 50% of patients had CSF pleocytosis,[4] which is similar to our case series (4 out of 7, 57%). In most patients in our study, CSF leukocytes mainly consisted of lymphocytes, but two of our cases with leptospiral meningitis had predominantly polymorphonuclear leukocytes in their CSF. This may be due to the timing of the lumbar puncture; polymorphonuclear leukocytes are often predominant early in the clinical course, and later replaced by lymphocytes.[16]

The necessity of a lumbar puncture in patients with leptospirosis has not been studied. In general, if the diagnosis of leptospirosis has not been confirmed in

patients with suspected meningitis, cerebrospinal fluid examination is vital to determine whether the patient has meningitis, and what the cause is. However, in patients with confirmed leptospirosis, cerebrospinal fluid examination does not have additional value since the treatment is similar in patients with and without leptospiral meningitis, unless a second diagnosis is being considered.

In our review, we found a significantly increased mortality in patients not treated with antibiotics compared with those who were treated with antibiotics (13% vs 2%; p = 0.04). However, only a small number of the patients (8%) did not receive antibiotics and the reasons for not treating those patients were unknown. In a recent Cochrane review, there was insufficient evidence for using antibiotics in leptospirosis, but no conclusions for 'severe leptospirosis' (not specified) could be drawn.[57] No association was established between the different antibiotic treatments ceftriaxone, doxycycline, cefotaxime and penicillin in leptospirosis and outcome. Most patients with leptospiral meningitis are treated with doxycycline or penicillin, which is the currently advised treatment regimen for leptospirosis (doxycycline 100 mg twice a day, or penicillin 1.5 million units four times a day).[54,57,58]

Our study has several limitations. We did not have clinical information about patients with leptospirosis attending other hospitals in the Netherlands, and therefore our case series is not representative for leptospirosis in the Netherlands. This is reflected in the high proportion of patients in our hospital who contracted leptospirosis abroad (95%) compared with the national average (53%). Furthermore, patients may have contracted leptospirosis and thus have a positive serology, but may have another diseases as well, such as Epstein-Barr viral infection or hepatitis.

For our review, we could not include articles written in non-West-European languages, e.g. Polish and Russian, due to insufficient knowledge of the language. Finally, there could be a publication bias since physicians may not report patients with leptospirosis and meningeal symptoms in whom no CSF abnormalities are found, when CSF culture was negative, or when no lumbar puncture was performed.

In conclusion, leptospirosis in the Netherlands had an annual incidence of 0.30 per 100,000 inhabitants in the period 2011-2014 and was contracted abroad in 53% of the cases. In the case of suspected meningitis and a history of travel to tropical areas or direct/indirect contact with animal urine, tests for leptospirosis should be considered. Leptospirosis commonly presents with headache and fever, but only a proportion of patients have meningitis. Approximately 50% of patients with suspected leptospiral meningitis have CSF pleocytosis and most have a normal CSF glucose and protein. When the diagnosis of leptospiral infection has been confirmed, lumbar puncture does not have clinical consequences, unless there is a differential diagnosis that needs to be considered. Treatment with penicillin or doxycycline usually leads to a favourable outcome.

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DISCLOSURES

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ORIGINAL ARTICLE

Behçet's disease, hospital-based prevalence and manifestations in the Rotterdam area

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ABSTRACT

Introduction: Behçet's disease is most prevalent in countries along the former Silk Road. Prevalence varies from 70-420 per 100,000 in Turkey, and 13.5-20 and 1-2 per 100,000 in Asia and Western Europe, respectively. Additionally, disease severity and morbidity might be correlated with ethnicity. We studied demography and morbidity in the Dutch cohort of patients with Behçet's disease and compared those with known figures.

Patients and methods: The prevalence of Behçet's patients in the Rotterdam area was determined by comparing the total number of patients within the ethnic population with the number of patients diagnosed with Behçet's disease. Patient files of the Erasmus University Medical Centre (Erasmus MC) were reviewed for morbidity figures and compared with existing data.

Results: In total 84 Behçet's patients of Dutch, Turkish or Moroccan descent were identified in the Rotterdam area. Prevalence of Behçet's disease differed per ethnicity: 1, 71 and 39 per 100,000 for Dutch-Caucasians, Turks, and Moroccans, respectively. These figures are comparable with occurrence in West Turkey and Morocco. Within the studied Erasmus MC cohort no significant differences in morbidity appeared between the ethnic groups. However, uveitis and pustules were significantly more common in the Erasmus MC cohort as compared with UK, German, Turkish and Moroccan cohorts.

Discussion and Conclusions: We present the first epidemiological study of Behçet's disease in the Netherlands. The prevalence of Behçet's disease in the studied Dutch region and in countries of ancestry is similar. Morbidity is equally spread, compared with other countries, but uveitis and pustules seem to be more common in the Netherlands.

KEYWORDS

Behçet's disease, epidemiology, prevalence, dutch cohort, disease manifestations

INTRODUCTION

Behçet's disease, first described by Hulusi Behçet in 1937, is an idiopathic systemic vasculitis with variable clinical manifestations.[1] The diagnosis of Behçet's disease is based on clinical criteria with the presence of recurrent oral ulceration together with genital ulcers, ocular inflammation and skin lesions.[2] Less often arthritis, central nervous system and gastrointestinal tract inflammation is present.[3-5] The aetiology still needs to be unravelled. The inflammatory symptoms are considered to be caused by an excessive T-cell mediated inflammatory response, triggered by an environmental antigen in a genetically susceptible host.[3,6,7] Over the years several genetic associations with Behçet's disease have been identified.[8-14] Furthermore, a positive family history can be found in 12% of non-Caucasian patients and a sibling risk ratio of 11-52 in Turkish patients.

Behçet's disease typically occurs in countries along the former Silk Road, an ancient route of commerce between the Mediterranean (Spain and Portugal) and the Far East (China). The highest prevalences of Behçet's disease are seen in Turkey (20-420 per 100,000, with about 70 per

100,000 in its European region). In Asian countries, such as Japan, Korea, China, Iran, and Saudi Arabia, prevalence varies from 13.5 to 20 cases per 100,000. In Western countries prevalences of approximately 1 per 100,000 have been reported.[3,15,16] Morbidity is reported to be lower in Western populations, in comparison with Eastern Mediterranean and Middle and Far Eastern countries.[3,15,16] Behçet's disease can develop at any age, but the disease appears most frequently between the second and fourth decade of life.[17] In countries along the former Silk Road, Behçet's disease is more frequent among men, whereas in Western countries it is more prevalent in women.[17-22] Demographic and morbidity data of Behçet's disease in Northern Europe and the Netherlands are sparse. Demographic data from other Northern European countries are restricted to two cohorts, one German and one British.[23,24] It has been suggested that lifestyle or environmental factors could be influential in the immuno-aetiology of Behçet's disease, hence influencing the prevalence in patients migrating to other countries.[20,25] In this light, countries to which patients from high incidence countries migrate, such as the Netherlands, can be helpful to address this issue.

Therefore, we initiated a demographic study in Dutch Behçet's patients to elucidate variability of prevalence and morbidity amongst different ethnic groups and changing figures upon migration.

MATERIALS AND METHODS

All patients included in our study fulfilled the diagnosis of Behçet's disease by the criteria of the International Study Group for Behçet's disease.[2] For prevalence analyses, the numbers of Behçet's patients were collected from the hospital records of four hospitals in the Rotterdam area (Erasmus University Medical Center (Erasmus MC), Vlietland Hospital, Maasstad Hospital, Sint Franciscus Gasthuis). Only Dutch, Turkish and Moroccan ethnicities were included in this analysis since the occurrence of Behçet's disease in other ethnic backgrounds in the Netherlands is known to be too low to reach significant power. Public information on populations and ethnicities of inhabitants of the Rotterdam postal area is freely accessible from the governmental institute for statistical data (Centraal Bureau voor de Statistiek).

The morbidity analyses were performed by reviewing files on the presence of disease symptoms from all Behçet's patients visiting Erasmus MC (also from outside the Rotterdam postal area) up to January 2012. To compare our data with other cohorts, we performed a PubMed survey on epidemiological data and Behçet's disease. Statistical analyses were performed with SPSS 17.0 version (Chicago Illinois). The chi-square test method was used, a p-value < 0.05 was considered to be statistically significant.

RESULTS

Prevalence

In total 84 Behçet's patients of Dutch, Turkish or Moroccan descent were identified in the area with the postal code 2900 - 3319 (*table 1*). The other 16 patients were of a different origin. The prevalence of Behçet's disease in the Rotterdam area differed per ethnicity: 1 per 100,000 for Dutch, 71 per 100,000 for Turkish and 39 per 100,000 for Moroccans. We identified 11 Turkish and 3 Moroccan Behçet's patients who were born in the Netherlands.

Disease features

The Erasmus MC cohort of 110 Behçet's disease patients comprised three subpopulations: Dutch-Caucasian, Turkish and Moroccan patients. The remainder constituted a mix of various ethnicities. Patient characteristics are presented in *table 2a*. The average age of the patients was 44 years (*table 2a*). The male-female ratio was 1 for the entire group; 0.64 for the Dutch patients, 1.31 for the Turkish, and 1.66 for the Moroccan patients, respectively. Oral and genital ulcers and skin involvement were most prevalent. No significant

Table 1. *Prevalence of Behçet's disease in the Rotterdam area*

Rotterdam area (Postal code 2900 - 3319)	Inhabitants	BD patients	Per 100,000 (95% CI)	Born in the Netherlands
Total	1,319,680	100	7.6 (6.1; 9.1)	
Dutch-Caucasian	874,162	12	1.4 (0.6; 2.1)	
Turkish	73,028	52	71.2 (51.9; 90.6)	11
Moroccan	51,218	20	39.0 (21.9; 56.2)	3

BD = Behçet's disease.

differences were observed between the ethnic groups in any of the symptoms of the diagnostic criteria (*table 3*).
Other clinical symptoms were again split up per ethnicity (*table 2b*). Fatigue, headache and arthralgia were often present. Of all the symptoms, significant differences between the ethnic cohorts were only demonstrated for the prevalence of arthritis and arthralgia between Dutch and Moroccan patients ($p < 0.038$) and arthralgia between Dutch and Turkish patients ($p < 0.04$); an increased incidence in Turkish and Moroccan patients was seen (*table 3*). There was no significant difference between the occurrence of anterior uveitis when comparing Dutch patients with either Moroccan or Turkish patients ($p = 0.50$ and $p = 0.36$ respectively). In both the Moroccan and the Turkish groups, uveitis was also present in patients who were born in the Netherlands (second-generation migrants). There was no significant difference between morbidity in male and female patients (data not shown).

Comparison with other cohorts

We compared our data with Turkish, Moroccan, German and British cohorts (*table 4a and 4b*).[23,24,26,27] The German cohort consisted of two main ethnicities: German (38.5%) and Turkish (45.3%). For the empty

Table 2a. *Ethnic comparison of Dutch Behçet's patients for diagnostic criteria in Behçet's disease*

n = 110	All	The Netherlands	Turkey	Morocco	Others
	100% (110)	**37.3% (41)**	**34.5% (38)**	**14.5% (16)**	**13.7% (15)**
Average age	44.2	43.0	44.3	46.5	
♂:♀ ratio	1	0.64	1.31	1.66	
Oral ulcers	100% (110)	100% (41)	100% (38)	100% (16)	100% (15)
Genital ulcers	79.1% (87)	85.4% (35)	84.2% (32)	62.5% (10)	66.7% (10)
Erythema nodosum	31.8% (35)	24.4% (10)	36.8% (14)	37.5% (6)	33.3% (5)
Pustules	80.9% (89)	73.2% (30)	81.6% (31)	93.8% (15)	86.6% (13)
Uveitis*	61.8% (68)	51.2% (21)	60.5% (23)	68.8% (11)	86.6% (13)
Positive pathergy test	57.1% (32/56)	66.7% (16/24)	38.1% (8/21)	40% (2/5)	100% (6/6)

*Overall 21% anterior uveitis, 79% posterior/panuveitis, respectively: Dutch 36% and 64%, Turks 20% and 80%, Moroccan 22% and 78%, respectively. There were no significant differences between anterior or posterior/panuveitis between the ethnic groups (Dutch vs Moroccan patients; $p = 0.50$, Dutch vs Turkish patients; $p = 0.36$).

Table 2b. *Ethnic comparison of Dutch Behçet's patients for other features present during the disease course*

n = 110	All	The Netherlands	Turkey	Morocco	Others
	100% (110)	**37.3% (41)**	**34.5% (38)**	**14.5% (16)**	**13.7% (15)**
Fatigue	68.2% (75)	61.0% (25)	76.3% (29)	68.8% (11)	66.7% (10)
Headache	60.0% (66)	48.8% (20)	57.9% (22)	75.0% (12)	80% (12)
Arthralgia	67.3% (74)	**51.2% (21)**	**73.7% (28)**	**81.3% (13)**	80% (12)
Arthritis	30.9% (34)	**22.0% (9)**	34.2% (13)	**50.0% (8)**	26.7% (4)
Gastrointestinal symptoms	44.5% (49)	36.6% (15)	42.1% (16)	62.5% (10)	53.3% (8)
Diarrhoea	22.7% (25)	24.4% (10)	18.4% (7)	31.3% (5)	20.0% (3)
Neurological involvement	12.7% (14)	12.2% (5)	5.3% (2)	12.5% (2)	33.3% (5)
HLA-B51 positivity	43.3% (13/30)	40.0% (6/15)	44.4% (4/9)	33.3% (1/3)	66.7%(2/3)
Major vessel involvement	10.9% (12)	12.2% (5)	5.3% (2)	12.5% (2)	20% (3)

Data in bold are statistically significant.

Table 3. *P-values for ethnic comparison of Dutch Behçet's patients for diagnostic criteria and other features in the disease*

Parameter	Compared for ethnicity	p-value*	Table
♂:♀ ratio	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.093 0.110 0.753	2a
HLA-B51 positivity	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.831 0.829 0.735	2a
Genital ulcers	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.886 0.057 0.080	2a
Erythema nodosum	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.229 0.332 0.964	2a
Pustules	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.373 0.087 0.250	2a
Uveitis	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.405 0.231 0.568	2a
Pathergy test positivity	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.055 0.264 0.937	2a
Fatigue	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.143 0.585 0.562	2b
Headache	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.417 0.073 0.235	2b
Arthralgia	Dutch – Turks Dutch – Moroccans Turks – Moroccans	**0.040**** **0.038**** 0.553	2b
Arthritis	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.225 **0.038**** 0.277	2b
Gastrointestinal symptoms	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.616 0.076 0.171	2b
Diarrhoea	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.519 0.597 0.300	2b
Neurological involvement	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.279 0.975 0.354	2b
Major vessel involvement	Dutch – Turks Dutch – Moroccans Turks – Moroccans	0.279 0.975 0.354	2b

*All p-values were calculated using a Chi-square test method in SPSS. **All p-values ≤ 0.05 were considered to be significant and are therefore rendered in bold.

cells in the table no data were available in the original articles. The male-female ratio was 0.5 in the UK cohort and 1 or higher in the other cohorts. Oral and genital ulcers and skin involvement were most prevalent. In contradiction to observations in our own cohort, disease manifestations differed between the different populations (*table 4a and table 5*). Pustules appeared to be more prevalent in the Erasmus MC cohort as compared with Germany and Morocco. Uveitis was more prevalent in Western as compared with Turkish and Moroccan cohorts. Furthermore, major vessel involvement was less prevalent in the Erasmus MC cohort as compared with the UK and Moroccan cohort.

In the other cohorts, data on other disease features related to Behçet's disease were limited (*table 4b*). We did find a significant difference between prevalence of arthralgia (common in the UK), arthritis and neurological involvement (*table 5*).

DISCUSSION

We present the first epidemiological and morbidity data of Behçet's patients living in the Netherlands. In this population the majority of patients are Dutch-Caucasian, Turkish or Moroccan. The prevalence of Behçet's disease in the Rotterdam area amongst these groups reflects epidemiological studies in comparable populations and does not appear to shift after migration.

Comparable data from Germany showed that the prevalence of Behçet's disease in the Turkish population was similar to our findings, and equals the reported prevalence in the European part of Turkey.[22] Thus, our observation of next-generation immigrants with Behçet's disease and the fact that the disease can also develop in non-Turkish (or Asian) patients contradicts with the suggestion that it does not develop after migration. This suggestion of causative land-based disease was based on the observation that Behçet's disease did not occur in Japanese immigrants on Hawaii[25] and on the presence of a decreasing prevalence of Behçet's disease after migration from Turkey to Germany.[20] However, the latter could not be confirmed in a second study by the same group in 2012.[22] Unfortunately, our cohort was too small to perform sub-analyses of prevalences of Turkish and Moroccan patients who were born in the Netherlands and those born in Turkey and Morocco. Also other prevalence studies fail to present this data. However, in one study about the age of immigration and the risk of developing Behçet's disease, no correlation was found.[28]

We would like to stress that the pathogenesis of Behçet's disease does not appear to be decisively determined by the country of residence. Whether the disease severity is

Table 4a. *International comparison between the Erasmus MC and four other cohorts for diagnostic criteria for Behçet's disease*

	The Netherlands	Germany (23)	UK (24)	Turkey (26)	Morocco (27)
N	110	590	419	2147	1034
♂:♀ ratio	1	1.4	0.5	1.03	2
Oral ulcers	100%	98%	100%	100%	100%
Genital ulcers	**79.1%**	**64%**	**89%**	**88%**	**86%**
Erythema* nodosum	**31.8%**	**42%**	**-**	**-**	**16%**
Pustules*	**80.9%**	**62%**	**-**	**-**	**64%**
Uveitis	**61.8%**	53%	68%	**29%**	**44%**
Positive pathergy test	**57.1%****	**34%**	**32%**	56%	53%

Data in bold are statistically significant. *86% of UK Behçet's patients had skin manifestations; this was not specified in the original study. **Not all Dutch patients underwent a pathergy test; therefore this figure was based on all positive tests in the 56 patients who underwent this test.

Table 4b. *International comparison between the Erasmus MC and four other cohorts for other features in the course of Behçet's disease*

	The Netherlands	Germany (23)	UK (24)	Turkey (26)	Morocco (27)
N	110	590	419	2147	1034
Arthralgia	67.3%	-	**93%**	-	**32%**
Arthritis	30.9%	-	-	-	**45%**
Gastrointestinal symptoms*	48.2%	-	-	-	-
Gastrointestinal involvement**	-	12%	7%	2.8%	11%
Neurological involvement	**12.7%**	11%	**31%**	**2.2%**	17%
Major vessel involvement***	**10.9%**	13%	**32%**	17%	**20%**

Data in bold are statistically significant. *Gastrointestinal involvement included one of the following: nausea, vomiting, abdominal pain, diarrhoea. Ulceration of the gastrointestinal tract was not necessarily found. **Ulceration of the gastrointestinal tract was objectivised. ***Major vessel involvement included either arterial and venous involvement.

influenced could not be studied, since there is no validated severity scoring system for Behçet's disease.

The average age of the Behçet's patients in the Erasmus MC cohort was similar amongst the various ethnicities.[17,29] The Dutch-Caucasian male-female ratio tended to be lower as compared with Moroccans and Turks. Apparently a female prevalence occurs in Western and Asian countries as observed in other cohorts (*table 2a*).[24,27] Saylan et al. reported female predominance in the United States, the United Kingdom, Korea, and China, whereas a male predominance was found for almost all Middle Eastern countries.[30] A low male/ female ratio is often seen in autoimmune diseases. However, Behçet's disease is generally not associated with autoimmunity, rather with autoinflammation.[31] The latter is not associated with female predominance, leading to uncertainty about the significance of the mentioned observations.[32]

Prevalence of many symptoms was significantly different in our cohort as compared with other cohorts; differences in data collection can be of influence. The only clinically relevant differences in morbidity were skin lesions and uveitis. In Dutch patients a significantly higher percentage of pustules was seen as compared with Germany and Morocco. Prevalence of erythema nodosum was also statistically significantly higher in the Erasmus MC cohort and in the German study, as compared with Moroccan figures. It is widely thought that environmental components are essential in the pathophysiology of Behçet's patients. Therefore it was expected that skin involvement would have been higher in countries with high disease prevalence. Other factors, such as genetic susceptibility, could account for our observation.

A significantly higher prevalence of uveitis was seen in Western cohorts compared with Turkish and Moroccan

Table 5. *P-values for international comparison between the Erasmus MC and four other cohorts for diagnostic criteria for Behçet's disease and other features in the course of the disease*

Parameter	Compared for ethnicity	p-value*	Table
Genital ulcers	Dutch – German Dutch – British Dutch – Turkish Dutch – Moroccan	**0.002**** **0.006**** **0.006**** 0.052	4a
Erythema nodosum	Dutch – German Dutch – British Dutch – Turkish Dutch – Moroccan	**0.045**** *** *** **10^{-19}****	4a
Pustulas	Dutch – German Dutch – British Dutch – Turkish Dutch – Moroccan	**10^{-19}**** *** *** **10^{-19}****	4a
Uveitis	Dutch – German Dutch – British Dutch – Turkish Dutch – Moroccan	0.090 0.219 **10^{-19}**** **10^{-19}****	4a
Pathergy test positivity	Dutch – German Dutch – British Dutch – Turkish Dutch – Moroccan	**0.001**** **10^{-19}**** 0.863 0.545	4a
Arthralgia	Dutch – German Dutch – British Dutch – Turkish Dutch – Moroccan	*** **10^{-19}**** *** **10^{-19}****	4b
Arthritis	Dutch – German Dutch – British Dutch – Turkish Dutch – Moroccan	*** *** *** **0.005****	4b
Neurological involvement	Dutch – German Dutch – British Dutch – Turkish Dutch – Moroccan	0.603 **10^{-19}**** **10^{-19}**** 0.250	4b
Major vessel involvement	Dutch – German Dutch – British Dutch – Turkish Dutch – Moroccan	0.536 **10^{-19}**** 0.095 **0.021****	4b

*All p-values were calculated using a Chi-square test method in SPSS.**All p-values ≤ 0.05 were considered to be significant and are therefore rendered in bold. ***These fields were left blank, because of lack of data in the original study. Therefore no p-value could be determined.

populations. Since Behçet's disease is rare in the Netherlands, it is possible that a general physician could miss the diagnosis in a Dutch-Caucasian patient who presents with oral ulcers.[29] One could argue that a relative underdiagnosis of the less severe cases of Behçet's disease might lead to relatively higher prevalence of severe cases with uveitis. To determine whether severity in ophthalmic symptoms might be related to ethnic origin, we compared the less severe anterior uveitis with the more severe presentation (panuveitis and/or posterior uveitis) in the various ethnic groups. In these cohorts we could not demonstrate such a relation. Moreover, the occurrence of other severe symptoms, such as major vessel involvement, did not differ between the groups either. There are no other data available in epidemiological studies that present details of ocular involvement, or disease severity. A mainly Caucasian cohort of Behçet's patients in the US reports 11% anterior uveitis in a group of 168 of patients with ocular involvement.[33] A second additional reason for the high percentage of uveitis found in the Erasmus MC cohort is the close cooperation between our hospital and the Rotterdam Eye Hospital in respect of referral of patients.

In conclusion, the prevalence of Behçet's disease in different ethnic groups in the Rotterdam area is similar to that in the countries of origin of these patients. It does not appear to shift after migration. However, a substantial additional amount of patient data is necessary to elucidate migration effects on the occurrence and morbidity of Behçet's disease more robustly. This warrants international cooperation between treating physicians.

DISCLOSURES

None of the authors have a financial or non-financial competing interest that could influence interpretation or presentation of any of the data.

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CASE REPORT

Complete resolution of autoimmune thyroiditis after R-CHOP in a patient with thyroid lymphoma

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ABSTRACT

Hashimoto's thyroiditis is a known risk factor for the development of primary thyroid lymphoma. How the treatment of primary thyroid lymphoma influences thyroid function is however largely unknown. This case shows that treatment with R-CHOP chemotherapy can lead to a recovery of thyroid function in a patient with severe hypothyroidism, without thyroid hormone supplementation. Furthermore, this case shows that in patients with primary hypothyroidism and a rapidly enlarging, asymmetrical thyroid, fine needle aspiration should be performed to rule out primary thyroid lymphoma.

KEYWORDS

Thyroid lymphoma, hypothyroidism, thyroiditis

What was known on this topic?
Hashimoto's thyroiditis is a known risk factor for the development of primary thyroid lymphoma. How the treatment of primary thyroid lymphoma influences thyroid function is, however, largely unknown.

What does this add?
This case shows that treatment of primary thyroid lymphoma with R-CHOP chemotherapy can lead to recovery of thyroid function in a patient with severe hypothyroidism, without thyroid hormone supplementation. Furthermore, this case shows that in patients with primary hypothyroidism and a rapidly enlarging, asymmetrical thyroid, fine needle aspiration should be performed to rule out primary thyroid lymphoma.

INTRODUCTION

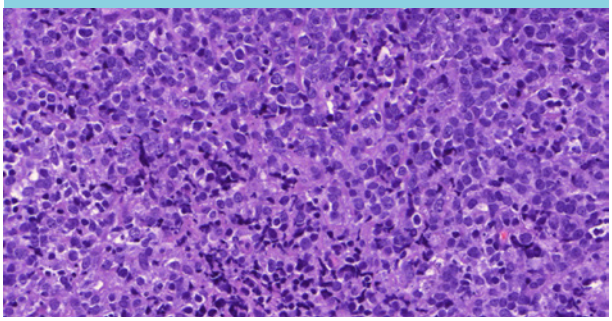
Primary thyroid lymphoma (PTL) is associated with (pre-existing) chronic autoimmune thyroiditis (Hashimoto's thyroiditis). Little is known about how treatment for PTL influences thyroid function.
We present a patient with Hashimoto's thyroiditis (HT) and PTL with recovery of thyroid function after treatment with R-CHOP chemotherapy without thyroid hormone supplementation.

CASE PRESENTATION

An otherwise healthy 63-year-old women presented to the outpatient clinic with complaints of a left-sided enlargement of the neck. She had noticed the painless swelling two months before and reported that it had not grown since. There were no B-symptoms and no symptoms of thyroid dysfunction. Physical examination showed a large (approximately 7 cm) palpable mass on the left side of the neck and an enlarged thyroid. There was additional lymphadenopathy, hepatosplenomegaly and no signs of thyroid disease. Laboratory studies showed a slightly elevated sedimentation rate (33 mm/h, normal < 30 mm/h) and severe primary hypothyroidism with an undetectable fT4 level (< 4.5 pmol/l, normal 10.0-24.0 pmol/l) and an elevated thyroid-stimulating hormone level (65 mU/l, normal 0.400-4.00 mU/l). The patient tested positive for anti-TPO-antibodies (379 mU/l, normal < 60 mU/l). All other laboratory measurements, including haemoglobin, lactate dehydrogenase levels and serum protein electrophoresis, were normal (haemoglobin: 8.9 mmol/l, normal 7.2-9.5 mmol/l; lactate dehydrogenase:

237 U/l, normal < 248 U/l). A computed tomography (CT) scan showed extensive bilateral lymphadenopathy of the neck and an asymmetrical enlarged thyroid. PET-CT yielded no evidence of extranodal localisations. A biopsy of a lymph node was taken and showed a diffuse large B-cell lymphoma (DLBCL) (*figure 1*). Bone marrow aspiration revealed no localisation. The patient was diagnosed with stage IIE DLBCL of the thyroid with severe hypothyroidism because of autoimmune thyroiditis. The age-adjusted International Prognostic Index score was 0 (low risk). Treatment was started with six courses of R-CHOP chemotherapy, consisting of rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (with a maximum of 2 mg) on day 1 and prednisone 100 mg on day 1 to 5. Because of the lack of symptoms and a possible effect of R-CHOP treatment on thyroid function, no levothyroxine supplementation was started. Thyroid function indeed improved quickly after the start of chemotherapy (*figure 2*), and only mild subclinical hypothyroidism persisted after six courses of R-CHOP. Anti-TPO antibodies were undetectable and imaging studies, including PET-CT, showed complete remission.

Figure 1. *Histology of excision biopsy of a cervical lymph node, HE staining, 40x. Immunophenotyping: monotone lymphoid population, positive for lymphoid and B-cell markers (CD45, CD20, CD79A and PAX-5). The population is also positive for BCL 6, weakly positive for CD10 and CD21. The population is negative for CD3, CD5, CD30, BCL2 and CD15 and CD68. Ki67 is positive in almost 100% of nuclei*

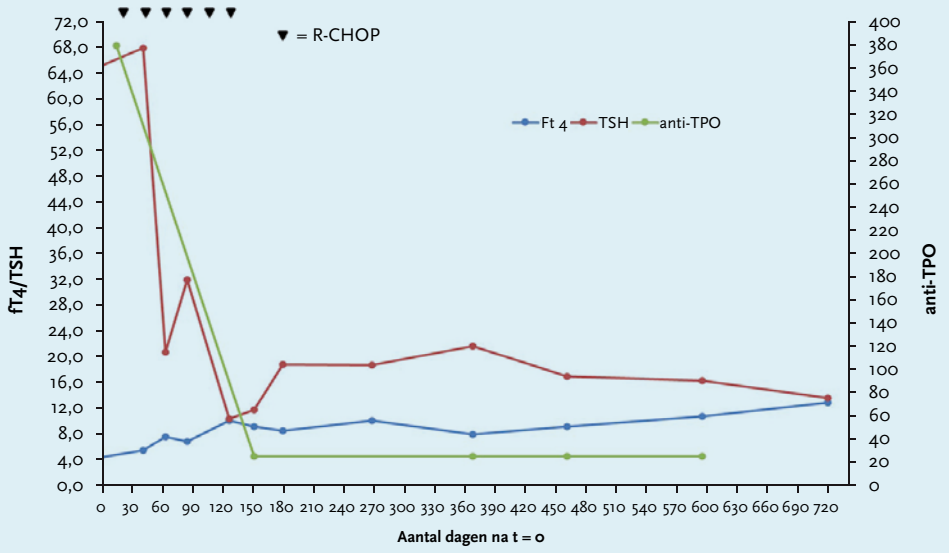


DISCUSSION

Primary thyroid lymphoma is a rare disease, as it accounts for only about 2% of extranodal lymphomas and less than 5% of primary thyroid malignancies. There is a female predominance, with a peak age incidence in the sixth or seventh decade of life. A rapid enlarging goitre is the major presenting symptom. B-symptoms, such as fever, night sweats and weight loss, occur in approximately 10% of patients. Primary thyroid lymphoma is almost always of the malignant B-cell lymphoma type. The most common subtypes are DLBCL and mucosa-associated lymphoid tissue (MALT) lymphoma. A known risk factor for primary thyroid lymphoma is pre-existing chronic autoimmune thyroiditis (Hashimoto's thyroiditis), which is found in 60-90% of patients. Patients with primary thyroid lymphoma are often euthyroid or already being treated for Hashimoto's thyroiditis, but hypothyroidism can be present.[1,2]

In Hashimoto's thyroiditis, autoimmune-mediated destruction of the thyroid gland leads to gradual thyroid failure. It is characterised by diffuse infiltration of the thyroid with B and T lymphocytes. The T cells are, however,

Figure 2. *Results of thyroid function and anti-TPO levels before and after R-CHOP chemotherapy in a patient with primary thyroid lymphoma*



thought to play a dominant role in the pathogenesis of Hashimoto's thyroiditis. Dysfunction of suppressor T cells is thought to lead to overgrowth of Th1 cells, which leads to cytokine production. Cytokines activate cytotoxic T cells, which in turn cause apoptosis of epithelial thyroid cells. Cytokines also stimulate B cells in the thyroid to produce antithyroid antibodies. Nearly all patients with Hashimoto's thyroiditis display antibodies to thyroid peroxidase (TPO) and thyroglobulin. These antibodies, however, are thought to arise as a result of thyroid tissue damage and are thus considered markers of the underlying autoimmune process. The antibodies are polyclonal and are unable to induce disease when transferred to animal models, thus anti-TPO antibodies are probably of limited biological significance.[3-5] On the other hand, in animal models where spontaneous autoimmune thyroiditis is induced, it has been shown that although T cells are the main effector cells involved in the pathogenesis, B-cell-depleted mice cannot develop autoimmune thyroiditis, suggesting a crucial role for B cells as well.[6]

The reason why patients with Hashimoto's thyroiditis develop malignant lymphoma is not fully understood but it has been hypothesised that chronic antigenic stimulation of lymphocytes in the thyroid in these patients may lead to malignant transformation.

We present a case of severe primary hypothyroidism in a patient with primary thyroid lymphoma, with almost complete recovery of thyroid function after R-CHOP chemotherapy, without levothyroxine supplementation. Since previous thyroid function tests were unavailable and the patient did not experience symptoms associated with thyroid dysfunction, it is unknown for how long the Hashimoto's thyroiditis was present in our patient. More important, the exact mechanism of the recovery of thyroid function after chemotherapy without supplementation of thyroid hormone remains to be elucidated. Since rituximab is used for the treatment of various autoimmune diseases, a specific effect of rituximab on thyroid function in this case might be implied. Little is known about the effect of rituximab on thyroid function in patients with Hashimoto's thyroiditis, with or without thyroid lymphoma. In anti-TPO positive, euthyroid patients treated with rituximab for rheumatological disorders, no effect was seen on anti-TPO antibody levels or levels of TSH and fT4.[7] A case series of three patients treated with R-CHOP or rituximab monotherapy for thyroid MALT lymphoma did show a decrease of anti-TPO antibody levels, with a concomitant decrease in thyroid-stimulating hormone levels, albeit within the normal range.[8] Raterman et al., on the other hand, reported a case of a patient with Hashimoto's thyroiditis, treated with rituximab because of rheumatoid arthritis, who developed hyperthyroidism under a stable dose of levothyroxine, accompanied by a decrease in anti-TPO antibody levels. The authors suggested that B-cell depletion due to rituximab may have led to a decrease in anti-TPO production with a direct effect on thyroid function.[9] However, since anti-TPO antibodies are probably not a direct cause of hypothyroidism, as discussed previously, this seems unlikely. Apart from B-cell depletion caused by rituximab, a direct effect of chemotherapy on infiltration of the thyroid by the lymphoma may have influenced thyroid function in our patient. Also, T-cell depletion caused by the chemotherapy (cyclophosphamide, prednisone) or even by rituximab,[10] may have played a role.

CONCLUSION

In conclusion, we present a case of severe primary hypothyroidism in a patient with primary thyroid lymphoma, with almost complete recovery of thyroid function after R-CHOP chemotherapy. The exact mechanism by which R-CHOP chemotherapy led to the spectacular improvement in thyroid function remains to be elucidated. Furthermore, this case shows that in patients with primary hypothyroidism and a rapidly enlarging, asymmetrical thyroid, fine needle aspiration should be performed to rule out primary thyroid lymphoma.

DISCLOSURES

The authors declare that they have no competing interests. This work received no financial support.

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CASE REPORT

A cluster of tularaemia after contact with a dead hare in the Netherlands

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ABSTRACT

Tularemia is thought to be rare in the Netherlands. Here we describe a cluster of two patients who contracted tularaemia after field dressing of a hare found dead. Additionally, infection from the same source is suggested in three animals.

KEYWORDS

Tularaemia, *Francisella tularensis*, hare, ferret, dog

What was known on this topic?
Tularaemia is a highly contagious disease caused by *Francisella tularensis*. This infection occurs throughout the Northern Hemisphere, however, it is thought to be rare in the Netherlands.

What does this add?
The cases described here may indicate that the incidence of tularaemia is increasing in the Netherlands. Clinicians should be aware of tularaemia, especially in people who are in close contact with wildlife.

INTRODUCTION

Tularaemia is a bacterial zoonotic disease occurring throughout the Northern Hemisphere, caused by *Francisella tularensis*. *F. tularensis* subspecies vary with their geographic distribution. *F. tularensis* subspecies *tularensis* (type A) is regarded as the most virulent subspecies and is predominantly present in North America. *F. tularensis* subspecies *holarctica* (type B) generally causes mild disease and is present on the entire Northern Hemisphere.[1] In the Netherlands, tularaemia is thought to be rare; between 1953 and 2011, no indigenous cases were reported. Here we describe a cluster of two patients who contracted tularaemia from a single source. Additionally, infection from the same source is suggested in three animals.

CASE DESCRIPTION

A 34-year-old man presented to the emergency room with malaise and swelling of the distal phalanx of the second finger of his left hand, four days after an accidental injury from a sharp bone when dressing a hare (*Lepus europaeus*). This hare was found dead in the field by his father and brought home to feed to the patient's ferrets. On physical examination, his temperature was 39.4°C. A tender and enlarged lymph node was noticed in his left axilla. The X-ray taken of his finger revealed no remaining hare bone. The consulted surgeon prescribed amoxicillin/clavulanic acid 500/125 mg three times a day for a suspected wound infection. Three days later the patient returned because three pustules had developed on his finger. These pustules were incised and drained. A coagulase negative staphylococcus was cultured from the collected pus. Four weeks later, the patient again presented to the emergency department because of fever, malaise and headache. The index finger of his left hand was lightly swollen but neither warm nor red; no pus was seen. The

patient himself wondered whether his complaints could be caused by tularaemia. He considered this diagnosis based on information he found about tularaemia on a hunters website[2] and because his father had similar symptoms.

His father had visited his general practitioner with malaise, nausea, vomiting, headache and fever. Ten days after handling the hare, he had developed sores on both hands. On clinical examination he had multiple small sores on his hands, enlarged lymph nodes in elbows and axillae but no fever. The malaise persisted for weeks.

For both the patient and his father, high titres of antibodies strongly suggestive of tularaemia were detected using a micro-agglutination test (BD Difco 241050™ BBL™, Breda, the Netherlands). No cross-reacting *Brucella* antibodies were found. Fluoroquinolones, such as ciprofloxacin, and tetracyclines, such as doxycycline, are regarded as the first-line oral treatment.[3] Both men were treated with doxycycline 100 mg twice daily for 14 days, after which their symptoms resolved. However, the lymphadenopathy on the father's elbow persisted for weeks; five months after finding the hare, a persistent suppurative lymph node in his right axilla was drained.

In addition, the patient reported that his dog had been suffering from lethargy and loss of appetite for about a week, after licking the hare's carcass. In the two ferrets that were fed meat of the hare, no clinical signs were observed. Blood samples from the dog and the ferrets were collected for serology. Because of haemolysis, interpretation of the agglutination test was not possible. All three sera tested positive in the Virapid® Tularaemia test (Virapid®, Vircell S.L., Santa Fé, Spain). These positive results should be interpreted with caution, since this test is validated in human sera only and false-positive results because of cross-reacting antibodies cannot be excluded.[4] However, the dog's clinical symptoms, in combination with a positive test, suggest exposure to *F. tularensis*.

DISCUSSION

F. tularensis can be transmitted to humans by various routes, including handling of infected animals, ingestion of contaminated food or water, inhalation of infective aerosols, and arthropod bites.[1] Both patients developed ulcero-glandular tularaemia after handling a dead hare, suggesting the hare served as the source of infection. However, the hare was no longer on hand for confirmatory testing. Dogs and ferrets are thought to be less susceptible to tularaemia and only a few cases of tularaemia have been reported in dogs.[5-7] In the Netherlands *F. tularensis* infected dogs have not been described before. It is not known whether dogs can transmit the disease to humans, although in a patient suffering from endocarditis caused by *F. tularensis*, transmission from a dog was suggested.[8]

Between October 2011 and January 2015, three other cases of tularaemia were reported in humans, and three out of 117 hares tested positive for tularaemia, either in the context of finding the source of a human infection or non-targeted wildlife disease surveillance in the Netherlands.[9-11] The number of reported tularaemia cases in Dutch hares seems to be in agreement with data from neighbouring countries.[9] However, making comparisons is difficult, because there is no standardised monitoring system among European countries.[12] Although tularaemia has long been considered to be rare in the Netherlands, these cases may indicate that the incidence is increasing. Clinicians should be aware of tularaemia, especially in people who are in close contact with wildlife.

DISCLOSURES

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CASE REPORT

Catecholamine-induced cardiomyopathy in a patient with malignant paraganglioma

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KEYWORDS

Malignant paraganglioma, catecholamines, cardiomyopathy, SDHA-germline mutation

What was known on this topic?
Malignant paragangliomas are rare neuroendocrine tumours with an estimated incidence of 0.16 cases per 100,000 persons. Most sympathetic paragangliomas are functional and can present with catecholamine hypersecretion, typically causing paroxysmal hypertension, pallor, palpitations and diaphoresis.

What does this add?
We point out that catecholamine-secreting paragangliomas can demonstrate a rapid increase in catecholamine release during their course. Clinicians should be aware of, and more importantly anticipate this catecholamines release in order to prevent cardiovascular complications.

INTRODUCTION

Paragangliomas are rare neuroendocrine tumours deriving from chromaffin cells. Only 15-20% of chromaffin-cell tumours are extra-adrenal paragangliomas, 80-85% being adrenal pheochromocytomas.[1] Most paragangliomas occur as sporadic tumours, but 30-35% are associated with hereditary syndromes or germ-line mutations in susceptibility genes. Malignancy, defined as metastasis in non-chromaffin tissue, is reported in 10-17% of all paragangliomas.[1-2,3] Paragangliomas commonly produce one or more types of catecholamines: epinephrine, norepinephrine and dopamine. High levels of catecholamines can result in cardiovascular complications, varying from hypertension and palpitations to acute ventricular dysfunction due to a catecholamine-induced cardiomyopathy. Stress cardiomyopathy (or Takotsubo cardiomyopathy) is an acute, transient ventricular dysfunction displaying severe left ventricular wall motion abnormalities. It often mimics an acute coronary syndrome in the absence of coronary artery disease. Precipitants of Takotsubo cardiomyopathy are numerous but catecholamine mediated β2-adrenoceptor stimulation is thought to be an important common component in the aetiology.[4] Here, we report a case of a patient suffering from a malignant paraganglioma who died as a result of an overwhelming catecholamine-release and subsequent cardiopulmonary complications.

CASE REPORT

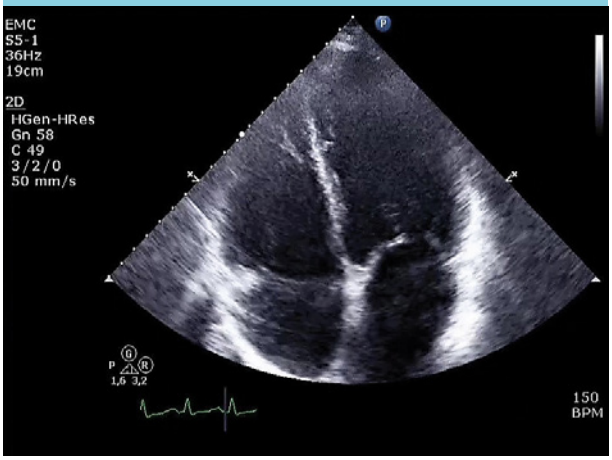
A 36-year-old man was diagnosed with a retroperitoneal malignant paraganglioma. Further evaluation included a CT scan showing irresectable, retroperitoneal masses, and liver and bone metastases; MIBG scintigraphy and Octreoscan which did not yield treatment options for ^{131}I-MIBG therapy or peptide-receptor radiotherapy with ^{177}Lutetium octreotate. Therefore it was decided to start palliative chemotherapy treatment. Although the more commonly used chemotherapy regimens for malignant paragangliomas include cyclophosphamide, vincristine, and dacarbazine, it was decided to treat this malignant paraganglioma as a small-cell malignancy because of a

small-cell component that was found at histopathology and the aggressive nature of the tumour. The patient was started on four-weekly cycles of intravenous carboplatin (AUC 5 on day 1) and etoposide (100 mg/m^2 days 1-3). A follow-up CT scan after the second cycle showed disease progression and the chemotherapy was discontinued. Thereafter the patient was evaluated for phase I study treatment. However, within six weeks, our patient was admitted because of an impending thoracic paraplegia at the level of Th7. The patient was started on dexamethasone and received emergency radiotherapy (8 Gy) at Th 5-Th9 and L1-L4 and extensive radiation to the retroperitoneal mass. Treatment resulted in stabilisation of his neurological symptoms. After four days the patient developed a sudden tachypnoea with SpO2 92% and marked jugular venous distention. A chest X-ray showed bilateral pulmonary oedema. An ECG showed a sinus tachycardia of 148 bpm, with signs of left ventricular hypertrophy with abnormal repolarisation. Blood pressure was 110/70 mmHg. Transthoracic echocardiogram revealed severely impaired left ventricular function which was described as almost functionally asystolic (echocardiography images are available in the online supplement). There was no pericardial effusion and intravenous diuretics were started. The possibility of a Takotsubo-like cardiomyopathy as a result of catecholamine release by the paraganglioma was suggested. At the time of diagnosis, the patient's normetanephrine excretion in the urine was increased (normetanephrine 5558 µmol/mol creatinine (reference: 70-260 µmol/mol creatinine)), and the patient was subsequently given doxazosin 4 mg once daily to pre-emptively reduce potential blood pressure elevation. Until now, our patient had never displayed any clinical signs of excessive catecholamine production (e.g. hypertension or flushes); however, during the current admission he started complaining of sweats and palpitations. A urinary sample was collected to determine the current normetanephrine levels. The differential diagnosis included pulmonary embolism, but this was thought to be less likely because of the use of prophylactic low-molecular-weight heparin and an alternative explanation was sought. Meanwhile, the patient's condition deteriorated rapidly. Due to the underlying malignant disease without any therapeutic options, it was decided together with the patient and his family that inotropic support or admission to the intensive care unit was not an option. Eventually palliative sedation was started and our patient passed away the subsequent day. Autopsy surprisingly revealed a saddle embolus in the pulmonary artery. The heart was found to be enlarged (610 grams (reference: 330 grams in males)) with dilated, non-hypertrophic, ventricles, without obstructive coronary artery disease. DNA analysis revealed an SDHA-germ line mutation, explaining the occurrence of a malignant paraganglioma at our patient's young age. This rare mutation has a dominant autosomal inherence pattern. Currently there are only 14 known patients in the Netherlands with SDHA-germline mutations associated paragangliomas. The pathologist's first conclusion was: 'death as a result of pulmonary embolism'. However, the urinary sample came back revealing astounding amounts of normetanephrine (37,240 µmol/mol creatinine (reference: 70-260 µmol/mol creatinine)) and 3-methoxytyramine (8218 mmol/mol (reference 0.4-1.5 mmol/mol creatinine)). These results led to the second hypothesis of catecholamine-induced cardiomyopathy as we will now continue to discuss.

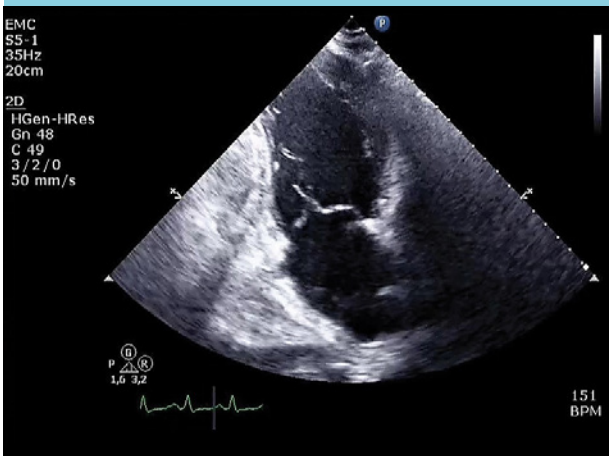
DISCUSSION

Catecholamine-secreting paragangliomas produce one or more catecholamines. The sensitivity of catecholamine measurement in plasma is limited by the episodic release from tumour cells.[5] A more accurate test involves measurement of metanephrines (normetanephrine and metanephrine) in plasma or urine.[6] These metabolites are produced continuously within the tumour, independent of intermittent catecholamine release. As depicted in the case report, the normetanephrine and metanephrine levels in our patient were raised dramatically. Assuming that our patient died as a result of cardiac failure and the formation of a pulmonary embolism due to excessive catecholamine release, the question arises whether this could have been prevented. Retrospectively, there were accumulating factors that might have negatively influenced the patient's outcome. First of all, the disease was rapidly progressive in this patient. Furthermore, little is known about the effects of radiation therapy in the treatment of malignant paraganglioma, which is usually reserved for inoperable or relapsed cases. Vogel et al.[7] showed that radiation therapy can be safely used in the case of skeletal metastasis, but no recommendations are available on soft-tissue metastasis. We hypothesise that extensive radiation on the surrounding retroperitoneal mass might have led to increased release of catecholamines from the tumour by cell lysis. The two chemotherapy cycles in this patient were not accompanied by haemodynamic changes, but perhaps insufficient cell lysis was induced, besides a 24-hour blood pressure measurement was never performed. Nevertheless, there might be a rationale for a higher degree of alpha-adrenergic receptor blockade during radiotherapy and chemotherapy for malignant pheochromocytoma/paraganglioma, similar to the preoperative treatment with doxazosin or phenoxybenzamine in patients with these disorders.[8] Secondly it is known that certain medications may alter catecholamine levels, such as dopamine D2-receptor antagonists, opioid analgesics,

Echo 1. *Subcostal, four chamber view showing a dilated left ventricle, no septal bulging (no signs of right ventricular pressure overload)*



Echo 3. *Apical two chamber view of the left ventricle and atrium; showing the anterior and inferior wall of the left ventricle and the apex (no typical ballooning)*



corticosteroids, β-adrenergic receptor blockers and SSRIs. On admission, our patient was on transdermal fentanyl, oxycodone immediate release (IR), dexamethasone, and metoclopramide. Because of the radiotherapy the dexamethasone dose was altered from 3 mg daily to 8 mg twice daily after a single intravenous bolus of 10 mg. Simultaneously fentanyl was raised from 50 to 100 µg along with oxycodone IR 20 mg six times a day. Of course these were sensible clinical actions but we cannot exclude exacerbation of catecholamine release. The acute management of catecholamine-induced cardiomyopathy should be aimed at lowering sympathetic activation by means of an α-adrenergic receptor blocker, diuretics in case of volume overload, β-blocker administration to slow the heart rate and increase end-systolic volume and anticoagulation with heparin to prevent left ventricular thrombus formation.[9]

CONCLUSION

We want to emphasise that clinicians should be aware of the potentially life-threatening increase in catecholamine release in paragangliomas during the course of disease and treatment. In the case of catecholamine-producing tumours we would advise to regularly check for clinical signs of raised catecholamine release (e.g. palpitations, diaphoresis, flushed of raised blood pressure (consider ambulatory blood pressure measurement)), consider increase of α-adrenergic receptor blocking medication prior to radiotherapy on soft-tissue metastasis, avoid medications that can raise catecholamine excretion and increase awareness among the medical staff with regard to the potential clinical signs of excess catecholamine levels in order to respond rapidly and, hopefully, avoid cardiovascular collapse.

Online supplement: echocardiography images of this patient, showing the severely impaired left ventricular function:
Echo 1. Subcostal, four-chamber view showing a dilated left ventricle with impaired function, no septal bulging (no signs of right ventricular pressure overload), and a reasonable longitudinal contractility of the right ventricle compared with the left ventricle
Echo 2. Short-axis, mid-ventricular view, again showing globally impaired contractility of the left ventricle
Echo 3. Apical two-chamber view of the left ventricle and atrium, showing the anterior wall of the left ventricle, the apex (no typical ballooning) and inferior wall
Echo 4. Apical three-chamber view, showing the aortic valve and aortic root and the impaired contractility of the anterolateral and posterior walls of the left ventricle

DISCLOSURES

The authors declare no conflict of interests.

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PHOTO QUIZ

A relapsing swelling of the nasal tip

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CASE REPORT

The dermatologist referred a 59-year-old male to the otorhinolaryngology department for further analysis of a progressive, intermittent tingling and swelling of the left nasal tip. His symptoms started one year before without any preceding trauma. Local skin biopsy had revealed signs of rosacea telangiectatica, insufficiently explaining these symptoms. Physical examination showed a solid, subcutaneous swelling with a diameter of 1.5 cm in the area of the left lower lateral cartilage. A more prominent columellar show on the ipsilateral side was suggestive of skin retraction, either secondary to the biopsy or to the lesion (*figure 1*). Inflammatory parameters and autoimmune markers were normal (WBC, CRP, ESR, p- and cANCA, rheumatoid factor, anti-CCP, ANA and subtypes). To rule out a malignancy causing skin retraction an external rhinoplasty was performed, exposing amorphous irregular cartilage on the vestibular side of the lower lateral cartilage, which was resected (*figure 2*). Histologically, the cartilage was irregular, covered by fibrous connective tissue and perivascular inflammatory cells.

What is your diagnosis?

See page 488 for the answer to this photo quiz.

Figure 1 *Frontal and basal view of the nose showing the lesion (dashed yellow circle and asterisk). Left and right profile view showing increased columellar show caused by alar retraction (area between yellow lines)*

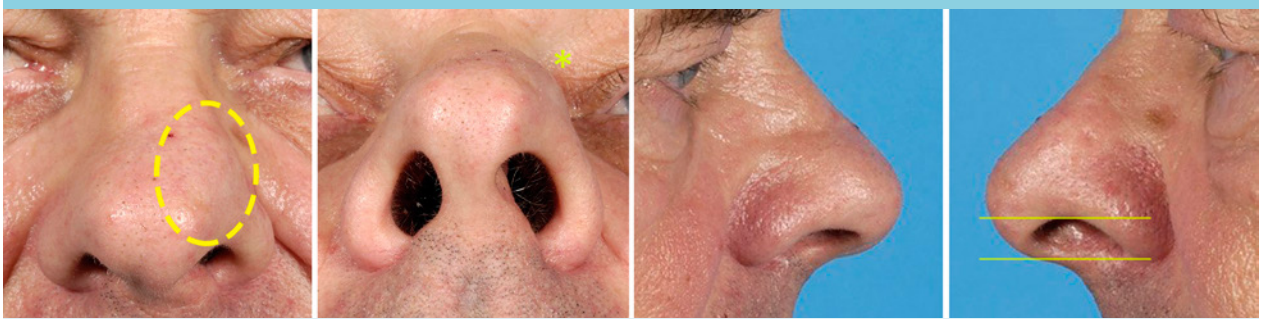
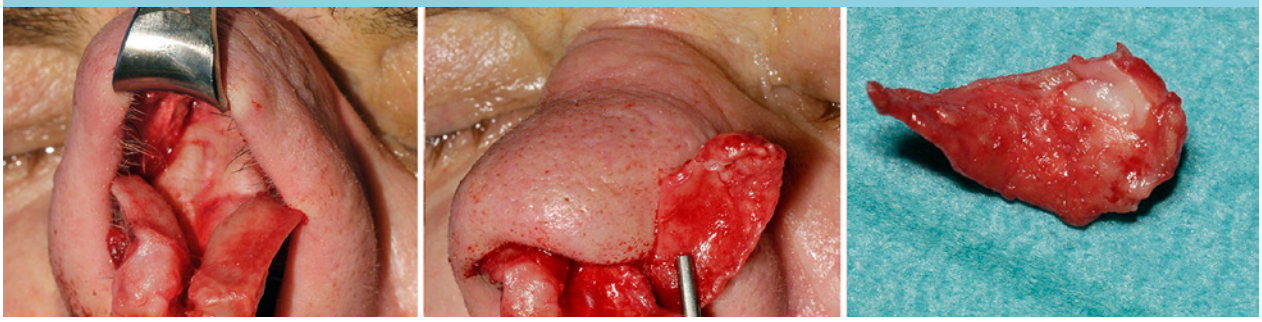


Figure 2 *Elevated skin-soft tissue envelop exposing the cartilaginous framework of the nasal tip. While the dorsal side appears normal (left), the vestibular side of the lateral portion of the lower lateral cartilage shows irregularities (middle). The irregular part was resected (right)*



ANSWER TO PHOTO QUIZ (PAGE 487)

A RELAPSING SWELLING OF THE NASAL TIP

DIAGNOSIS

The histological diagnosis was relapsing polychondritis. The same diagnosis was made after sample revision in a second academic teaching hospital. The patient initially responded well to a tapered two-week dose of 20 mg prednisone but his symptoms reappeared after two months. In the following two years, the patient was symptom-free using immunosuppressive medication (first prednisone and methotrexate and later prednisone, dapsone and mycophenolate) but he gradually developed dyspnoea and general weakness, considered to be side effects of the medication. While lowering the immunosuppressive dose, his nasal symptoms fully reappeared. Eventually a revision rhinoplasty was performed in which the remaining lower lateral cartilage was resected and replaced with unaffected conchal ear cartilage (*figure 3*). Histology revealed a resting phase of relapsing polychondritis. One year following surgery, the patient remains free of symptoms without immunosuppression and with a normal form and function of the nose.

Relapsing polychondritis is classified as a rare immune-mediated disease of unknown aetiology and in some cases is associated with connective tissue, autoimmune, rheumatological and malignant disorders.[1] The wide variety of clinical manifestations and lack of disease-specific laboratory findings make relapsing polychondritis difficult to diagnose and frequently causes a diagnostic and therapeutic delay. At the moment, reviews and case reports help us to get a better understanding of disease presentations and response to a variety of treatment modalities.[2-4] We hope that this unusual presentation and surgical management of a 'relapsing monochondritis' forms an addition to our understanding of the disease.

Figure 3. *Elevation of the skin-soft tissue envelope during second open rhinoplasty (left). The left lower lateral cartilage was completely resected and replaced with conchal cartilage of the right ear (right)*

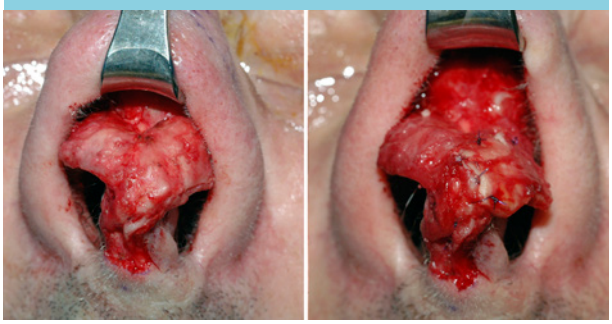


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PHOTO QUIZ

A 65-year-old female with poorly controlled type 2 diabetes mellitus

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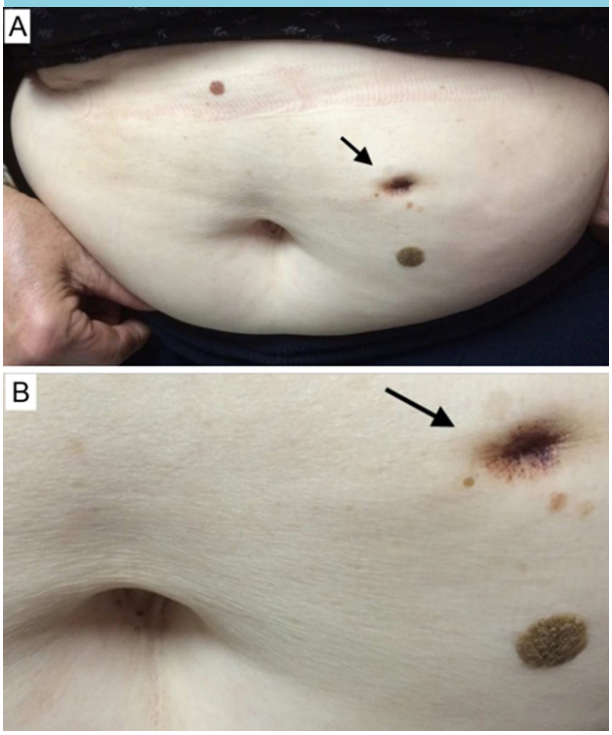
CASE REPORT

A 65-year-old female was diagnosed with type 2 diabetes mellitus two years earlier, after she had suffered an ischaemic stroke. Her post-stroke disability resolved completely. She was prescribed metformin and premixed insulin analogue (aspart + aspart-protamine) twice daily after clear instructions were given. The patient's general practitioner continued medical care and scheduled her control visits. The patient was adherent to the insulin therapy, but did not reach target glucose levels despite the use of 90 units daily. The general practitioner made a telephone consultation with our centre and confirmed that the patient did not have any technical complaints regarding the insulin therapy. We instructed the general practitioner to switch to a thrice daily premixed insulin analogue regimen and to increase the dose to 125 units daily. Nevertheless, her glycated haemoglobin level remained above 9.5%. The patient was finally referred to our centre and was asked to demonstrate her insulin injection technique. The patient confirmed that she had been injecting insulin consistently in the same area over the two-year period. A painless, necrotic skin lesion with no signs of acute inflammation was found at the injection site in the periumbilical abdominal wall (*figure 1A and B*).

Figure 1. *Periumbilical skin defect consistent with necrotic insulin-induced lipoatrophy (A,B)*



What is your diagnosis?

See page 490 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 489)

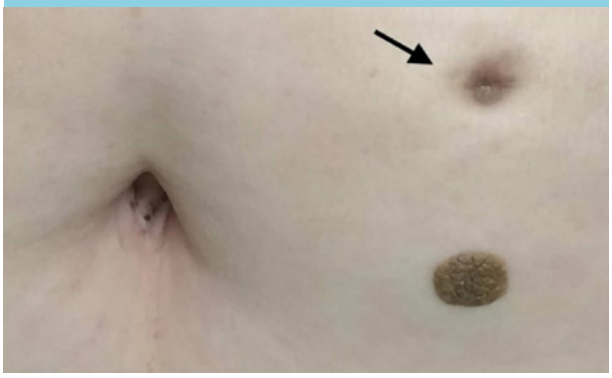
A 65-YEAR-OLD FEMALE WITH POORLY CONTROLLED TYPE 2 DIABETES MELLITUS

DIAGNOSIS

Although the patient did not allow us to perform a skin biopsy, the findings were consistent with severe necrotic insulin-induced lipoatrophy. We told her that it is mandatory to rotate injection sites and the dose of premixed insulin was decreased to 68 units daily. Four months later, her glycated haemoglobin level had decreased to 7.1%, along with marked improvement in the lipoatrophic area (*figure 2*).

Some patients tend to use the same injection site, since it leads to reduction of pain sensation. However, this increases the risk of dermatological complications of insulin therapy: insulin-induced lipohypertrophy and lipoatrophy.[1] Lipohypertrophy is far more common, but both conditions may lead to poor glycaemic control. Insulin-induced lipoatrophy is considered to be an immune complex-mediated inflammatory lesion.[1] Any insulin formulation can in principle cause lipoatrophy. The prevalence of this condition was 2.5% in patients who used older bovine and porcine insulins.[2] But its prevalence has tremendously decreased with the use of newer insulin analogues.[3] Only 13 cases associated with the use of lispro, aspart, glargine or detemir insulin have been reported so far.[3] There are no strict guidelines for the treatment of lipoatrophy. Topical disodium cromoglycate, topical and systemic glucocorticoids have been occasionally used for the treatment of insulin-induced lipoatrophy.[4] However, randomised clinical trials have not been performed to assess their true efficacy. Rotation of injection sites has the most important role in lipoatrophy treatment, as seen in our case. In conclusion, it is important for clinicians to recognise lipoatrophy as a potential complication of therapy with insulin analogues, since it may lead to impaired insulin absorption and poor glycaemic control.

Figure 2. *Improvement of lipoatrophic defect after rotation of insulin injection sites*



INFORMED CONSENT

The patient gave her written consent for this case study.

DISCLOSURES

The authors declare that they have no conflict of interest. This research did not receive any financial support.

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