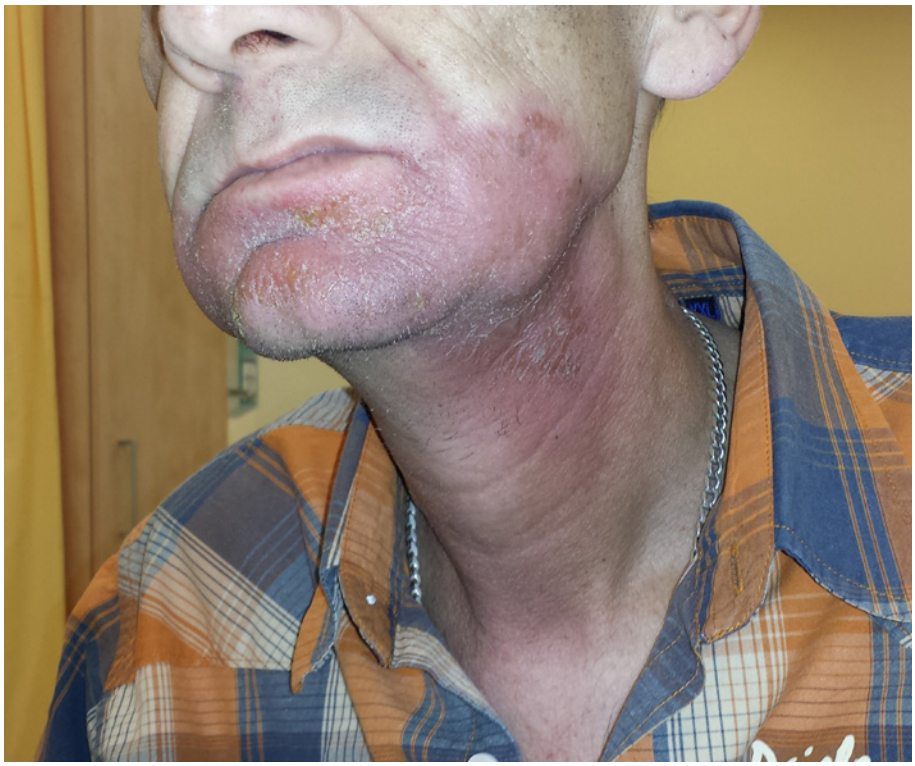
The Netherlands Journal of Medicine

PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE



Acute facial erythema following methotrexate administration; what is your diagnosis?

January 2016, VOL. 74, NO. 1, ISSN 0300-2977

VAN ZUIDEN COMMUNICATIONS

The Netherlands Journal of Medicine

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ISSN: 0300-2977

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LETTERS TO THE EDITOR

EDITORIAL

Pamidronate in complex regional pain syndrome: effective therapy in CRPS

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Complex regional pain syndrome (CRPS) is a debilitating disorder of which the underlying pathogenesis is poorly understood. Often, after trivial trauma, patients develop severe signs of pain and autonomic dysfunction in the affected limb leading to substantial loss in quality of life. Women are more often affected than men.
CRPS is mostly monophasic but some patients develop a relapsing remitting course.[1] A small group of patients develop chronic symptoms that can be so severe that ultimately amputation appears to be the sole solution. Two forms of CRPS can be distinguished: type I and type II. Different from CRPS type II, in type I no nerve damage can be demonstrated.

Although the underlying pathogenesis is not well known, inflammation is often considered the hallmark of the disease, but central sensitisation is probably also important. Dirckx et al. indicated the importance of mast cells in the pathogenesis of the disorder.[2]

In the past, various anti-inflammatory treatments have been tried with varied success. Remarkably, in a meta-analysis by Wertli et al., not immunosuppression but drugs usually used in disorders of calcium and bone metabolism appeared to be most effective in reducing pain.[3] Especially bisphosphonates were able to reduce pain in both early and longstanding disease. The effect of bisphosphonates is thought to be twofold. Bisphosphonates exert an effect on bone cells but probably also work in an anti-inflammatory manner. Other drugs that have been tried include anti-TNF, thalidomide and mannitol.

Although most cases of CRPS appear to be associated with trauma, CRPS can also develop after stroke. Petchkrua et al. calculated the incidence of CRPS after stroke to be 1.56%.[4]

In the current issue of the journal, Eun Young et al. describe the effect of treatment with pamidronate on patients with CRPS type I following stroke and compare the effect with that of a two-week, high-dose corticosteroid treatment.[5] The results showed pamidronate to be as effective as corticosteroids to reduce pain in this group, but corticosteroids were somewhat better at reducing swelling. In their discussion, the authors suggest to use pamidronate in patients whose dominant symptom is pain and to combine pamidronate with steroids in those who suffer from severe swelling. As the authors state, corticosteroids have substantial side effects in a group of patients with cardiovascular disease. Alternatives for corticosteroids are available. In a very small study, anti-TNF treatment appeared to reduce symptoms as well.[6] However, anti-TNF treatment is expensive. Combining anti-TNF with pamidronate might be more interesting when human studies corroborate the findings in animal studies that anti-TNF might protect the brain from ischaemic damage.[7]

For now, pamidronate appears to be the drug of choice in both post-traumatic and post-stroke CRPS type I. However, as with many illnesses, therapy should not be restricted to only providing medication. A multidisciplinary approach involving pain management, physiotherapy and cognitive behavioural therapy next to drug treatment is most likely to benefit patients.

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ORIGINAL ARTICLE

Safety and long-term effects of renal denervation: Rationale and design of the Dutch registry

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ABSTRACT

Background: Percutaneous renal denervation (RDN) has recently been introduced as a treatment for therapy-resistant hypertension. Also, it has been suggested that RDN may be beneficial for other conditions characterised by increased sympathetic nerve activity. There are still many uncertainties with regard to efficacy, safety, predictors for success and long-term effects. To answer these important questions, we initiated a Dutch RDN

registry aiming to collect data from all RDN procedures performed in the Netherlands.
Methods: The Dutch RDN registry is an ongoing investigator-initiated, prospective, multicentre cohort study. Twenty-six Dutch hospitals agreed to participate in this registry. All patients who undergo RDN, regardless of the clinical indication or device that is used, will be included. Data are currently being collected on eligibility and screening, treatment and follow-up.
Results: Procedures have been performed since August 2010. At present, data from 306 patients have been entered into the database. The main indication for RDN was hypertension (n = 302, 99%). Patients had a mean office blood pressure of 177/100 (±29/16) mmHg with a median use of three (range 0-8) blood pressure lowering drugs. Mean 24-hour blood pressure before RDN was 157/93 (±18/13) mmHg. RDN was performed with different devices, with the Simplicity™ catheter currently used most frequently.
Conclusion: Here we report on the rationale and design of the Dutch RDN registry. Enrolment in this investigator-initiated study is ongoing. We present baseline characteristics of the first 306 participants.

KEYWORDS

Blood pressure, cardiovascular disease, hypertension, kidney function, renal denervation

INTRODUCTION

Renal denervation

Percutaneous renal sympathetic denervation (RDN) is currently being used as a potential treatment for therapy-resistant hypertension and other conditions associated with increased sympathetic activity. The treatment aims to disrupt afferent and efferent nerves travelling around the renal artery with the intention to lower systemic sympathetic activity.

At the beginning of the initiative for the current registry in 2010, RDN was an upcoming therapy for resistant hypertension. The initial report in *The Lancet* showing the results from the first 50 patients, was followed by great enthusiasm for RDN.[1] Because of many uncertainties at that time and still, we initiated a national registry.

Since 2009, a range of studies has been conducted including many cohort studies (uncontrolled) and some randomised controlled trials. Almost all studies reported a significant decrease in blood pressure, six to twelve months after the procedure.[1-5] However, not all trials showed superiority of RDN when compared with a control group.[6,7] The largest, the Simplicity HTN-3 trial, a randomised, blinded trial, showed no statistically significant effect of RDN compared with a sham procedure and so the RDN landscape changed in 2014.[7] A recently published meta-analysis acknowledged the safety of the procedure and argued for the identification of responders in future trials.[8]

Effects

Not only blood pressure effects have been studied; various cohort studies showed positive results on other aspects, such as an improvement in glucose metabolism and cardiac function.[9,10] Although these studies were not properly controlled, the findings are in line with the pathophysiology.[11,12] Since nerve ablation is non-selective, one can imagine that sensory nerves will also be affected. Case reports have been published in which patients with kidney-related pain syndromes were successfully treated by RDN.[13,14]

Predictors

Effort has been made to identify characteristics, both patient and procedure related, that seem to predict a better outcome after RDN. For example, the use of aldosterone antagonists, the number and location of ablations, office systolic blood pressure at baseline, the estimated glomerular filtration rate (eGFR) and the presence of diabetes mellitus have been mentioned as predictors for efficacy of RDN.[15-19] Most of these possible predictors could not be confirmed in other studies or even contradicting relations were suggested.[15,17,18,20] These conflicting data underscore the need for more extended research.

Safety

Overall, the intervention appeared to be safe. Some cases of renal artery stenosis during follow-up were reported. The reported rates of vascular complications range from 0.3% to 4.3%.[4,7,20-23] Time between procedure and renal artery imaging varied from six months to three years. Three years is the longest follow-up after RDN that has been described in literature, for both efficacy and complication rate.[21,24] To date, there are no reports on the effects of RDN on the cardiovascular event rate or mortality.

Registration

It is clear that there are still many uncertainties with regard to patient selection, effectiveness and complications, especially long-term outcomes. Available information is predominantly based on small and strictly selected patient groups. Follow-up details are scarce and reports on the comparison of different devices, or on consistently shown predictors for success, are lacking. The Dutch RDN registry initiative is designed to combine all Dutch data on RDN from routine clinical practice in order to contribute to clarifying the effects of this treatment.

OBJECTIVES

The main goal is to collect data concerning three important issues: safety, predictors for success and the long-term effects of RDN.

Safety

1. What are the short- and long-term procedural-related complications?

Predictors

2. What are the predictors for a beneficial effect on blood pressure, in particular patient-related factors and procedural-related factors?
3. Is the effectiveness of the currently available RDN devices comparable?

Long-term effects

4. What is the effect on blood pressure at various time points, up to at least five years after RDN?
5. What is the effect on kidney function at various time points, up to at least five years after RDN?
6. What are the cardiovascular event rates, in strata of achieved blood pressure level?

MATERIALS AND METHODS

Design and population

The Dutch RDN registry is an ongoing investigator-initiated, prospective, multicentre cohort study. Twenty-six Dutch hospitals agreed to participate in this registry (*Appendix A*). This is approximately 28% of all hospitals in the Netherlands and includes, to our knowledge, all hospitals in which RDN is being performed. Despite willingness to share data on RDN, not all participating centres have entered data at the time of writing. All patients who underwent RDN, regardless of indication for RDN or the device that was used, are to be included in the registry. Patients must be at least 18 years of age, but there are no other specific inclusion or exclusion criteria. The indication for RDN is left to the discretion of the treating physician. Endpoint analyses will be stratified according to indication for treatment, and analyses on safety and long-term effects will be performed based on the total cohort. The registry was originally initiated to include 1000 patients within 36 months, with a minimal duration of five years. Given the current enrolment rate, this period is being extended.

Sample size considerations

At the start of the registry, several sample size considerations were discussed, based on addressing the research questions. With 1000 participants we estimated to detect a procedural complication rate of at least 1% with sufficient precision (between 0.38% and 1.6%). Based on the reports by Esler et al., 8% of the participants who underwent RDN actually increased usage of blood pressure lowering drugs.[2] In the same study, 10% of the patients who underwent RDN had a systolic arterial pressure drop < 10 mmHg. If these findings are consistent, we expect that 80-100 patients in our cohort of 1000 patients can be considered to be 'failures' or 'non-responders'. This would allow for the evaluation of 8-12 factors for the development of a prediction rule to estimate the risk of failure based on baseline characteristics.[25-28] Importantly, to be able to identify responders, we believe that blood pressure change after RDN should be adjusted for the change in blood pressure lowering medication.

With regard to the long-term effects, we assume to have sufficient precision to estimate treatment effects on blood pressure and renal function overall and for various subgroups (age, sex, baseline blood pressure, renal function). Furthermore, event rates observed in the registry will be compared with unpublished estimates of cardiovascular event risks in patients with therapy-resistant hypertension, obtained from existing Dutch cohorts (approximately 8% (95% CI 6.3, 9.6)) within three years.[29,30] Potential confounding factors will be taken into account. We will be able to detect an event rate of 5% (95% CI 3.6, 6.4) or lower in the RDN cohort, which means a statistically significant reduction in cardiovascular risk.

Baseline, procedure and follow-up

Information from the first visit to the outpatient clinic and subsequently the investigations to determine eligibility will be collected (*table 1*).

Recommended follow-up visits are at 3, 6, 9, 12, 18, 24, 30, 36, 48 and 60 months after RDN. We aim to continue annual follow-up of the patients after these 60 months as well. *Table 1* shows a list of proposed pre-procedural, procedural and follow-up variables that are recommended to be registered. All participating centres received the list of variables at the start of the study. This can be used as a guideline and is not mandatory. Nevertheless, some data are specifically recommended and part of the standard care in most hospitals following the Dutch guideline on RDN:[31] office blood pressure and heart rate (both as a mean of three measurements), serum creatinine, weight and data on medication use, events and complications. Moreover, 24-hour ambulatory blood pressure measurement data are collected, as is annual measurement of urine creatinine and protein levels and imaging of the kidneys (and renal arteries) at 12 and 36 months. For follow-up imaging, the same modality as during screening for eligibility is preferably used.

As stated before, most objectives and therefore most information will be gathered from patients who suffer

Table 1. *Measurements, laboratory testing and imaging variables, largely as part of routine clinical care in the Netherlands*[31]

	Parameters	Time points
Patient characteristics and history	- Age, sex, medical history, height - Medication review, weight, complaints, renal or cardiovascular events requiring admission	First visit Every visit
Blood pressure and heart rate	- Office BP and heart rate (average of 3 readings) - Orthostatic hypotension test - 24-hour ABPM	Every visit 6 months Pre-procedural and annually
Renal imaging	MR angiography *or* CT angiography *or* Angiogram *or* Duplex ultrasound	Pre-procedural, 12 and 36 months
Laboratory testing: blood	- Sodium, potassium, creatinine, haemoglobin, CRP, insulin, C-peptide, glucose, cholesterol, triglycerides, HDL, LDL, norepinephrine, ACE, renin, aldosterone - Creatinine	Pre-procedural Every visit
Laboratory testing: urine	- Sample: Creatinine, albumin, C/A ratio - 24-hour collection: Sodium, potassium, creatinine, protein, albumin, catecholamines, cortisol	Annually Pre-procedural
Renal denervation	Treated arteries, successful ablations, ablation time, mean temperature, mean impedance drop, mean power, periprocedural complications, device used, amount of contrast and radiation used	Procedural

BP = blood pressure; ABPM = ambulatory blood pressure measurement; MR = magnetic resonance; CT = computed tomography; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ACE = angiotensin converting enzyme; C/A = creatinine/albumin.

from therapy-resistant hypertension and we expect this to be the predominant indication for RDN. Event follow-up (defined below) is obtained in two ways. Firstly, information is collected through the data entry in the database by the individual investigator. Secondly, the dataset is linked with the Dutch Hospital Discharge Register (HDR) (the LMR) and with Statistics Netherlands (the CBS) to obtain information on hospital discharge diagnoses and causes of death, respectively.

Outcome parameters, definitions and data analysis

Outcome of the stated objectives will be based on the following parameters.

Short-term procedural complications: haematoma, bleeding, false aneurysm, renal artery perforation or dissection, renal failure, adverse contrast effects, infection, and death. This will be presented as percentages by age and sex with corresponding 95% confidence limits. Additional analyses will be performed to relate patient characteristics to the risk of short-term complications. For these analyses, multilevel multivariable (logistic) regression models will be used.

Long-term procedural and effect complications: renal artery stenosis or other vascular complications, decline in kidney function, (orthostatic) hypotension. Data will be presented as incidence rates (per person-years of follow-up) by age and sex with 95% confidence limits. Additional analyses will be performed to relate patient characteristics and procedural aspects to the risk of short- and long-term complications using multilevel multivariable regression models. Results will be reported as hazard ratios with corresponding 95% confidence limits.

Change in blood pressure and kidney function at various time points: change over time will be analysed by use of linear mixed-effects models. Factors that contribute to the initial effects and to the long-term effects will be assessed. ('Responder' has already been defined). Multilevel multivariable regression models will be used to explore the relation between responders and non-responders and baseline characteristics /procedural characteristics. Results will be presented as hazard ratios with corresponding 95% confidence limits. Stratified analyses will be performed in strata of 'blood pressure measurement with and without being on medication'. The results from the regression model will be used to make a prediction rule with which the absolute probability of success or failure will be estimated from baseline characteristics.

Safety analyses and effectiveness endpoints stratified per device: the different devices will be related to the magnitude of the blood pressure change using univariable

and multivariable regression models. Multilevel multivariable regression models will be used to adjust for potential confounding (by indication) variables.
Rate of events requiring admission: acute coronary syndrome, transient ischaemic attack, ischaemic or haemorrhagic cerebrovascular accident, peripheral arterial ischaemia, congestive heart failure, renal failure and mortality. Analyses with regard to risk of events, in strata of baseline and/or follow-up characteristics, will be performed using multilevel multivariable regression models.
Furthermore, as a general approach, in all analyses differences across centres will be explored.

Ethical considerations
The registry is being conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (the WMO). Patients are informed about the procedure by their treating physician. This registry is approved by the Medical Research Ethics Committee of the University Medical Centre Utrecht and registered at ClinicalTrials.gov: NCT02482103.

Data management
All data are entered into a web-based electronic Case Report Form. Data management is performed by the Julius Center for Health Sciences and Primary Care at the University Medical Centre Utrecht, Utrecht, the Netherlands.

Sponsoring
This study is initiated and supported by the University Medical Center Utrecht in the Netherlands. Funding is in part obtained from the Dutch Kidney Foundation (Nierstichting), project number CPI12.02.

RESULTS

General description
On 23 March 2015, data of 306 patients had been entered into the database (inclusions per centre are shown in Appendix B). Procedures have been performed since August 2010. *Table 2* shows the available baseline characteristics of these patients, enrolled by 20 hospitals. In 302 patients, the indication for RDN was hypertension. Four patients were treated because of kidney-related pain syndromes.

Blood pressure
Blood pressure is shown as office measurements and as 24-hour measurements when available (*table 3*). In almost half of the patients, the 24-hour measurement was performed during a period of partial or complete medication stop, due to centre-specific investigations.[32] The overall mean systolic 24-hour blood pressure was 157±18 mmHg. Approximately 25% of the patients had a mean daytime systolic blood pressure of more than 175 mmHg. Mean office blood pressure was 177±29 mmHg.

Medication
In *table 2* the medication details are presented. The prescribed medications of the patients who temporarily stopped their treatment are taken into account in this table. Therefore, medication use corresponds with office blood pressure values but not with 24-hour values. The most commonly used drugs were renin-angiotensin-aldosterone system (RAAS) inhibitors (79%), diuretics (70%), calcium-channel blockers (64%), beta-blockers (61%) and alpha-blockers (23%). The use of other blood pressure lowering drugs (centrally-acting sympatholytic agents, direct-acting vasodilating drugs and nitrates) was low (11%). Aldosterone antagonists (mainly spironolactone) were used by 25% of the individuals. The median number of prescribed antihypertensive drugs was three, ranging from 0-8, with a mean daily use of 5.4±3.7 units. Interestingly, 14 patients did not use any blood pressure lowering drugs at all. Five of these patients were intolerant to many different drugs. Another five of these patients have never used any antihypertensive drugs, due to borderline hypertension. Of the remaining four patients, it was unknown why no antihypertensive drugs were prescribed.

Device
The most frequently used device for RDN was the Symplicity™ catheter (Medtronic, Santa Rosa, CA, USA) (88%). Apart from the Simplicity™ catheter, four other devices were used in more than 10% of the cases.

Comorbidities
The presented comorbidities in *table 2* are based on the medical history (not on medication use). Dyslipidaemia was present in 42% of the cases and approximately 21% of the patients were diagnosed with diabetes mellitus.

DISCUSSION

We report the first baseline characteristics from an investigator-initiated national registry for RDN. The Dutch RDN registry strives for complete coverage, which means that all patients who underwent an RDN procedure in the Netherlands are to be included. Inclusion is not restricted by specific criteria. Therefore, these data represent real-world clinical practice of RDN in the Netherlands.
The main underlying reason for this initiative is that including the data from all centres and all patients in

Table 2. *Selection of baseline characteristics from participants in the Dutch RDN registry*

	All patients (n=306)
Age (years)	59 (±11)
Sex (male/female)	165/141
Indication	
Hypertension	302 (99%)
Pain	4 (1%)
eGFR (ml/min/1.73 m²)	82 (±20)
eGFR<60	12%
Body mass index (kg/m²)	29.4 (±5.0)
Comorbidity	
Dyslipidaemia	42%
Diabetes mellitus type 2	21%
Cardiovascular diseases	21%
Cerebrovascular diseases	11%
Device used	
Medtronic Symplicity™	88%
EnligHTN™ SJM	9%
OneShot™ Renal Denervation System[a]	1%
Vessix™ Renal Denervation System[b]	1%
Other	0.5%
No. of antihypertensive drugs	3 (0-8)
Daily use (units)[c]	5.4 (±3.7)
RAAS inhibitor	79%
ACEi	33%
ARB	48%
Renin inhibitor	9%
Double RAAS inhibition	8%
Calcium channel blocker	64%
Beta-blocker	61%
Alpha-blocker	23%
Diuretic	70%
Aldosterone antagonist	25%
Other blood pressure lowering drugs	11%

Continuous variables are presented as a mean (±SD) or as median (range). Categorical variables are presented as absolute number and/or percentage. eGFR = estimated glomerular filtration rate; RAAS = renin-angiotensin-aldosterone system; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker. [a]Covidien, Mansfield, MA, USA. [b]Boston Scientific, Marlborough, MA, USA. [c]calculated by use of conversion factors as provided by the World Health Organization (http://www.whocc.no/atcddd/).

Table 3. *Baseline blood pressure values*

	All patients (n = 306)
Office blood pressure	
Systolic (mmHg)	177 (±29)
Diastolic (mmHg)	100 (±16)
Ambulatory blood pressure	
24-hour systolic (mmHg)	157 (±18)
24-hour diastolic (mmHg)	93 (±13)
24-hour heart rate (bpm)	74 (±12)
Daytime systolic (mmHg)	162 (±19)
Daytime diastolic (mmHg)	97 (±13)
Nighttime systolic (mmHg)	146 (±20)
Nighttime diastolic (mmHg)	84 (±13)
Mean daytime blood pressure categorised	
Systolic <135 (mmHg)	3%
Systolic 135-154 (mmHg)	34%
Systolic 155-174 (mmHg)	38%
Systolic ≥175 (mmHg)	25%

Continuous variables are presented as a mean (±SD). Categorical variables are presented as percentage; bpm=beats per minute.

one study provides faster and more valuable insight into complications and effectiveness when compared with single-centre reports with relatively small numbers of patients. This is especially important for RDN since this new procedure is at the beginning of evaluation in routine clinical practice. Furthermore, a registry may lead to uniformity in data collection, which allows for pooling of the data. Finally, for identification of predictors of response, a large number of patients is needed.

Globally, RDN has been performed on a large scale. Unfortunately, only a fraction of the treated patients has been adequately registered. We estimate, based on correspondence with manufacturers and hospitals, that approximately 70% of the performed procedures in the Netherlands are currently included in this registry. Several registries exist world-wide, of which the Global SYMPLICITY registry, initiated by Medtronic, contains the largest number of patients. Its baseline data were published in 2013 and the first results in 2015.[33,34] An important aspect is that the Symplicity™ catheter was exclusively used in the Global SYMPLICITY registry. Due to former reimbursement policies, this device was also most frequently used in the Netherlands up to 2014. Since late 2014, the multi-electrode EnligHTN™ catheter

Table 4. *Overview of renal denervation registries from PubMed, Google and trial registers as of 1 June 2015*

Registry name	Publications	Recruiting	Single/multi centre	Initiator	Device used
Global SYMPLICITY Registry (incl. GREAT from Germany)	2014[33]	Yes	Multi	Medtronic	Symplicity™
UK Renal Denervation Affiliation (UK)	No[1]	Yes	Multi	Investigator	No restriction
IRRD (Italy)	No[2]	Yes	Multi	Investigator	Unknown
Heidelberg registry (Heidelberg, Germany)	2014[37]	Unknown	Single	Investigator	Symplicity™
ALSTER BP registry (Hamburg, Germany)	2014[17]	Yes	Single	Investigator	Symplicity™
Symplicity Venezuelan Registry (Venezuela)	Poster abstract JACC 2013[3]	Unknown	Multi	Investigator	Symplicity™
RDN-POL (Poland)	Presentation at LINC 2013[4]	Unknown	Multi	Investigator	Symplicity™
RDN registry (Lisbon, Portugal)	2014[38]	Unknown	Single	Investigator	No restriction
TREND (Austria)	Abstract J. für Hypertonie 2014[5]	Yes	Multi	Investigator	No restriction
IBERIS – HTN Registry	No[6]	Yes	Multi	Terumo Europe N.V.	Iberis™ system
OneShot Renal Denervation Registry	No[6]	No	Multi	Covidien	OneShot™ System

1: http://www.era-edta2015.org/en-US/free-communication-11;
2: http://www.ashabstracts.com/abstract.asp?MeetingID=797&id=105818;
3: http://content.onlinejacc.org/article.aspx?articleid=1759802;
4: http://www.leipzig-interventional-course.com;
5: http://www.kup.at/kup/pdf/12463.pdf;
6: https://www.clinicaltrials.gov

(St Jude Medical, St Paul, MN, USA) has also been approved for conditional reimbursement.

In the literature, RDN was introduced as treatment for therapy-resistant hypertension, defined as a blood pressure ≥ 140/90 mmHg despite appropriate lifestyle measures and the use of a diuretic and two other antihypertensive drugs (adequately dosed).[35] These data show that in clinical practice, this definition was not guiding the selection of patients: several patients did not use three or more drugs and diuretics were only prescribed in 70% of the cases.

There are few other RDN registries that we are aware of. *Table 4* gives an overview of the results of our search in PubMed, trial registers and Google on 1 June 2015, using the search terms "renal denervation" and "registry". Multicentre investigator-driven registries for RDN regardless of device, such as the present registry, seem to be scarce. However, we may not have found all registries using the above-mentioned sources and search terms. It is of importance to note that patients registered in our registry can also be registered elsewhere, since it is up to the principal investigator of the centre to decide whether or not to participate in other registries. This is a relevant issue when data from various registries are pooled. The Dutch registry and the Global SYMPLICITY registry differ in several ways, for example with regard to comorbidities and prescribed drugs. In the Global SYMPLICITY registry, the prevalence of diabetes mellitus and chronic kidney disease is considerably higher (41% vs. 21% and 22% vs. 12% in the Dutch RDN registry) and sympathetic blocking agents, both beta-blockers and centrally-acting sympatholytic drugs, are prescribed far more often (77% vs. 61% and 40% vs. < 11% in the Dutch RDN registry).

Although hypertension is the main indication for RDN in the majority of patients, the dataset contains a few patients who underwent RDN to treat kidney-related pain syndromes. So far, percutaneous RDN for this specific indication has only been described in case reports.[13,14]

Furthermore, the Dutch registration aims to collect detailed procedural information that might be related to outcome. In the literature, several procedural aspects have been related to a better outcome. A previous study revealed a positive correlation between the number of ablation points and the reduction in office blood pressure after RDN.[15] Also a positive relation between the ablation

points placed close to the kidney and the reduction in blood pressure was found.[15,16] Follow-up data from the RDN registry might contribute to these findings.

Methodological challenges

The initiation of a national registry using data that are routinely collected has a number of methodological challenges that may hamper the validity of the findings. Without being exhaustive, a few important ones are mentioned. Firstly, the issue around 'confounding by indication', that is the effect of patient selection on the outcome of the study, is likely to be of importance, especially when investigating predictors for success.[36] Measurement of potential confounders may take away part of the problem.

Secondly, differences across centres in contribution to the registry (size) and difference in measurement protocols are inevitable, but may prove to be important. Therefore, as mentioned in the 'Materials and Methods' section, differences across centres will be explored in all analyses.

The third challenge, especially in RDN, is adherence to medication. Our registry in its current phase is based on routine clinical practice. In that setting, information on adherence is not routinely collected. In addition, tools to monitor adherence all have their limitations, and drug levels in blood are generally not measured in these patients.

CONCLUSION

Renal denervation is a promising treatment for patients suffering from therapy-resistant hypertension or other diseases related to sympathetic overactivity. The Dutch RDN registry is a collaboration of 26 hospitals in the Netherlands, initiated with the intention to increase our knowledge of this therapy by pooling data of all patients treated with RDN in the Netherlands. Combining data from all centres in one registry should result in faster and more valuable insight into complications and effectiveness, when compared with single-centre cohorts. At the time of writing, 306 patients have been included. Detailed analyses will follow, reporting on safety, effectiveness, predictors of response and potential differences between currently available devices.

DISCLOSURES

M.F. Sanders has nothing to disclose. P.J. Blankestijn reports grants from the Dutch Kidney Foundation during the conduct of the study; grants from Medtronic and St. Jude, other from Medtronic and St. Jude, grants from ZonMw (The Netherlands Organisation for Health Research and Development) outside the submitted work. M.L. Bots reports grants from the Dutch Kidney Foundation during the conduct of the study; grants from Medtronic and ZonMw (The Netherlands Organisation for Health Research and Development) outside the submitted work. The other authors have nothing to disclose.

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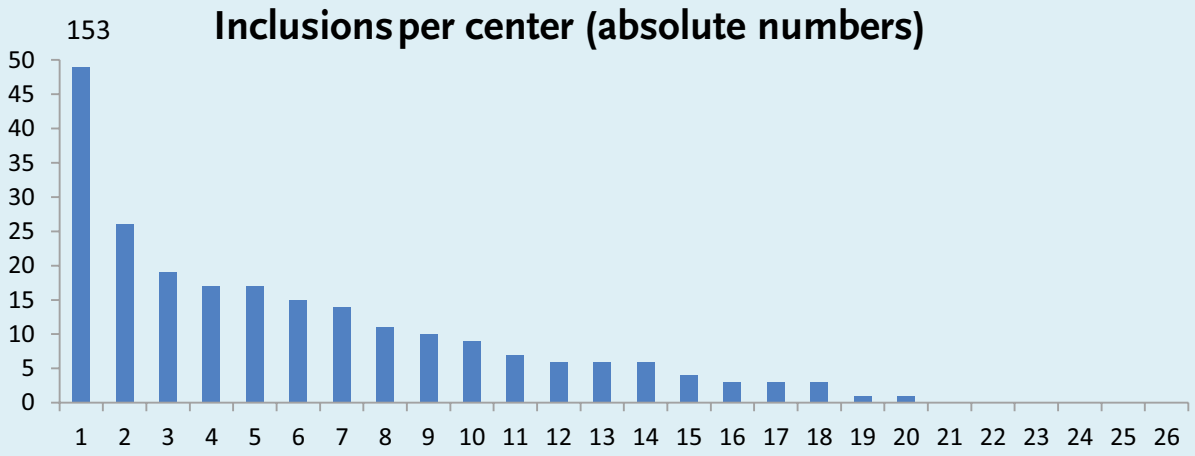
Appendix A. *Participating centres (alphabetical order)*

Academic Medical Center	Amsterdam	B.J.H. van den Born[1], MD, PhD P.M. van Brussel[2], MD [1]Department of Internal Medicine [2]Department of Cardiology
Albert Schweitzer Hospital	Dordrecht	P.H.M. van der Valk[1], MD P.J.H. Smak Gregoor[2], MD, PhD M.R. Korte[2], MD, PhD [1]Department of Radiology [2]Department of Nephrology
Amphia Hospital	Breda	M. Meuwissen[1], MD [1]Department of Cardiology
Canisius-Wilhelmina Hospital	Nijmegen	M.E.R. Gomes[1], MD, PhD T. Oude Ophuis[1], MD, PhD M. Kruisbergen[1] [1]Department of Cardiology
Catharina Hospital	Eindhoven	E. Troe[2], MANP W.A.L. Tonino[1], MD, PhD C.J.A.M. Konings[2], MD, PhD P. Douwes-Draaijer[2], MD, PhD M.R.H.M. van Sambeek[3], MD, PhD B.R.G. Brueren[1], MD, PhD H.J.T.M. Hendrix- van Gompel[1] [1]Department of Cardiology [2]Department of Internal Medicine [3]Department of Surgery
Erasmus Medical Center	Rotterdam	J. Daemen[1], MD, PhD A.H. van den Meiracker[2], MD, PhD [1]Department of Cardiology [2]Department of Vascular Medicine
Haga Hospital	The Hague	M. Bax[1], MD I.M. van der Meer[2], MD, PhD H. van Overhagen[3], MD, PhD M. van Buren[2], MD, PhD L.C. van Dijk[3], MD, PhD C.E. Schotborgh[1], MD [1]Department of Cardiology [2]Department of Internal Medicine [3]Department of Radiology

Hospital Group Twente	Almelo/Hengelo	P.A.M. de Vries[1], MD A. van Balen[1] [1]Department of Internal Medicine
Isala Clinics	Zwolle	J.E. Heeg[1], MD, PhD J.J.J. Smit[2], MD, PhD A. Elvan[2], MD, PhD M.R. de Jong[2], MD B.A.A.M. van Hasselt[3], MD [1]Department of Internal Medicine [2]Department of Cardiology [3]Department of Radiology
Leiden University Medical Center	Leiden	J.I. Rotmans[1], MD, PhD B.L. van der Hoeven[2], MD, PhD A. Hage[1] A.J. Rabelink[1], MD, PhD M.J. Schalij[2], MD, PhD [1]Department of Nephrology [2]Department of Cardiology
Maasstad Hospital	Rotterdam	
Maastricht University Medical Center	Maastricht	A.A. Kroon[1], MD, PhD M.W. de Haan[2], MD, PhD M. Das[2], MD, PhD H.A. Jongen-Vancraybex[1] E.G.M. Herben[1] [1]Department of Internal Medicine [2]Department of Radiology
Martini Hospital	Groningen	R. Steggerda[1], MD S.M.L. Niamut[2], MD [1]Department of Cardiology [2]Department of Internal Medicine
Medical Center Alkmaar	Alkmaar	J.O.J. Peels[1], MD, PhD J.B.R.M. de Swart[1], MD [1]Department of Cardiology
Medical Center Haaglanden	The Hague	A.J. Wardeh[1], MD, PhD J.H.M. Groeneveld[2], MD E. van der Linden[3], MD, PhD [1]Department of Cardiology [2]Department of Internal Medicine [3]Department of Radiology
Medical Center Leeuwarden	Leeuwarden	M.H. Hemmelder[1], MD, PhD R. Folkeringa[2], MD [1]Department of Nephrology [2]Department of Cardiology
Medisch Spectrum Twente	Enschede	M.G. Stoel[1], MD, PhD G.D. Kant[2], MD [1]Department of Cardiology [2]Department of Internal Medicine
Onze Lieve Vrouwen Gasthuis	Amsterdam	J.P.R. Herrman[1], MD, PhD S. van Wissen[2], MD, PhD M. Khan[1], MD J.G.A.M. Blomjous[3], MD K. Koers[1], MD J. van Etten[1], MD [1]Department of Cardiology [2]Department of Internal Medicine [3]Department of Radiology
Radboud University Medical Center	Nijmegen	J. Deinum[2], MD, PhD S.W. Westra[2], MD [1]Department of Internal Medicine [2]Department of Cardiology
Rijnstate Hospital	Arnhem	W.R.M. Aengevaeren[1], MD, PhD K.J. Parlevliet[2], MD, PhD [1]Department of Cardiology [2]Department of Nephrology

Scheper Hospital	Emmen	A. Schramm[1], MD, PhD G.A.J. Jessurun[1], MD, PhD [1]Department of Cardiology
St. Antonius Hospital	Nieuwegein	B.J.W.M. Rensing[1], MD, PhD [1]Department of Cardiology
TweeSteden Hospital	Tilburg	M.H.M. Winkens[1], MD T.K.A. Wierema[2], MD, PhD E. Santegoets[1] [1]Department of Cardiology [2]Department of Internal Medicine
University Medical Center Groningen	Groningen	E. Lipsic[1], MD, PhD E. Houwerzijl[2], MD, PhD M. Kater[3], MD [1]Department of Cardiology [2]Department of Internal Medicine [3]Department of Radiology
University Medical Center Utrecht	Utrecht	M.F. Sanders[1], MD P.J. Blankestijn[1], MD, PhD M.L. Bots[2], MD, PhD M. Voskuil[3], MD, PhD W. Spiering[4], MD, PhD E.J. Vonken[5], MD, PhD M.M.A. Beeftink[3], MD R.L. de Jager[1], MD W.L. Verloop[3], MD, PhD E.E. Vink[1], MD, PhD P.A. Doevendans[3], MD, PhD [1]Department of Nephrology [2]Julius Centre for Health Sciences and Primary Care [3]Department of Cardiology [4]Department of Vascular Medicine [5]Department of Radiology
VU Medical Center	Amsterdam	C.P. Allaart[1], MD, PhD A. Nap[2], MD, PhD [1]Department of Cardiology

Appendix B. *Frequency of inclusions per center, with a total number of 306*



ORIGINAL ARTICLE

Surprisingly few psychological problems and diabetes-related distress in patients with poor glycaemic control

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ABSTRACT

Objective: Poor glycaemic control is an undesirable, but frequently encountered problem in diabetes. Reasons for not achieving optimal glycaemic control are not yet clear. A common belief is that psychological factors contribute importantly. This study compared general psychological problems and diabetes-related distress between patients with persistently poor glycaemic control to patients with optimal glycaemic control.

Methods: Patients from an outpatient clinic with type 1 or type 2 diabetes with a mean HbA1c ≥ 86 mmol/mol (≥ 10%) over two consecutive years (poor-control, n = 32) and those with diabetes and a mean HbA1c ≤ 53 mmol/mol (≤ 7%) over two consecutive years (optimal-control, n = 53) were studied. Clinical characteristics were obtained from the medical records. Psychological characteristics were investigated cross-sectionally using questionnaires.

Results: Patients in the poor-control group had a higher BMI compared with the optimal-control group. Self-reported previous anxiety was more prevalent in the poor-control group (34 versus 9%). All other mean test scores and proportions of subjects above cut-off levels were similar in the two groups.

Conclusions: Patients with diabetes and persistently poor glycaemic control have surprisingly few psychological problems and diabetes-related emotional distress. It seems that people with diabetes do not see persistent poor glycaemic control as a problem.

KEYWORDS

Diabetes, glycaemic control, depression, emotional distress, fear

INTRODUCTION

There is strong consensus that excellent glycaemic control improves microvascular outcomes. Still, many people with diabetes cannot obtain optimal glycaemia. Reasons for not achieving optimal glycaemic control are considered multifactorial. Several psychological characteristics, diabetes-related distress, depressive symptoms, and eating problems are importantly related to glycaemic control, adherence and self-management behaviour,[1-11] but results are inconsistent. Interventions aimed at improving glycaemic control, diabetes-related distress, or depression have only small effects, and interventions fail to improve glycaemic control and depression simultaneously.[12-14] To develop accurate interventions, there is a great need to elucidate the psychological processes involved in diabetes in more detail.

Based on the literature[1-11] it is assumed that people with diabetes and poor glycaemic control have more general psychological problems, and more diabetes-related distress. In the present study we compared patients with diabetes with a persistently poor glycaemic control to those with diabetes with optimal glycaemic control.

METHODS

Patients

Medical records of all outpatient clinic patients with type 1 or type 2 diabetes presenting for routine care at our tertiary centre were reviewed. Patients who had a mean HbA1c ≥86 mmol/mol (≥ 10%) (poor-control group) and those with a mean HbA1c ≤ 53 mmol/mol (≤ 7%) (optimal-control group) for two consecutive years were invited to participate in the study. Women who were pregnant or were planning

to become pregnant and persons who had undergone organ transplantation were excluded.

Measurements

Clinical characteristics were collected from the medical records and concerned type of diabetes, age, age at onset of diabetes, gender, body mass index (BMI), HbA1c, diabetes-related complications, and number of outpatient visits. Psychological characteristics, frequency of hypoglycaemic episodes and self-management behaviour were assessed cross-sectionally, using questionnaires. Self-management behaviour was assessed using questions about physical exercise, and self-monitoring of blood glucose (SMBG). Questionnaires were sent after informed consent had been obtained.

General psychological problems were assessed by a questionnaire asking about lifetime depression, anxiety, and eating disorders (PreDis-Diab questionnaire). Lifetime psychological problems were measured because of the assumption that especially people more prone to suffer from psychological problems would also be more prone to neglect self-management.

Diabetes-related distress was measured using the Problem Areas in Diabetes (PAID) scale,[15] the Hypoglycaemic Fear Survey (HFS)[16] and the Diabetes Fear of Injecting and Self-testing Questionnaire (D-FISQ).[17] The PAID scale consists of 20 items concerning negative emotions related to diabetes. The cut-off score for serious emotional distress is 40, average reported scores are 24.6±18.7 for type 1 diabetes and 22.5±19.8 for type 2 diabetes.[15] The Hypoglycaemic Fear Survey Worries Subscale consists of 13 items, with a cut-off score of 20. The behaviour subscale is not validated and not used. The Diabetes Fear of Injecting and Self-Testing questionnaire, subscale fear of injecting, consists of six items with a cut-off score of 4. The subscale fear of self-testing consists of 9 items with a cut-off score of 6 to indicate anxiety.[8]

All patients received a reminder after six weeks, non-responders were reminded by their own physician.

Analyses

SPSS 12.0 program was used for the analyses. Clinical characteristics were compared for those who had returned the questionnaire. Analyses included an unpaired t-test for differences between means and Chi-square test for differences between proportions. Nonparametric tests were used for not normally distributed variables. For each questionnaire, mean (± standard deviation) or median (interquartile range) scores and the proportion of patients above cut-off scores were calculated. Post-hoc analyses were performed to explore differences between type 1 and type 2 diabetes.

RESULTS

Of all 199 persons fulfilling the inclusion criteria (*figure 1*), nine had died, two had emigrated, 16 women were pregnant or were planning to become pregnant and 13 were excluded because they had undergone organ transplantation. Five people were excluded due to incomplete clinical data, 14 could not complete the questionnaires due to severe comorbidity. In the poor-control group, 32 (20 DM1, 12 DM2) of 61 eligible patients returned questionnaires, in the optimal-control group this was 53 (37 DM1, 16 DM2) of 79, a response rate of 52% and 67% respectively (non-significant). Clinical characteristics of responders and non-responders did not differ from those of all eligible persons. Mean HbA1c was 97±9 (11±1%) for the poor-control group and 48±7 (7±1%) for the optimal-control group.

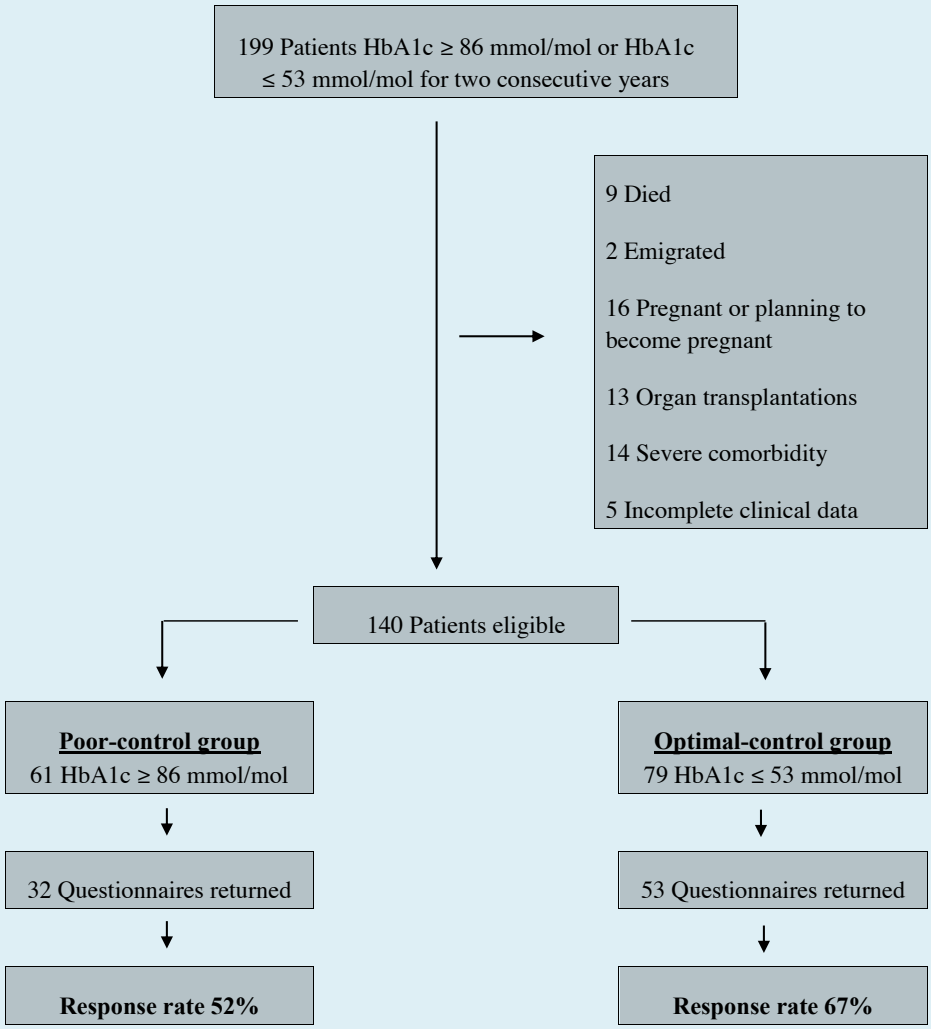
Clinical characteristics between the two groups did not differ, except that those in the poor-control group had a higher BMI and were more often using a combination of oral and insulin medication (29 ± 8 vs. 25 ± 5, p = 0.00 and 28 vs. 4%, p = 0.02 respectively).

Daily SMBG use and physical exercise were significantly higher in the optimal-control group (38 vs. 74%, p = 0.03 and 50 vs. 68%, p = 0.05 respectively). The poor-control group visited the clinic more frequently (25 vs. 4% more than four times a year, p = 0.01).

Scores regarding general psychological problems as well as diabetes-related distress were similar in the two groups. Only the proportion of patients reporting lifetime anxiety was higher in the poor-control group (34 vs. 9%, p=.01). The anxiety episode dated back more than ten years in all subjects in this study. All results are displayed in *table 1*.

To detect potential differences between and within type 1 and type 2 diabetes, we performed post-hoc subgroup analyses. Lifetime depression, anxiety, and eating disorders all seemed most prevalent in the diabetes type 2 poor-control subgroup as compared with the other subgroups. The diabetes type 2 poor glycaemic-control subgroup also tended to report more diabetes-related emotional distress and more fear of hypoglycaemia compared with persons with type 2 diabetes in optimal glycaemic control. The reverse was observed in the type 1 subgroups, where those with diabetes type 1 in the poor-control group tended to report less emotional distress and less fear of hypoglycaemia as compared with those with diabetes type 1 in the optimal glycaemic-control group. However, due to the low numbers, none of these differences attained statistical significance (data not shown).

Figure 1. *Inclusion*



DISCUSSION

The main finding of our study is that persons with diabetes and persistently poor glycaemic control have surprisingly few lifetime psychological problems and diabetes-related distress. In contrast to common belief and to our own expectations, it seems that these people with diabetes do not see persistent poor glycaemic control as a problem. Neither did we find any evidence that poor glycaemic control is a consequence of psychological distress. Except for a significantly higher prevalence of lifetime anxiety, none of the other psychological variables were significantly different between the groups. While the poor-control group had numerically a slightly lower response rate, the overall response rate was relatively high, above 50% in both groups, and not significantly different between the two groups.

We expected patients with poorly controlled diabetes to experience more general psychological problems, and more diabetes-related distress, being associated with a deterioration in glycaemic control. Our study shows that this is not the case. In the literature to date, no explanation for our findings can be found. Former studies predominantly show that depression and non-adherence are associated,[3] and that patients who are depressed and distressed by their diabetes are in significantly poorer glycaemic control relative to those not depressed nor distressed.[7] However, de Vries et al. stated earlier that psychological mechanisms in diabetes may be complicated.[1]

Some potential mechanisms may explain our findings. Persons in the poor-control group may try to avoid hypoglycaemias by keeping their blood glucose levels high, in this way diminishing their fear of hypoglycaemia.

Table 1. *Clinical characteristics, general psychological problems, diabetes-related distress and health behaviour*

	Poor control (n = 32)	Optimal control (n = 53)	p-value
Clinical characteristics			
Men (%)	41	51	0.38
Age (± SD, years)	54 ± 14	52 ± 14	0.73
Age at onset of diabetes (± SD, years)	31 ± 16	30 ± 16	0.75
Duration of diabetes (± SD, years)	23 ± 10	23 ± 15	0.98
BMI (± SD, kg/m²)*	29 ± 8	25 ± 5	0.00
Medication (%)			
Oral	3	4	0.65
Insulin	69	45	0.11
Combination*	28	4	0.02
Type 1 diabetes (%)	63	70	0.63
Complications (%) Microvascular Macrovascular	 53 34	 38 42	 0.59 0.65
Hypoglycaemia previous week (%)	44	60	0.34
Self-management behaviour			
Exercise >1 hour/week (%)*	50	68	0.05
SMBG daily (%)*	38	74	0.03
Outpatient clinic visits/year			
<3 (%)*	3	19	0.05
3-4 (%)	72	77	0.61
>4 (%)*	25	4	0.01
General psychological problems			
PreDis Lifetime self-reported depression (%) Lifetime self-reported anxiety (%)* Lifetime self-reported eating disorders (%)	 31 34 19	 21 9 13	 0.31 0.01 0.54
Diabetes-related distress			
PAID Mean (± SD) Above cut-off (%)	 17 ± 15 9	 19 ± 19 17	 0.28 0.52
D-FISQ fear of injecting			
Median (IQR)	0 (0)	0 (0)	0.36
Above cut-off (%)	3	8	0.65
D-FISQ fear of testing			
Median (IQR)	0 (1)	0 (0)	0.41
Above cut-off (%)	6	2	0.55
HFS worries Mean (± SD) Above cut-off (%)	 10 ± 9 5	 12 ± 10 12	 0.31 0.52

*p < 0.05, poor- vs optimal-glycaemic control. SD = standard deviation; BMI = body mass index; SMBG = self-monitoring of blood glucose; PreDis = premorbid dysfunctioning; PAID = Problem Areas in Diabetes scale; D-FISQ = Diabetes Fear of Injecting and Self-testing Questionnaire; IQR = interquartile range; HFS = Hypoglycaemic Fear Survey.

Furthermore, as a consequence of keeping blood glucose levels high, diabetes care may need less attention in daily life and therefore may lead to less diabetes-related emotional distress than was expected. On the other hand, optimal control needs effort and attention which in turn may increase diabetes-related distress and fear of hypoglycaemia. Our post-hoc analyses suggest that this may only be the case in diabetes type 1. In diabetes type 2 poor glycaemic control seems to be associated with higher diabetes-related emotional distress and increased fear of hypoglycaemia. While our study group was too small to compute statistically significant differences, it might be hypothesised that optimal glycaemic control and low diabetes-related emotional distress are incompatible in diabetes type 1, whereas in type 2 diabetes the inverse may exist. This may explain why interventions predominantly fail to improve glycaemic control, diabetes-related distress and depression simultaneously.[12-14] It also stresses the need to distinguish type 1 and type 2 diabetes concerning the psychological processes involved.

In our study, we found that the proportion of patients reporting lifetime anxiety was higher in the poor-control group. Post-hoc analyses suggest that lifetime depression, lifetime anxiety, and lifetime eating disorders are all most prevalent in the diabetes type 2 poor-control group. For type 1 diabetes, general psychological problems may more often be a consequence of having diabetes, being prevalent in the same proportions in the poor as well as in the optimal glycaemic-control group, except for lifetime anxiety, which was hardly prevalent in the diabetes type 1 optimal-control group. For type 2 diabetes psychological problems may be a preceding factor, which has been suggested before.[8,18-20] These psychological problems may result in obesity, and may interfere with reaching optimal glycaemic control.

The response rate of our study is relatively high, but we cannot exclude the possibility that patients with more severe psychological problems were less likely to respond. However, clinical characteristics of the responders being similar to those of all eligible patients argues against this possibility. The fact that this study concerned tertiary care patients as well as our small sample sizes may limit the generalisability of our results.

To study psychological processes in diabetes it is essential that several general and diabetes-specific psychological variables are studied simultaneously in relation to diabetes self-management and glycaemic control, for type 1 and type 2 diabetes separately. Only in this way is it possible to disentangle the psychological processes involved.

CONCLUSION

In conclusion, except for a higher prevalence of self-reported previous anxiety episodes, patients with persistent poor glycaemic control do not differ in any of the general or diabetes-related psychological characteristics from patients in the optimal-control group. These patients do not seem to consider poor glycaemic control to be a problem.

DISCLOSURES

The authors have no competing interests to report.

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Appendix

PREDIS_DIAB – Questionnaire
This questionnaire concerns lifetime psychological problems. Please answer the questions that apply to you.

1. Did you ever suffer from depression?
☐ no *(you can skip the rest of this question)*
☐ yes
What year was the last time you suffered from depression?
In . . . .
Have you ever been treated for this depression?
(more than one answer allowed)
☐ no
☐ yes, by a psychiatrist
☐ yes, by a psychologist
☐ yes, by a social worker
☐ yes, but not by one of the above

2. Did you ever suffer from anxiety?
☐ no *(you can skip the rest of this question)*
☐ yes
What year was the last time you suffered from anxiety?
In . . . .
Have you ever been treated for this anxiety?
(more than one answer allowed)
☐ no
☐ yes, by a psychiatrist
☐ yes, by a psychologist
☐ yes, by a social worker
☐ yes, but not by one of the above

3. Did you ever suffer from eating disorders (anorexia or bulimia)?
☐ no *(you can skip the rest of this question)*
☐ yes
What year was the last time you suffered from eating disorders?
In . . . .
Have you ever been treated for these eating disorders?
(more than one answer allowed)
☐ no
☐ yes, by a psychiatrist
☐ yes, by a psychologist
☐ yes, by a social worker
☐ yes, but not by one of the above

ORIGINAL ARTICLE

Perinatal outcomes in gestational diabetes in relation to ethnicity in the Netherlands

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ABSTRACT

Background: The influence of ethnicity in women with gestational diabetes in relation to maternal, pregnancy and neonatal outcome is not well defined.

Aim: To compare the perinatal outcome in women with gestational diabetes between different ethnic groups reflecting the multi-ethnic population in the Netherlands.

Methods: Patients with gestational diabetes (n = 388) who visited the multidisciplinary outpatient clinic for Diabetes Care and Obstetrics of the Sint Franciscus Gasthuis in Rotterdam between 2010 and 2013 were included. Ethnicity was distinguished into six groups: Moroccan (n = 100); Turkish (n = 43); Caucasian (n = 146); Suriname-Creole (n = 23); Suriname-Hindu (n = 32); and Miscellaneous (n = 44).

Results: Caucasians were the largest group with gestational diabetes (37.7%), followed by Moroccans (25.8%). Body mass index before pregnancy was highest in Surinamese-Creole women, followed by Turks and Moroccans ($p < 0.001$). Gravidity and parity were highest in Moroccans. Gravidity was lowest in Surinamese-Hindus and parity was lowest in Caucasians ($p < 0.001$). There was also a remarkable, significant difference in the mode of delivery between the ethnicities with the lowest number of normal deliveries in Caucasians and the highest in Moroccans ($p = 0.03$). Assisted delivery occurred most frequently in Caucasian women, although there was no difference in the frequency of caesarean sections. Birth weight was the only neonatal parameter showing significant differences between the ethnicities, with the highest birth weight for Moroccan children and the lowest for Surinamese children (3542 g vs. 3200; $p = 0.001$).

Conclusion: This study did not show major differences in maternal or neonatal complications, however there are significant disparities in (percentile) birth weight and mode of delivery across the different ethnic groups.

KEYWORDS

Birth weight, epidemiology, pregnancy

INTRODUCTION

Gestational diabetes mellitus (GDM) has been associated with an increased risk for perinatal complications such as pregnancy-induced hypertension, prematurity, caesarean section, shoulder dystocia and macrosomia.[1-4] Pregnancy is an insulin-resistant state, in part mediated by the action of human placental lactogen, human chorionic somatomammotropin, growth hormone and corticotrophin-releasing hormone.[5,6] The diabetogenic placental hormones increase with placental size and, therefore, gestational diabetes is usually not present until the second or third trimester of the pregnancy.[5]

Several reports from the Netherlands confirmed a high frequency of complications in pregnancies of diabetics.[7-10] Data from an epidemiological study in the Netherlands suggested that there was an important ethnic difference in foetal mortality with significantly elevated risk in nulliparous women of South Asian and African origin.[11] A possible explanation was that non-Western women have cultural and educational barriers, which influence the access to regular care or its effectiveness.[11] There is only

limited information on pregnancy-related complications in ethnic minorities with diabetes in the Netherlands. Moreover, these studies were only carried out in diabetes mellitus type 2 (T2DM) patients.[7,8] In this study, we aimed to compare perinatal outcomes in women with GDM between different ethnic groups.

METHODS

Patients

The local medical ethics committee of the Maasstad Hospital in Rotterdam approved this study. Consecutive patients with a diagnosis of GDM, who visited the outpatient clinic for Diabetes Care of the Department of Internal Medicine of the Sint Franciscus Gasthuis in Rotterdam between 2010 and 2013, were included. Women were referred to our clinic and were first treated with lifestyle measures. In case of insufficient response to lifestyle intervention, patients started insulin therapy. All diabetic patients are extensively evaluated during the regular multidisciplinary meetings once a month, which were attended by obstetricians, internist-endocrinologists, dietitians and specialised diabetes nurses. The department serves as a referral centre for pregnant women with diabetes in the Northern part of the Rotterdam region.

Maternal, foetal and neonatal data were recorded by each professional following protocols and data were entered into the database. Patients had to have a diagnosis of GDM, defined as an abnormal 75-gram oral glucose tolerance test (OGTT). Reference values for the OGTT were < 7.0 mmol/l for fasting glucose and < 7.8 mmol/l two hours after glucose load. Patients who were referred to our centre, but had their delivery in another centre or at home, were asked permission to obtain the birth data from the general practitioner. If no permission was given, data for these subjects were not included in the final analysis. Multiple births were also not included in the analyses.

Outcome measures

Maternal characteristics

Maternal age in years and body mass index (BMI) in kg/m^2 before the pregnancy were collected as continuous data. Gestational age at first antenatal visit in weeks was counted from the first day of the last menstruation. The presence of chronic hypertension was recorded based on the use of specific medication and medical history. Chronic hypertension in pregnancy was defined as hypertension that had been diagnosed before 20 weeks of gestation and if it persisted three months after delivery.[12] Conception by means of in vitro fertilisation (IVF) was recorded separately. The referring physician was also recorded (general practitioner, obstetrician or internist). Ethnicity was divided into six groups: Moroccan, Turkish, Caucasian, Surinamese-Creole, Surinamese-Hindu and Miscellaneous. Finally, diabetes treatment was scored as diet only or diet and insulin. Insulin regimens were defined as receiving long-acting insulin once a day and/or short-acting insulin once, twice or three times a day.

Obstetric complications

Gravidity and parity were registered as categorical data. The duration of pregnancy was recorded in weeks. Prematurity was defined as delivery before 37 weeks of gestation. The mode of delivery was recorded as normal, assisted or as caesarean section, and could be either spontaneous or induced. The indications for induction of labour were gestational age over 38 weeks in the case of inadequate control of the diabetes or unstable serum glucose levels, and a deteriorated condition of the foetus or mother. Caesarean section was carried out when an estimated weight above 4000 grams was established, or based on obstetric history or location or condition of the foetus.

Pregnancy-induced hypertension (PIH) was diagnosed as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after 20 weeks gestation, measured twice, in a previously normotensive woman. Preeclampsia was classified as the combination of PIH with proteinuria (≥ 300 mg/24 hours). HELLP syndrome was classified as the combination of haemolysis, elevated liver enzymes, and lowered thrombocytes.[13]

Complications during delivery were recorded as shoulder dystocia,[14] episiotomy or more than 1000 cc blood loss.

Neonatal outcome

Miscarriage was defined as spontaneous abortion up to a gestational age of 24 weeks. Foetal perinatal mortality was defined as death after 28 weeks of gestation or in the first seven days postpartum. Birth weight was recorded as a continuous variable (in percentiles), according to the Netherlands perinatal registry which also takes into account the number of pregnancies, gender and ethnicity.[15] Macrosomia was defined as birth percentile ≥ 90 and dysmaturity as birth percentile ≤ 10.[15] Congenital malformations were recorded as fatal, potentially life-threatening, likely to lead to serious handicap or as a major cosmetic defect, or requiring major surgery.[9] Neonatal hypoglycaemia was defined as a capillary blood glucose < 2.6 mmol/l in the infant in the first 24 hours after birth. We used that definition because abnormalities of the neonatal brain on magnetic resonance imaging have been detected if the plasma glucose falls below that value.[16] Hyperbilirubinaemia was recorded if the newborn required at least one period of phototherapy.

Laboratory analyses

Glycaemic control was established by HbA1c measurements. The target value of HbA1c was between 20 and 42 mmol/mol. HbA1c values were recorded as pre-conceptional and at trimester 1, trimester 2, trimester 3 and postpartum. Because GDM is generally diagnosed in trimester 2 or 3, only the HbA1c values of trimester 2, 3 and postpartum were used for analysis. In the case that more than one HbA1c value was available in the trimester, the mean HbA1c value of that trimester was used.

HbA1C concentrations were only determined if the patient required insulin. In most women treated with lifestyle, only self-measurement of capillary glucoses was recorded. In the years 2010 and 2011, most women with GDM were referred based on an increased capillary glucose day curve. From the year 2012 an OGTT was used for diagnosing GDM following guidelines.[17] Women were screened at their first antenatal visit. The 75-gram OGTT was performed if a random and fasting venous glucose was determined above 6.1 mmol/l and in women with risk factors. Women with a history of GDM underwent an OGTT at 16 weeks of pregnancy and between 24 and 28 weeks of pregnancy. Women with risk factors for GDM also had an OGTT between 24 and 28 weeks of pregnancy. Risk factors for GDM are: history of GDM, BMI > 30 kg/m^2 at the first antenatal visit, previous child with a birth weight > P95 or > 4500 gram, first-degree family member with diabetes, certain ethnic groups where diabetes is common (Hindus, Afro-Caribbeans, women from the Middle East, Morocco and Egypt), unexplained foetal death in the history or polycystic ovary syndrome. Venous samples were obtained for glucose measurements at baseline and two hours after glucose load. Reference values for glucose are < 7.0 mmol/l at baseline and 7.8 mmol/l at two hours. If one of these values was increased, the diagnosis GDM was established and lifestyle measures were taken, followed by insulin therapy when necessary. Short-acting insulin was initiated if postprandial values were > 6.7 mmol/l and long-acting insulin was prescribed if fasting glucose was above > 5.3 mmol/l.

All laboratory measurements were carried out in our clinical chemistry laboratory following standard procedures.[18] For the OGTT, blood samples were obtained fasting and two hours after ingestion of 75 grams of oral anhydrous glucose. Blood was drawn from a peripheral vein of the forearm. Some women were referred by a different hospital or a midwife and those data were used when available.

Three months after the delivery, HbA1c was again determined in all women who used insulin during pregnancy.

Statistical analysis

Statistical analysis was carried out using SPSS version 22.0 (IBM Corp, Armonk, NY, USA). Results for continuous variables are given as mean and standard deviation, differences between groups were tested by analysis of variance, post-hoc analysis was tested by Fisher's least significant difference test. For categorical variables, data are given as frequencies and percentages, and Chi-square test was used to evaluate differences between the groups. P-values < 0.05 were considered to be significant. To evaluate a relationship between HbA1c values during pregnancy and hypoglycaemias of the newborn within 24 hours after birth, Spearman correlation analyses were carried out.

RESULTS

General characteristics

A total of 388 pregnancies of women with GDM were recorded. The number of women increased gradually due to the intensified screening programme. Over the four years there were 388 pregnancies, with one miscarriage (0.3%); therefore, 387 were included.

Characteristics and outcome based on ethnicity

Table 1 shows the general characteristics of the women with GDM based on ethnicity. Caucasians formed the largest group followed by Moroccans. BMI before pregnancy was highest in Surinamese-Creoles, followed by Turkish and Moroccan women.

Gravidity and parity rates were highest in Moroccan females, gravidity was lowest in Surinamese-Hindus and parity was lowest in Caucasian women. PIH occurred most frequently in Caucasian and Surinamese-Hindu women. A normal delivery was most frequently observed in the Moroccans, followed by the Turkish and caesarean section was most frequently carried out in the Caucasian group. Assisted delivery differed significantly between the ethnicities, due to a high frequency in Caucasians and it did not occur in Turkish women. An episiotomy was more frequently performed in Caucasian females. *Table 2* shows the obstetric characteristics and complications of the women, based on ethnicity.

Neonatal characteristics and complications based on ethnicity are given in *table 3*. Birth weight was highest in newborns from Moroccan mothers and lowest in Surinamese-Creole and Surinamese-Hindu newborns. Birth weight percentiles were highest in Moroccans, followed by Surinamese-Hindu newborns. Birth weight in the miscellaneous group of newborns was in the lowest percentile. There were no significant differences between the ethnicities and neonatal complications.

Table 1. *General characteristics of women with GDM based on ethnicity*

		Caucasian n = 146	Moroccan n = 100	Turkish n = 43	Surinamese-Creole n = 23	Surinamese-Hindu n = 31	Miscellaneous n = 44	Total n = 387	P-value
Age (years)#		32.2±5.1	33±4.6	32.6±4.7	30.6±6.3	32.9±4.9	33.4±5.2	32.6±5	0.256
BMI (kg/m²)*#		28.9±6.4	30.3±5.6	31.5±5.8	32.8±6.5	28.5±6.8	25.6±4.9	29.5±6.2	<0.001
Gestational age when referred (weeks)#		29.2±6.1	30±5.7	29.8±5.4	29.9±4.6	27.7±6.6	29±5.9	29.4±5.8	0.499
Chronic complications	None	142(97.3)	98(98)	41(95.3)	23(100)	29(93.5)	41(93.2)	374(96.6)	0.507
	Hypertension	4(2.7)	2(2)	2(4.7)	0	2(6.5)	3(6.8)	13(3.4)	
IVF		8(5.5)	3(3)	3(7)	0	3(9.7)	2(4.5)	19(4.9)	0.551
Referring physician	General practitioner	0	1(1)	2(4.7)	0	1(3.2)	0	4(1)	0.102
	Obstetrician	144(98.6)	98(98)	41(95.3)	22(95.7)	29(93.5)	44(100)	378(97.7)	0.364
	Internist	2(1.4)	1(1)	0	1(4.3)	1(3.2)	0	5(1.3)	0.578
Therapy	Diet only	100(68.5)	68(68)	23(53.5)	17(73.9)	20(64.5)	33(75)	261(67.4)	0.347
	Insulin	46(31.5)	32(32)	20(46.5)	6(26.1)	11(35.5)	11(25)	126(32.6)	
Medication	None	146(100)	99(93.2)	42(97.7)	23(100)	31(100)	44(100)	385(99.5)	0.486
	Metformin	0	1(1)	1(2.3)	0	0	0	2(0.5)	

Data are recorded in numbers with percentage in parentheses N(%) for categorical variables and in mean with ± SD(#) for continuous variables. BMI = body mass index, Caucasians: n=120, N Moroccan=85, N Turkish=38, N Surinamese-Creole=21, N Surinamese-Hindu=29, N Miscellaneous=31, N Total=324.

HbA1c changes during pregnancy

Table 4 shows the course of HbA1c during the pregnancy for each ethnicity. The data for HbA1c were incomplete and only the HbA1c values of trimesters 2, 3 and postpartum were used. Caucasian, Moroccan, Turkish, Surinamese-Hindu and Miscellaneous women showed almost the same trend with almost equal values in trimesters 2, 3 and postpartum. Only Surinamese-Creole women showed a different pattern with a higher mean HbA1c value in trimester 3. Univariate correlation analyses using Spearman correlation coefficients between HbA1c and hypoglycaemia showed only a trend in the third trimester with a Spearman's rho of 0.176 (p = 0.052).

DISCUSSION

This single-centre, retrospective study performed over four years shows the outcomes of pregnancies of women of different ethnicities with GDM. There were no major differences between the ethnic groups in neonatal complications related to diabetes. However, there was a significant difference in (percentile) birth weight and mode of delivery.

To the best of our knowledge, this is the first study in the Netherlands comparing pregnancy outcomes in women with GDM of different ethnicities. Previous studies in the Netherlands reported differences in T2DM and ethnicity.[7,8] Both studies showed no differences in perinatal outcomes between native and non-native (Moroccan) women.[7,8] However, the caesarean section rate was higher in native Dutch women.[8] The authors concluded that in a setting of easy access to, and compliance with the local healthcare system, outcome in non-native women can be similar to that in native women. This easy access to care might be positively affected by the fact that medical care in the Netherlands is fully reimbursed with insurance coverage for basically all inhabitants, resulting in an absence of any financial barriers to receiving medical care.[8]

Studies from other countries in women with GDM included other ethnicity groups.[3,4,19-23] Hispanic neonates in the USA were more likely to experience adverse neonatal outcomes.[4,19] Afro-Caribbean women, comparable to the Surinamese-Creole women in our study, were more likely to have a normal delivery in comparison with Caucasian women.[24] Our study confirms these results. A study from New York suggested ethnic variations, with a relatively higher incidence of complications in

Table 2. *Obstetric characteristics and complications of women with GDM based on ethnicity*

		Caucasian n = 146	Moroccan n = 100	Turkish n = 43	Surina-mese-Creole n = 23	Surina-mese-Hindu n = 31	Miscel-laneous n = 44	Total N = 387	P-value
Gravidity#		2.2±1.3	4±1.9	3.1±1.4	3.2±1.4	2.1±1.1	2.9±1.7	2.9±1.7	<0.001
Parity#		0.7±0.9	2.4±1.8	1.6±1.2	1.4±1.3	0.8±0.8	1.2±1.3	1.3±1.4	<0.001
Gestational age (weeks)#		38.8±1.3	38.6± 1.5	38.5±1.2	38.5±1.8	38.5±1.2	38.6±1.4	38.6±1.4	0.736
Mode of delivery	Normal	87(59.6)	78(78)	34(79.1)	18(78.3)	21(67.7)	28(63.6)	266(68.7)	0.027
	Assisted delivery	19(13)	2(2)	0	1(4.3)	3(9.7)	4(9.1)	29(7.5)	0.011
	Caesarean section	40(27.4)	20(20)	9(20.9)	4(17.4)	7(22.6)	12(27.3)	92(23.8)	0.719
Priming		98(67.1)	55(55)	31(72.1)	14(60.9)	19(61.3)	21(47.7)	238(61.5)	0.098
Pregnancy	None	125(85.6)	97(97)	41(95.3)	22(95.7)	27(87.1)	41(93.2)	353(91.2)	0.032
	PIH	18(12.3)	1(1)	1(2.3)	1(4.3)	3(9.7)	2(4.5)	26(6.7)	0.011
	Pre-eclampsia	3(2.1)	2(2)	1(2.3)	0	1(3.2)	0	7(1.8)	0.886
	HELLP syndrome	0	0	0	0	0	1(2.3)	1(0.3)	0.167
Parturition	None complications	106(72.6)	80(80)	39(90.7)	22(95.7)	23(74.2)	33(75)	303(78.3)	0.042
	>1 complication	40(27.4)	20(20)	4(9.3)	1(4.3)	8(25.8)	11(25)	84(21.7)	
	Episiotomy	37(25.3)	10(10)	2(4.7)	0	6(19.4)	6(13.6)	61(15.8)	0.001
	Fluxus>1000cc	4(2.7)	5(5)	1(2.3)	1(4.3)	2(6.5)	7(15.9)	20(5.2)	0.024
	Shoulder dystocia	3(2.1)	5(5)	1(2.3)	0	2(6.5)	0	11(2.8)	0.360

Data are recorded in numbers with percentage in parentheses N(%) for categorical variables and in mean with ± SD(#) for continuous variables.

Caribbean, Sub-Saharan African, and African-American women, while North African, South Central Asian, and Chinese women showed a relatively smaller incidence of complications but a higher baseline risk of GDM.[3]

In the four years of our study, the number of patients included each year increased from 64 in 2010 to 153 in 2013. This was mainly due to changed guidelines for identification of GDM, which were introduced in our hospital in 2012.[17] Furthermore, GDM prevalence is increasing in many populations worldwide concomitantly with the observed increase in T2DM.[25] The increasing age of pregnant women and the increased number of minority immigrants have likely contributed to this increase in prevalence.[1,25-27]

PIH was significantly different between the ethnicities in our study, with the highest rate in Caucasian women. In another study, Caucasians also had the highest rate of PIH.[19] Episiotomy was not recorded in previous studies. The higher rate of episiotomy in Caucasians and Surinamese-Hindu ethnicities and the increased frequency of assisted deliveries and caesarean sections in Caucasians may be associated to the observed lower parity in these groups. Indeed, it has been published that a higher number of deliveries in women is associated with a higher rate of normal deliveries.[8,28]

Neonatal outcome

We expected that the outcome in non-native women with diabetes would be poorer as compared with Caucasian women. There was a significant difference in birth weight and percentile birth weight. Remarkably, children from Surinamese-Hindu mothers had the lowest birth weight, but when considering the percentile, they had the highest mean percentile after Moroccans. This can be explained by the fact that we used special birth weight curves for Hindu children. A study from Australia also included the Pacific Islanders ethnic group and they had a mean birth weight of 3700 gram with a mean percentile of 70.5.[22]

The stillbirth rate in our study (0.3%) cannot be compared with other studies due to a lack of data in the literature.

Table 3 *Neonatal characteristics and complications at GDM based on ethnicity*

		Caucasian n = 146	Moroccan n = 100	Turkish n = 43	Surinamese-Creole n = 23	Surinamese-Hindu n = 31	Miscellaneous n = 44	Total n = 387	P-value
Complications child	None complications	91(62.3)	70(70)	27(62.8)	14(60.9)	22(71)	25(56.8)	249(64.3)	0.624
	>1 complications	55(37.7)	30(30)	16(37.2)	9(39.1)	9(29)	19(43.2)	138(35.7)	
Birth weight#		3482.7± 473.7	3542± 456.5	3469± 535.9	3238.6± 456	3200.2± 583.7	3306.4± 497.5	3439.3± 497.4	0.001
Percentile birth weight#		52.6±31.4	54.4±27.4	47.9± 30.9	39.1±20.5	52.9±26.7	38.4±27.7	50.2±29.4	0.015
Complications child	Prematurity	3(2.1)	5(5)	1(2.3)	3(13)	1(3.2)	4(9.1)	17(4.4)	0.112
	Dysmaturity	5(3.4)	2(2)	1(2.3)	1(4.3)	0	5(11.4)	14(3.6)	0.083
	Macrosomia	33(22.6)	13(13)	8(18.6)	1(4.3)	5(16.1)	4(9.1)	64(16.5)	0.102
	Congenital malformations	4(2.7)	1(1)	0	0	0	0	5(1.3)	0.505
	Hypoglycaemia	43(29.5)	22(22)	12(27.9)	7(30.4)	7(22.6)	14(31.8)	105(27.1)	0.749
	Hyperbilirubinaemia	3(2.1)	7(7)	1(2.3)	0	1(3.2)	3(6.8)	15(3.9)	0.289

Data are recorded in numbers with percentage in parentheses N(%) for categorical variables and in mean with ± SD(#) for continuous variables.

Table 4 *HbA1c values during pregnancy based on ethnicity*

	Caucasian	Moroccan	Turkish	Surinamese-Creole	Surinamese-Hindu	Miscellaneous	Total	P-value
Trimester 2	(18) 35.7±5.3	(13) 34.2±4.6	(8) 37.8±8.2	(1) 32	(5) 35.6±3.0	(5) 36.2±5.5	(50) 35.6±5.4	0.786
Trimester 3	(51) 37.2±4.6	(43) 36.7±6.1	(22) 39.8±6.0	(12) 44.3±11.1	(14) 39.9±4.7	(14) 38.6±5.7	(156) 38.4±6.3	0.003
Postpartum	(35) 37.4±4.0	(20) 37.2±4.5	(16) 38.7±4.1	(5) 40.6±4.8	(11) 37.9±7.3	(9) 40.8±5.8	(96) 38.1±4.8	0.332

Data are recorded in numbers (N) and mean with ± SD. Post-hoc analysis shows that there was a statically significant difference between HbA1c values in the third trimester from Surinamese-Creole women compared to all other ethnicities.

We have to take into consideration that miscarriage is difficult to confirm and often occurs in the first weeks of pregnancies. Perinatal death after 28 weeks of gestation did not occur in our study.

Congenital malformations are a common complication in the offspring of women with T1DM or T2DM.[7,9,24,29-38] The increased risk of anomalies is predominantly for cardiovascular defects, followed by musculoskeletal and central nervous system anomalies.[33,38,39] For GDM, risk of congenital malformations is not an issue because they arise in the first trimester of the pregnancy.

Neonatal hypoglycaemia rates in our study were high in comparison with a recent study were the authors compared untreated and treated GDM. There were no major differences, but Hispanic women had more frequent neonatal hypoglycaemia.[4]

Limitations

Several limitations of this study should be noted. Firstly, the number of patients in some ethnic groups such as Turkish, Surinamese-Creole and Surinamese-Hindu were small. Secondly, women entered care at different gestational ages. GDM was often referred in the third trimester, because the diabetes usually reveals at that stage. However, there were some women who were already referred with elevated disturbed glucose values in the

first trimester. Since the diabetes was discovered during pregnancy, the diagnosis of GDM was established by definition, but one has to take into consideration that some women may have had a longer existing T2DM.

National database

In our hospital there is a structured, multidisciplinary approach for the pregnant women with diabetes mellitus. Therefore, it was expected that the results would be better than previous reports where care for these women was less strict. The Netherlands Perinatal Registry recently published the trends in deliveries from 1999-2012.[40] The mode of delivery in the national database reports 74.5% normal deliveries, 10.2% assisted deliveries and 15% caesarean sections, but data on ethnicity are not available. The total percentage of prematurity was 7.7% in the total population of pregnant women. It is only in the Surinamese-Creole ethnicity and miscellaneous group that prematurity occurred more frequently. The rate of congenital malformations in newborn babies of women with GDM was comparable to the normal population of pregnant women in all the six types of ethnicities.[41] Other perinatal outcomes such as macrosomia or hypoglycaemia were not recorded in the Netherlands Perinatal Registry.

Predictive variables

In a study of pregnancies complicated by gestational diabetes or impaired glucose tolerance, in the late second and early third trimester, maternal BMI and macrosomia in a previous pregnancy seemed to have the strongest influence on foetal growth, while maternal fasting glycaemia during 32-35 weeks was the strongest predictor of accelerated growth in the late third trimester.[42]

Patients with successful outcomes for the composite endpoints, preterm delivery and large for gestational age/macrosomia have lower HbA1c levels than patients with poor outcomes, and this is evident throughout pregnancy.[43] In our study Surinamese-Creole women had a significantly higher HbA1c value in trimester 3 compared with the other ethnic groups; however they did not show a higher birth weight, macrosomia or prematurity compared with other ethnicities. Since there were many missing data, no definitive conclusion can be drawn. According to a study from the USA, there is only limited evidence of an increased risk of large for gestational age/macrosomia among women with an HbA1c from 44 to 96 mmol/mol at diagnosis.[44] The HbA1c ≥ 41 mmol/mol identified all women with diabetes and a group at significantly increased risk of adverse pregnancy outcomes according to a recent study from New Zealand.[45] But not only should the HbA1c be maintained at a low level throughout pregnancy, also glucose profiles should be kept stable and high peaks of glucose should be avoided. Different studies support the association of hyperglycaemia with increased maternal, foetal and perinatal morbidity.[32,35] In a randomised clinical trial, treatment of women with GDM, including dietary advice, blood glucose monitoring and insulin therapy, reduced the rate of serious perinatal outcomes (defined here as death, shoulder dystocia, bone fracture or nerve palsy) from 4% to 1% and a lower birth weight.[46]

CONCLUSIONS

In conclusion, in contrast to our hypothesis we did not find significant differences in neonatal complications between the six ethnicities. However, there are significant disparities in women with GDM in (percentile) birth weight and mode of delivery across different ethnic groups.

DISCLOSURES

We have no conflicts of interest to report.

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ORIGINAL ARTICLE

Pamidronate effect compared with a steroid on complex regional pain syndrome type I: Pilot randomised trial

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ABSTRACT

Objectives: This study aims to compare the effectiveness of a bisphosphonate (pamidronate) and a steroid (prednisolone) in complex regional pain syndrome (CRPS) type I during four weeks of follow-up in hemiplegic stroke patients.

Methods: Twenty-one hemiplegic stroke patients with CRPS type I were enrolled in the study. Patients were randomly assigned to receive either intravenous pamidronate (n = 11; total cumulative dose of 180 mg) or oral prednisolone (n = 10). Subjective pain and hand oedema (circumference of the middle finger, CMF, and the wrist, CW) were measured at baseline and at one, two and four weeks after the end of treatment.

Results: Both groups showed significant improvement in subjective pain VAS scores at 1-week follow-up and this effect was maintained until 4-week follow-up. Time-by-group interactions were not significant at 4-week follow-up. The reduction of the CMF observed at 1-week follow-up in both groups was maintained until 4-week follow-up in the steroid group, but until 2-week follow-up in the pamidronate group. A significant change in CW was observed at 4-week follow-up in the pamidronate group. There were no significant adverse effects in either treatment group during the follow-up period.

Conclusions: Intravenous pamidronate therapy was safe, well tolerated and appeared as effective as a steroid for pain control for post-stroke CRPS. However, this result should be interpreted with caution, since it included a relatively small number of patients. Further larger controlled studies followed over a longer period are needed to validate these findings and to determine clinical treatment standards.

KEYWORDS

Complex regional pain syndrome, pamidronate, steroid, stroke

INTRODUCTION

Complex regional pain syndrome (CRPS) is a neuropathic pain syndrome related to vasomotor and sudomotor nerve dysfunction. Some stroke patients subsequently develop dysesthesia, severe pain, hyperalgesia, temperature asymmetry, skin colour asymmetry, oedema, diaphoresis, decreased range of motion and trophic changes in their upper extremities. Although the pathophysiology of these findings, referred to as CRPS 1, is unclear, the incidence is significant.[1,2] The incidence of CRPS type I after brain lesion is as high as 1.5-61%.[3-6] Early therapeutic intervention is recommended for a better outcome since dystrophic changes in the skin, pain, and joint contractures in the affected limb might induce functional dysfunction and lengthen the hospital stay for rehabilitation.[7]

There are various invasive and non-invasive treatment options for CRPS, such as systemic and topical analgesics and steroids, neuropathic agents, physiotherapy and sympathetic nerve blocks.[8,9] A systemic steroid therapy for a short period of time is effective and commonly used.[10,11] However, clinicians frequently face difficulties in using steroids for CRPS patients with stroke, who often have comorbidities such as diabetes mellitus, hypertension and osteoporosis. Therefore, a safer and more effective therapeutic method is imperative for these patients.

Recently, a possible role for bisphosphonate in the treatment of CRPS was proposed.[12-14] Bisphosphonate has

an effect on pain control in bone-related diseases such as Paget's disease, metastatic bone disease, myeloma and spinal fracture,[15-17] and might therefore have a therapeutic effect on pain in CRPS where hyperactivity of osteoclasts is one of the conceivable pathogeneses.[14] In addition, bisphosphonate is a strong inhibitor of bone resorption and might prevent osteoporosis that is induced by hyperactive osteoclast and immobilisation in CRPS.[18] However, there is limited evidence for the therapeutic effect of bisphosphonate in CRPS type I after stroke. Therefore, the aim of the current study was to determine the therapeutic effect of pamidronate, a second-generation bisphosphonate, in the treatment of CRPS type I patients after stroke and to compare its effect with conventional steroid therapy.

MATERIALS AND METHODS

Subjects

This study was conducted in the rehabilitation ward of a university hospital from October 2010 to March 2012. Among 65 stroke patients, 39 patients who did not meet inclusion criteria were excluded and five patients declined to participate in the current study. Finally, 21 first-ever stroke patients with CRPS type I within six months of stroke onset were included in the present study. All patients were admitted to our rehabilitation centre for comprehensive rehabilitation therapy for stroke.

The diagnosis of CRPS type I was based on the 'Budapest' criteria.[19] Clinical diagnosis for CRPS was confirmed when the patient had continuing pain which was disproportionate to any inciting event and the patient had at least one sign in two or more of the categories: sensory, vasomotor, sudomotor/oedema, and motor/trophic, and at least one symptom in three or more of these categories. Once diagnosed, patients underwent three-phase bone scintigraphy and musculoskeletal ultrasonography for differential diagnosis. The musculoskeletal ultrasonography was performed by one physiatrist. All images of three-phase bone scintigraphy were interpreted by one nuclear radiologist. Patients were classified as CRPS positive when the images of blood flow, blood pool and delayed phases showed diffuse asymmetric uptake.

Exclusion criteria were as follows: 1) disease or trauma history other than stroke that might cause CRPS in the upper extremities; 2) past history of shoulder pain or limitation of motion on the hemiplegic side; 3) history of diabetes mellitus, hyperthyroidism, renal and liver dysfunction or peripheral neuropathy; 4) a score of less than 23 on the Korean version of Mini-Mental State Examination (K-MMSE); 5) history of treatment for CRPS; and 6) medical treatment with bisphosphonate for osteoporosis or with other drugs that may have an effect on bone metabolism within six months.

Written informed consent was obtained from each participant in the study, and approval for the study was obtained from the institutional review board. The study was performed in accordance with the amended Declaration of Helsinki and was approved by the appropriate local ethics and drug committees.

Protocol

All 21 patients completed informed consent and medical history forms, and were randomly assigned to either the intravenous bisphosphonate group or the oral steroid group. Patients underwent three-phase bone scintigraphy and a physical examination by one physiatrist who was blind to the study information. Throughout the study period, patients were encouraged to participate in their inpatient rehabilitation program.

Measurements of subjective pain and quantitative evaluation of hand oedema were performed at baseline and at one, two and four weeks after the end of each treatment. Subjective pain was measured using a visual analogue scale (VAS) that consisted of a horizontal line, 100 mm long, anchored at the left by the descriptor 'no pain' and at the right by the descriptor 'unbearable pain'.

Quantitative evaluation of hand oedema was performed by measuring the circumference of the middle (third) finger (CMF) and the wrist (CW) on the affected side.[20] We used this method because it is easy to perform and cost-effective. Before initiation of the current study, an intra- and inter-rater reliability test of this method (CMF and CW measurement) with healthy 25 subjects was performed. The interclass correlations for intra-rater and for inter-rater reliability were higher than 0.9. CMF was measured using a finger circumference gauge at the midpoint between the proximal finger crease and the middle finger crease and CW was measured using Roylan's flexible tape at the level of radial styloid process. Each circumference was measured in triplicate, and the median value was used as an estimate of hand oedema. Measurements of hand oedema were always conducted at 10.00 hours to avoid the influence of circadian variations.

Intervention

The steroid group received oral steroid therapy, prednisolone (Solondo®; Yuhanmedica Co., Cheongwon, Korea), at an initial dose of 1 mg per kg of body weight. The dose was tapered over two weeks. Therefore, the total duration of the steroid therapy was two weeks. The bisphosphonate group received pamidronate (Panorin®; Hanlim Pharm. Co., Seoul, Korea) infusion intravenously. Each infusion with 60 mg of pamidronate mixed with 500 ml of normal saline was delivered to the unaffected

upper extremity and lasted for more than four hours. The total dose of pamidronate was 180 mg, delivered via three infusions every other day. Therefore, the total duration of the pamidronate therapy was six days. Measurements of study parameters were performed at baseline and at one, two and four weeks after the end of each treatment.

Statistics

Statistical analysis was performed with IBM SPSS version 20.0 software for Windows (SPSS Inc., Chicago, IL, USA). The chi square and Mann-Whitney tests were used to compare the baseline characteristics of the two groups. In cases where the anticipated frequency was lower than 5, a Fisher exact test was applied. Repeated measures analysis of variance (ANOVA) was used for the comparison of all parameters of pain and hand swelling according to the time period and type of therapy until four weeks of follow-up. The interactions between clinical response and time were examined to determine if changes differed in the bisphosphonate and steroid groups. All data are presented as mean ± standard deviation; $p < 0.05$ was considered statistically significant.

RESULTS

General characteristics of patients

Of the 21 recruited patients, 10 were randomised to the steroid group and 11 to the bisphosphonate group. The mean age of participants was 65.19±9.07 years (range 44-77 years), with 11 males and 10 females. Onset duration since stroke occurrence was 51.57±26.60 days. There was no significant difference between the two groups in terms of age, sex, side of the affected hand, type of stroke, K-MMSE scores or onset duration since stroke occurrence (*table 1*). In addition, baseline subjective pain VAS, CMF and CW were not significantly different between the two groups. All patients in both groups completed the four-week study period after the end of each treatment (*table 1*).

Change in clinical parameters after treatment

Subjective pain

Both groups showed significant improvement in subjective pain VAS scores at 1-week follow-up and this effect was maintained until 4-week follow-up (*table 2*). Time-by-group interactions for VAS score were found until 2-week follow-up. However, this was not significant at 4-week follow-up (*table 2*).

Circumference of the middle finger

CMF of the affected hand was significantly reduced at 1-week follow-up in both groups, and this effect was maintained until 4-week follow-up in the steroid group, however only until 2-week follow-up in the pamidronate group (*table 3*). Time-by-group interactions for CMF change were non-significant (*table 3*).

Circumference of the wrist

CW of the affected side was significantly reduced at 1-week follow-up in the steroid group, and this effect was maintained until 4-week follow-up. In the pamidronate group, a significant change of CW was observed at 4-week follow-up (*table 4*). Time-by-group interactions for CW change were significant during the whole period of follow-up (*table 4*).

Adverse effects

In the intravenous bisphosphonate group, two patients (18.2%) had a fever higher than 38.0°C, which resolved within 6-24 hours after administration of acetaminophen. One patient (9.1%) reported general myalgia and another patient (9.1%) presented with a minor infusion site reaction, which improved without any intervention. In the steroid group, no steroid-induced side effects were observed.

DISCUSSION

Our results revealed that pamidronate was as effective as a steroid for pain control in CRPS type I after stroke, but less effective than a steroid for hand swelling. Post-stroke CRPS is usually observed in the paralysed upper extremity with pain, warmness and oedema involving the shoulder and hand. Inflammatory processes and sympathetic-afferent coupling contribute to the peripheral sensitisation of nociceptive fibres. The affected limb presents increased blood flow and vascular permeability and low norepinephrine concentrations from the venous effluent above the painful area, compared with contralateral one.[21] These inflammatory and vasomotor responses also play an important role in oedema.[22] Early and effective control of the inflammatory process is important to prevent disability and improve rehabilitation outcomes.[23,24]

Until now, steroids have been the main treatment option for CRPS in stroke patients. Oral steroids control the inflammatory processes of the patients with CRPS whose oedema, warmness and reddening of skin are clinically detectable.[25] However, steroids can cause serious side effects such as endocrine system disruption including adrenal insufficiency, deteriorating diabetes mellitus, deteriorating osteoporosis, high blood pressure and ulcerative change in the digestive system. Thus, physicians must pay close attention to the use of steroids in these patients.

In light of the need for an alternative safe treatment option, the current study was conducted to quantify the

Table 1. *General patient characteristics*

	Steroid (n = 10)	Pamidronate (n = 11)	*p* value
Age (years)	67.50±6.95	63.09±10.53	0.31
Gender (male:female)	5:5	5:6	1.00
Type of stroke (ischaemia: haemorrhage)	4:6	6:5	0.67
Side of affected hand (right:left)	5:5	3:8	0.39
MMSE score	26.00±1.70	26.0±1.41	0.91
Onset duration since stroke occurrence (days)	47.90±18.25	54.91±33.02	0.55
VAS	6.10±0.88	6.55±1.13	0.22
CMF-affected	7.34±0.34	7.51±0.48	0.22
CMF-unaffected	6.66±0.44	6.89±0.47	0.22
CW-affected	17.46±0.95	17.59±0.96	0.47
CW-unaffected	16.36±0.65	16.68±1.09	0.17

VAS = visual analogue scale; MMSE = mini-mental status examination; CMF = circumference of the middle finger; CW = circumference of the wrist. Values are presented as mean± standard deviation (SD).

Table 2. *Visual analogue scale change after the end of steroid and pamidronate therapy*

	VAS		
	Steroid	Pamidronate	Time-by-group Interactions (*p* value)
Baseline	6.10±0.88	6.55±1.13	
1 week	5.20±0.79†	4.64±1.29‡	0.014*
2 week	4.90±1.10‡	4.27±1.15‡	0.041*
4 week	4.60±0.84‡	4.00±1.90‡	0.205

VAS = visual analogue scale. Values are mean ± SD. Statistical significance compared with baseline at †p < 0.05 level, and ‡p < 0.01 (intra-group differences). Statistical significant time-by group interactions at *p < 0.05 level, and **p < 0.01 (inter-group differences).

Table 3. *Change in circumference of the middle finger after the end of steroid and pamidronate therapy*

	CMF: Affected side (cm)		
	Steroid	Pamidronate	Time-by-group interactions
Baseline	7.34±0.34	7.51±0.48	
1 week	7.09±0.36‡	7.31±0.42†	0.585
2 week	6.94±0.28‡	7.30±0.41†	0.092
4 week	6.94±0.33†	7.31±0.51	0.122

CMF = circumference of the middle finger. Values are mean ± SD. Statistical significance compared with baseline at †p<0.05 level, and ‡p<0.01 (intra-group differences).

effectiveness of a bisphosphonate alternative to steroid therapy on the treatment of post-stroke CRPS. In this study, both the steroid and the intravenous bisphosphonate groups showed significant improvement in pain at one week after drug administration, and this effect lasted until four weeks of follow-up. The effectiveness of pamidronate for pain control was not inferior to the steroid. There were no serious adverse effects during and after pamidronate administration. In addition, pamidronate is easy to administrate for stroke patients, who often have difficulty in taking lots of pills due to dysphagia. Therefore, we conclude that pamidronate infusions are well tolerated and

Table 4. *Change in the circumference of the wrist after the end of steroid and pamidronate therapy*

	CW: Affected side (cm)		*p* value
	Steroid	Pamidronate	Time-by-group interactions
Baseline	17.46±0.95	17.59±0.96	
1 week	16.95±0.78‡	17.51±0.91	0.021*
2 weeks	16.71±0.67‡	17.34±1.06	0.035*
4 weeks	16.70±0.62‡	17.32±1.06†	0.041*

CW = circumference of the wrist; Values are mean ± SD. Statistical significance compared with baseline at †p < 0.05 level, and ‡p < 0.01 (intra-group differences). Statistically significant time-by group interactions at *p < 0.05 level, and **p < 0.01 (inter-group differences).

easy to administrate, and are also as effective as steroid therapy for pain control in post-stroke CRPS. Furthermore, administration of pamidronate may help the disabled stroke patients who are at risk of osteoporosis in terms of preventing bone loss.

The mechanism of the analgesic effect of bisphosphonates remains undetermined. Bisphosphonates have antinociceptive properties in a variety of bone and joint disorders,[26,27] as well as in pain unrelated to bone and joint diseases.[28] Peripheral mechanisms predominate in the early phase of CRPS and central mechanisms dominate in the later phase.[29] The pain relief properties might be induced by inhibiting the production of either proinflammatory cytokines such as interleukin-1, prostaglandins, lactic acid and/or various neuropeptides and neuromodulators, all of which are possibly involved in the sensitisation of afferent nerve fibres and pain modulation.[28,30] Highly water-soluble bisphosphonates might also have a central antinociceptive action, possibly through mechanisms involving ionised calcium[31] by inhibiting the influx of calcium that is crucial for the release of neurotransmitters and other substances implicated in nociception and inflammation.[32,33]

The results of most studies on this topic show that bisphosphonates may be effective in the early phases of the disease,[34] when scintigraphic bone scan more frequently shows a local radiotracer accumulation that possibly means a high local concentration of the drug. These features probably represent the required conditions by which bisphosphonates might modulate various inflammatory mediators that are upregulated in CRPS-I.[35] In the current study, we included only stroke patients in the acute and subacute phases, and treatment was started as soon as possible after they were diagnosed as CRPS. This could have had a favourable effect on the outcomes of pamidronate treatment.

Few studies on the use of bisphosphonate to treat CRPS have achieved consistently positive results in a randomised, double-blinded, placebo-controlled setting.[8] Adami et al.[18] reported that after two weeks of treatment, patients receiving a three-day course of intravenous alendronate presented significant improvement in pain, swelling and range of motion compared with the control group. In the study by Manicourt et al.[14] participants receiving alendronate displayed better pain control and range of motion compared with controls at four, eight and 12 weeks. Moreover, oedema was also improved with alendronate at four and eight weeks. In 2000, Varenna et al.[36] reported that 40 days after treatment, subjects receiving clodronate displayed significantly greater improvement on pain, clinical global assessment and efficacy verbal scores compared with controls. In 2004, Robinson et al.[12] reported that at the three-month evaluation, subjects who had received bisphosphonate reported lower pain scores and higher functional assessment scores pertaining to physical function. However, these studies were in the placebo-controlled setting. To the best of our knowledge, no study has compared the effectiveness of bisphosphonate with steroids.

Pamidronate showed a therapeutic effect on hand oedema; however, its effectiveness was inferior to that of the steroid. From this result, we propose pamidronate as an alternative to steroid in the case of post-stroke CRPS where pain is a dominant symptom. Even with both pain and severe swelling, we could use a pamidronate first and add a steroid later if there is no improvement to the swelling after pamidronate therapy.

The current study has some limitations as it was only conducted in a small number of patients. In addition, hormones related to bone metabolism or bone densitometry, which may help to identify the mechanism by which of bisphosphonate works, were not evaluated. However, the current study showed important findings and has several advantages over previous studies. First, this study involved a homogeneous patient group, i.e., post-stroke CRPS patients. Second, this is the first randomised controlled trial to compare bisphosphonate with a steroid in stroke patients with CRPS for four weeks after the administration of bisphosphonate, and the first to make serial quantitative measures of hand swelling.

CONCLUSION

In this study we observed that intravenous pamidronate therapy was safe, well tolerated and appeared as effective as steroid for pain control of post-stroke CRPS. However, this result should be interpreted with caution, since it included a relatively small number of patients. Further larger controlled studies followed over a longer period are needed to validate these findings and to determine clinical treatment standards, i.e., the optimum dose and duration of administration when using bisphosphonate to treat CRPS after stroke.

DISCLOSURES

This work was supported by a grant from the Jeju National University Hospital Research Fund (2010).

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CASE REPORT

Fatal hyperammonaemia due to late-onset ornithine transcarbamylase deficiency

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ABSTRACT

In this case report we describe a 67-year-old male, admitted to the ICU with pneumonia who unexpectedly developed a fatal coma due to hyperammonaemia. At postmortem the diagnosis late-onset ornithine transcarbamylase deficiency was made. The non-specific clinical presentation, the rapid deterioration and incidentally the fatal outcome all underline the importance of recognition and knowledge of this genetic disorder. Several measures to treat and prevent potentially fatal episodes of hyperammonaemia are available, if only the disorder is recognised in time. In retrospect, several clues to the diagnosis were available in this fatal case, such as voluntary protein avoidance, as well as several male family members who died at a young age of an unknown cause. After his death, two daughters were discovered to be carriers of an OTC gene mutation, as well as his infant grandson. We emphasise the importance of obtaining ammonia levels in all patients with unexplained coma, seizures or cerebral oedema, irrespective of their age, especially in patients in the ICU or in an otherwise catabolic state.

KEYWORDS

Metabolic disorder, inborn error of metabolism, hyperammonaemia

INTRODUCTION

The urea cycle involves a series of biochemical steps in which nitrogen, a waste product of protein metabolism, is converted into urea. This urea is subsequently removed from the body by excretion in the urine. Urea cycle defect is a genetic disorder that results in a deficiency of one of the six enzymes of the urea cycle. These disorders all result in accumulation of nitrogen in the form of ammonia, leading to hyperammonaemia. High serum levels of ammonia are especially toxic for the brain, resulting in irreversible brain damage, coma and death. In late-onset ornithine transcarbamylase deficiency (OTCD) the genetic defect leads to partial enzyme deficiency. Under normal circumstances residual activity makes patients feel generally well. They may remain unrecognised. But in a catabolic state, ammonia levels can rise quickly causing imminent coma and death.

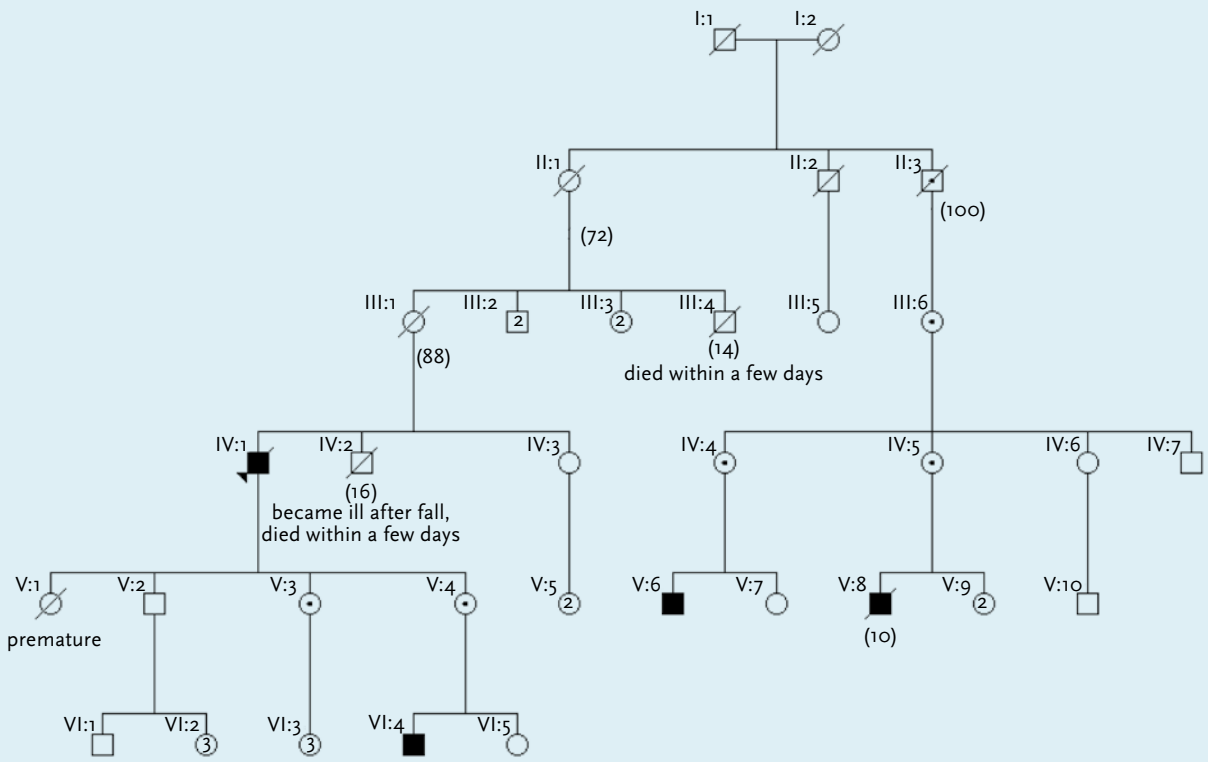
CASE REPORT

A 67-year-old male was admitted to our hospital because of progressive dyspnoea. He had a history of non-specific interstitial pneumonia (NSIP), for which he had never needed treatment with corticosteroids. On arrival, respiratory failure was established and the patient was transported to the ICU for intubation and inotropic support.

An exacerbation of NSIP was considered most likely, possibly combined with a superimposed infection. He was treated with high doses of prednisone, ceftriaxone and erythromycin.

After a few days he seemed to improve due to this treatment and the prednisone was decreased. However, a week after admission his pulmonary condition worsened dramatically. After thorough clinical, radiological and microbiological assessment, a focus of infection could not be found. Since a relapse of NSIP after decreasing corticosteroids seemed most obvious, methylprednisolone 1000 mg was given for three days.

Figure 1. *Pedigree*



After a short period of relative stabilisation the patient unexpectedly developed generalised seizures with signs of autonomic dysregulation. A cranial CT showed no pathology, neither was there any indication of meningitis or electrolyte disturbances.

After consultation of the neurologist, phenytoin and valproate were started, and when there was no improvement levetiracetam was added. Despite these measures the seizures increased in frequency and intensity. His pupils became dilated and unresponsive to light. Another CT scan, 12 hours after the first, showed a drastic change: diffuse cerebral oedema and signs of herniation, still without any indication of an intracerebral cause. Electroencephalography confirmed the clinical diagnosis of brain death.

In parallel, laboratory analysis was performed in search of a metabolic cause of the seizures. This revealed a strikingly high ammonia level of 2700 µmol/l (7-42 µmol/l). When repeated, analysis confirmed the result. The extensive differential diagnosis of hyperammonaemia[1] was taken into account. After hepatic failure was excluded (normal liver enzymes, albumin, prothrombin time/international normalised ratio and echography) we considered an inborn error of metabolism.

Urine analysis demonstrated a strikingly high excretion of uracil 84.8 mmol/mol creatinine (0-15.1 mmol/mol creatinine), orotic acid 11.6 nmmol/mol creatinine (0-1.2 mmol/mol creatinine) and uridine 9.1 mmol/mol creatinine (0-3.7 mmol/mol creatinine). This is suggestive of a urea cycle defect. Genetic testing was performed in his two daughters, since there was no suitable blood sample available from the patient. We found that both were carriers of an OTC gene mutation (c.622G>A, p.Ala208Thr), a mutation more often described in OTCD patients.[2,4] Later, screening revealed one of them to have passed the mutation on to her infant son. Also, family history revealed this mutation was found earlier in two distant cousins, genetically linked through the patient's grandmother (*figure 1*). These findings prove that the cause of the patient's fatal hyperammonaemia was late-onset OTCD.

In retrospect, other clues of OTCD were present. The patient had a tendency to avoid eating meat. He experienced light-headedness after consumption. This voluntary protein avoidance is characteristic for patients with a urea cycle defect.[2] Also, his brother had 'the flu' at the age of 15, developed a coma and died a few days later.

DISCUSSION

Ammonia is mainly produced in the gut, by enterocytes from glutamine or by bacterial degradation of urea and

other nitrogenous substances, such as ingested protein. Another source is protein catabolism and muscle exercise.[1] In the liver, ammonia is converted to carbamyl phosphate, which enters the urea cycle to be converted to urea. Urea is incorporated into amino acids or excreted in the urine. One of the enzymes required for the urea cycle is ornithine transcarbamylase (*figure 2*).

When the liver is unable to metabolise ammonia, elimination is carried out by the muscles, kidneys and brain. In the brain ammonia is metabolised to glutamine. Excessive amounts of intracerebral glutamine cause increased osmotic pressure and cerebral oedema.[1]

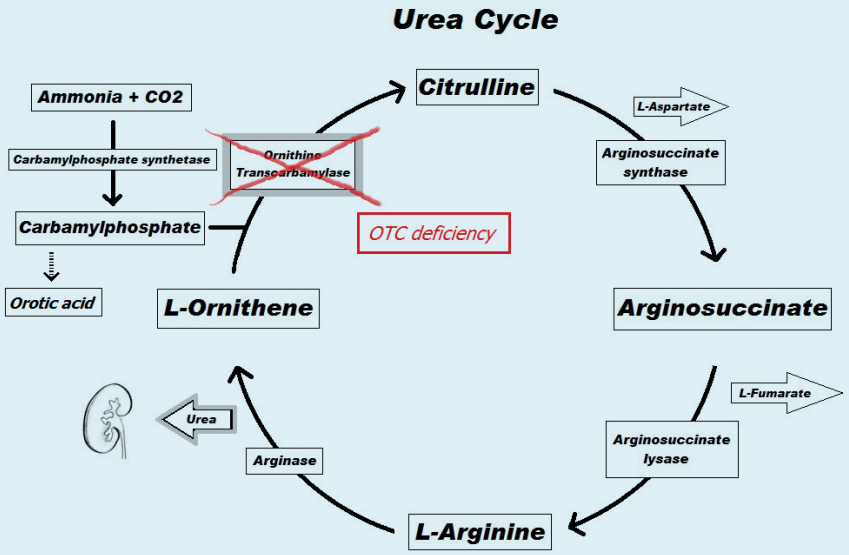
One of the causes of hyperammonaemia is a urea cycle defect. Ornithine transcarbamylase deficiency (OTCD) is the most common urea cycle defect in adults.[2] It is an X-linked disorder due to deleterious mutations in the OTC gene. In hemizygous males the phenotype depends on the type of mutation - 50% have no residual enzyme activity at all and develop hyperammonaemic coma and death in the neonatal period. When some residual activity is present symptoms develop when environmental factors that luxate hyperammonaemia are present (late-onset OTCD). Female carriers are often asymptomatic since the phenotype is influenced by the X-inactivation pattern.

There are many environmental factors that may luxate hyperammonaemia in late-onset OTCD.[1,3] With regard to our patient: he was in a catabolic state due to his illness, infection and prolonged ICU stay. He was given high-dose glucocorticoids, which are known to have a general catabolic effect primarily by enhancing protein turnover. There are at least four case reports of patients with OTCD who developed hyperammonaemic coma following steroid administration.[2] Furthermore, he received protein-enriched enteral feeding in accordance to ICU guidelines, resulting in an increased nitrogen burden. Lastly valproate can cause hyperammonaemia, in patients with defect in the urea cycle, even at therapeutic dosages through inhibition of carbamyl phosphate synthase.[1] However, the patient's seizures had already developed before administration of valproate so the ammonia levels were already neurotoxic.

The relevance of recognising this disorder lies in the reversibility of hyperammonaemia and prevention of permanent neurological damage and death.[4] Genetic counselling of all relatives is mandatory.
When a urea cycle defect is suspected, determination of plasma amino acids (ornithine, glutamine, alanine, citrulline), acylcarnitines (from blood or plasma), urinary organic acids and orotic acid is recommended.[3] After recovery from an acute episode, plasma amino acid levels and/or urinary orotic acid can be helpful. Molecular genetic analysis is generally performed on DNA from the blood. RNA analysis from a liver biopsy is only carried out when DNA analysis is negative.[3]
Treatment should not be delayed, since the prognosis is strongly influenced by the duration of coma and peak ammonia levels.[3,5]

In the acute phase, protein intake should be stopped and a high caloric intake guaranteed to prevent catabolism

Figure 2. *Urea cycle*



(use dextrose 10% and intralipids). Ammonia should be removed, in severe cases by haemodialysis,[6] otherwise by using ammonia scavengers (e.g. sodium benzoate, sodium phenylacetate). Supplementation of L-arginine, L-citrulline and L-carnitine improves ammonia excretion. The only curative treatment is liver transplantation; however, this has only rarely been performed in clinical practice and does not reverse sustained brain damage.

Chronic treatment consists of specialised dietary advice on protein restriction and optimal caloric intake. Catabolism should be prevented by all possible means. In addition ammonia scavengers, suppletion of citrulline and/or arginine can prevent hyperammonaemia.

In conclusion, we advise to obtain ammonia levels in all patients with unexplained coma, seizures or cerebral oedema. Lastly, voluntary protein avoidance could be one of the clues to the diagnosis of OTCD.

DISCLOSURES

No conflicts of interest for all authors. No funding. No prior abstract publication/presentation.

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CASE REPORT

An unexpected pulmonary bystander

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ABSTRACT

A 30-year-old man from Eritrea was admitted with a pulmonary bacterial abscess. Unexpectedly, histopathology of the resected lobe also revealed an infection with *Schistosoma mansoni* with surrounding granulomatous tissue and fibrosis. Patients from endemic areas are often asymptomatic with blood eosinophilia being the only diagnostic clue. Early recognition is important as ongoing fibrosing inflammation may result in organ damage.

KEYWORDS

Schistosomiasis, lungs

What was known on this topic?
Schistosomiasis leads to granulomatous tissue in the infected organs which, unrecognised, may result in fibrosis and organ damage.

What does it add?
Patients who are infected with *Schistosoma* and grew up in an endemic area, rarely experience acute symptoms. Therefore, eosinophilia can be the only diagnostic clue in this patient category.

INTRODUCTION

Recognizing an infection with Schistosoma is important to prevent severe complications. Patients from endemic areas with schistosomiasis are often asymptomatic with blood eosinophilia being the only diagnostic clue, as illustrated in the following case.

CASE REPORT

A 30-year-old male from Eritrea was referred to the University Medical Center Groningen because of a cavitary lesion in the left lower lobe, diagnosed on routine X-ray following immigration. His medical history was unremarkable. He had never been diagnosed with tuberculosis. Our patient had been coughing for several weeks, which was occasionally accompanied by haemoptysis. He had been experiencing fatigue, fever and weight loss. Laboratory results showed normocytic anaemia (haemoglobin 7.8 mmol/l, mean cell volume 87 fl), leukocytosis (leucocytes 12.3 x 10^9/l) with increased neutrophils (7.31 x 10^9/l) and eosinophils (1.14 x 10^9/l), and an increased C-reactive protein (68 mg/l). Laboratory tests including liver and kidney tests were in the normal range. A computed tomography scan of the chest confirmed a large cavitary lesion in the lateral region of the left lower lobe with a horizontal air-fluid level indicating either an abscess or empyema (*figure 1*). The fluid was aspirated by thoracocentesis. *Hemophilus influenza* was cultured from the pleural fluid as well as the collected sputum. Tuberculosis, echinococcosis and strongyloidiasis were ruled out (with repetitive negative sputum cultures, polymerase chain reaction and Ziehl-Neelsen staining and with negative serology, respectively). Under the working diagnosis of a bacterial pulmonary abscess caused by *Hemophilus influenzae* our patient was treated with amoxicillin 500 mg x 4/day. The eosinphilia was explained at that time by an asymptomatic infection with *Giardia lamblia* isolated from the faeces, which was left untreated. During the next five months of adequate antibiotic treatment, our patient clinically improved and inflammatory parameters normalised; however, there was no radiological improvement. Therefore, left lower lobe lobectomy was performed (*figure 2*). Tissue culture showed *Hemophilus influenzae* resistant to amoxicillin. Unexpectedly, histology of the lung revealed a worm (*figure 3a*) and an egg with a lateral spine (*figure 3b*), compatible with the parasite *Schistosoma mansoni*. The surrounding tissue showed granulomas with fibrosing

inflammation. The diagnosis of schistosomiasis was confirmed with serology performed on serum at the time of presentation (Schistosoma worm antigen IgM 1:128 and IgG 1:64). Additional analysis, using a formalin-glycerine sedimentation method, also showed *Schistosoma mansoni* eggs in the faeces. Praziquantel 40 mg/kg/bodyweight/day was prescribed for one day. Our patient had an uneventful recovery from surgery and has been well during eight months of follow-up.

DISCUSSION

Schistosomiasis should be considered in all patients with an unexplained eosinophilia who originate from, or have travelled to, an endemic area for schistosomiasis. Schistosomiasis is endemic in most parts of Africa, where the prevalence can exceed 50% in some local communities.[1-2] When exposed to contaminated water, individuals become infected by skin penetration with the larvae (cercariae) of the *Schistosoma* worm. The cercariae enter the venous circulation and migrate first to the lungs and then to the liver, where they reside during the early stages of infection.[1-2] During this acute phase, a febrile illness (Katayama fever) and pulmonary symptoms such as coughing, wheezing and shortness of breath may occur. The acute phase with pulmonary symptoms typically occurs 3-8 weeks after the initial infection.[1-2] Imaging at this stage often reveals transient nodular lesions.[3-4] However, as illustrated in the above case, patients who grow up in an endemic area rarely experience acute symptoms. Therefore, the acute phase of the disease often passes unnoticed in this patient category. Katayama fever mostly occurs in returning travellers who were exposed to a high worm burden and have little or no immunity against schistosomes. After the acute phase, the larvae mature to adult worms and descend through the venous system to their final habitat. Dependent on

Figure 1. *CT scan of the lungs shows a 7 x 11 cm large cavitary lesion in the left hemi-thorax, containing an air-fluid level compatible with an abcess or empyema*

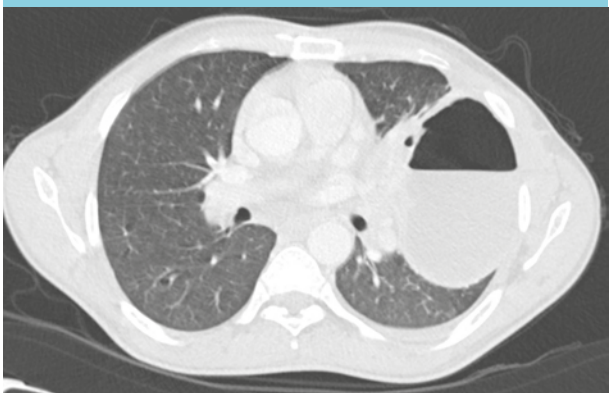


Figure 2. *Left lower lobe after lobectomy, showing a 4 cm cavitary lesion*

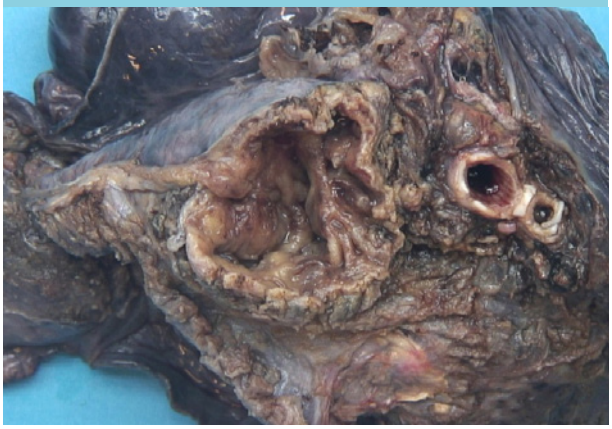
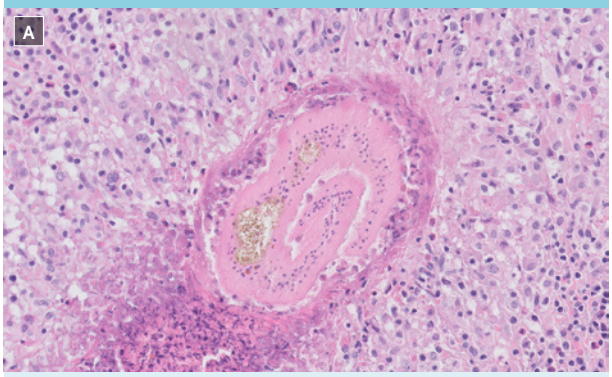
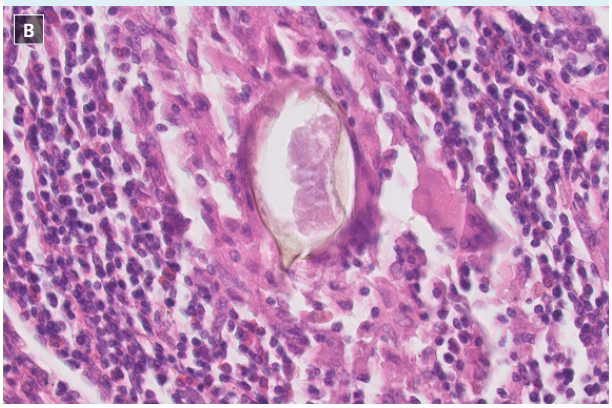


Figure 3A. *Deceased Schistosoma mansoni worm with surrounding granuloma. The surrounding parenchyma show extensive infiltrate with eosinophils, plasma cells and lymphocytes. Digestive tract remnants can be seen as brown pigment in the centre of the worm. (Haematoxylin and eosin; 200x).*
B. *Schistosoma mansoni egg with in surrounding granuloma in the lung. Note the characteristic lateral spine. (Haematoxylin and eosin; 200x)*





the type of *Schistosoma*, the worms usually settle in either the venous plexus of the bowel *(S. mansoni, S. japonicum*) or the urinary bladder (*S. haematobium)* and begin to lay eggs, which may occasionally be ectopically deposited throughout the body.[1,2] The chronic phase of infection can last for several years wherein patients may not experience any symptoms. Due to the presence of eggs in organs, local inflammation and formation of granulomas occur, leading to fibrosis. In the case of *S. mansoni*, portosystemic shunting may also allow eggs to pass directly to the lungs.[5,6] As in our patient, pulmonary infiltration results in pulmonary fibrosis. Roughly 5-10% of patients who are chronically infected develop pulmonary arterial hypertension which ultimately leads to right heart failure.[5,6] Other complications of intestinal schistosomiasis are polyposis of the colon, colon carcinoma and portal hypertension due to liver fibrosis. Complications of bladder schistosomiasis include recurrent urinary tract infections and bladder cancer. Cerebral schistosomiasis occurs in roughly 5% of infected patients and can be due to an infection with *S. Japonicum* as well as with *S. mansoni*. Because of these severe complications, recognising an infection with *Schistosoma* is important.[7] Therefore, any patient originating from, or travelling from an endemic area, who is found to have eosinophilia should be investigated for schistosomiasis.

DISCLOSURES

There are no conflicts of interests.

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CASE REPORT

Amyloid A amyloidosis secondary to hyper IgD syndrome and response to IL-1 blockage therapy

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ABSTRACT

A 62-year-old woman with a history of genetically confirmed hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) was admitted because of chronic diarrhoea. During admission she developed a rapidly progressive nephrotic syndrome. Reactive amyloid A (AA) amyloidosis was confirmed after colonic and renal biopsy which showed deposition of amyloid. After initial treatment with high-dosed corticosteroids, therapy was switched to anakinra, an IL-1 receptor antagonist, but her symptoms persisted. After cessation of anakinra, a marked exacerbation of the intestinal symptoms was noted. Nine months after the initial diagnosis of reactive amyloidosis without any amelioration of the symptoms and a decreasing quality of life, our patient declined further treatment and died soon after. This case demonstrates that AA amyloidosis does occur in patients with HIDS and can present with intestinal symptoms and proteinuria. Once amyloidosis is diagnosed the goal of treatment is to prevent further complications. In this case report we give an overview of previous cases with amyloidosis complicating HIDS with the treatments received and propose a step-up treatment plan for future cases.

KEYWORDS

AA amyloidosis, hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS), mevalonate kinase deficiency (MKD), anakinra; IL-1 blockage.

What was known on this topic?
AA amyloidosis is a known complication in periodic fever syndromes but rare in HIDS. If left untreated it can lead to intestinal disease and/or progressive cardiac and renal failure.

What does this add?
In this article we present the seventh patient with AA amyloidosis secondary to HIDS, describe treatment and outcome of treatment with anakinra, give an overview of literature on treatments used previously and propose a step-up treatment plan for future cases.

INTRODUCTION

Hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS), a hereditary periodic fever syndrome, is an autosomal-recessive, auto-inflammatory disorder mediated by mevalonate kinase deficiency. The main symptoms are recurrent febrile attacks, arthralgia, cervical lymphadenopathy, diarrhoea and rash.[1] Diagnosis is confirmed by genetic analysis since multiple mutations have been described in the mevalonate kinase (MVK) gene.[2] Little is known about the mechanism leading to an auto-inflammatory condition as a result of reduced MVK activity. Ex-vivo experiments suggest that peripheral blood mononuclear cells produce large amounts of IL-1, hypothetically as a result of either excess or lack of isoprenoid products.[3] Recently, it was hypothesised that a lack of 25-hydroxycholesterol, a metabolite in the cholesterol pathway, plays a role in the pathogenesis.[4]

AA amyloidosis is a known complication of hereditary periodic fever syndromes, especially familial Mediterranean fever in which the incidence has been reported to be as high as 60-75%.[5] Reactive amyloidosis secondary to HIDS is relatively rare. Only six cases of amyloidosis secondary to HIDS have been reported in the literature.[6-10] Literature on the treatment of patients with

AA amyloidosis secondary to hereditary periodic fever syndromes other than familial Mediterranean fever is very sparse.
We present the seventh case of a patient with reactive AA amyloidosis secondary to HIDS and evaluate the response to IL-1 blockage in the progression of amyloidosis.

CASE REPORT

We present a 62-year-old female patient with genetically confirmed HIDS. She was heterozygote for the I268T and V377I mutations of the MKV gene. The patient was admitted with chronic diarrhoea. During admission she developed a rapidly progressive nephrotic syndrome. Physical examination revealed marked oedema up to the patient's waist. Laboratory results showed: serum creatinine levels up to 194 µmol/l corresponding to an estimated glomerular filtration rate of 23 ml/min/1.73 m^2, blood urea nitrogen 10 mmol/l, phosphate 1.73 mmol/l, albumin 20 g/l and cholesterol 6.8 mmol/l. The highest concentration of serum amyloid A was 15 mg/l (reference value 0-4 mg/l). Mevalonic acid in the urine had a concentration of 3 µmol/mmol (reference value < 1 µmol/mmol).
Colonic and renal histological biopsies showed deposition of amyloid, present in small arteries and in the kidney, also in glomeruli. Positive Congo-red staining is shown in *figure 1*. Immunohistochemical staining for AA amyloid (antibody clone MC1, Dako bv, Belgium) was positive (*figure 1*).
Echocardiography, performed to assess cardiac involvement, revealed concentric hypertrophy with an echographic aspect of cardiac amyloidosis. On the computed tomography scan of the abdomen the walls of the terminal ileum and sigmoid showed signal enhancement and wall thickening.
Initial treatment with high-dosed corticosteroids showed no improvement in the patient's intestinal symptoms or proteinuria, hence treatment with anakinra, an IL-1 receptor antagonist (100 mg/day subcutaneously) was initiated. Several months after initiation of therapy with anakinra, the proteinuria persisted and no improvement in renal function was observed; for this reason the line of treatment was discontinued. However, after cessation of IL-1 blockage, a marked exacerbation of the intestinal symptoms was noted. Gastric biopsy revealed amyloid depositions in the gastric microvasculature. Nine months after the initial diagnosis of reactive amyloidosis without any amelioration of the symptoms and a decreasing quality of life our patient declined further treatment and died soon after.

DISCUSSION

We present the seventh case of AA amyloidosis complicating HIDS. Amyloidosis is often suspected in hereditary periodic fever syndromes in particular familial Mediterranean fever, cryopyrin-associated periodic syndromes (CAPS; e.g. Muckle-Wells syndrome) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS). However, in HIDS this major complication is rarely seen despite the favourable conditions for amyloidogenesis.[11] The defect in mevalonate kinase, which leads to a deficiency of isoprenoid products, seems to have a protective effect on the development of amyloidosis. Farnesylated proteins seem to play an

Figure 1. *Colon (A) and kidney (B and C) biopsies showing deposition of amyloid (arrows) in small arteries (A and B) and glomeruli (C). The amyloid stained bright green when viewed under polarised light (Congo red stain, 10x). Immunohistochemical stain of the kidney biopsy (D) for amyloid AA was positive (10x)*

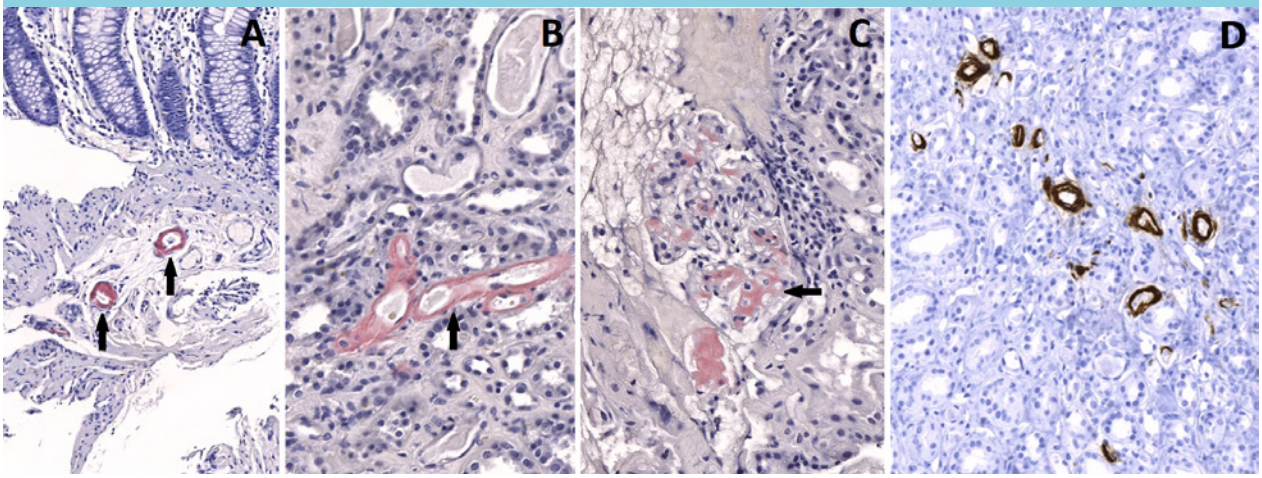

Table 1. *Published case reports of HIDS patients with amyloidosis. Treatment and results*

Authors	N°	Intervention	Outcome
Obici et al.[8]	1	Colchicine	No reduction of febrile attacks. No reduction of serum amyloid A levels
Lachmann et al.[6]	2	Anakinra	No clear benefit after 6 weeks trial
		Etanercept	Good clinical and biochemical response
Siewert et al.[9]	1	Etanercept	Cessation of febrile attacks. Death due to cardiac involvement
Li Cavoli et al.[7]	1	Anakinra	No results or follow-up published
Yel et al.[10]	1	Etanercept	Clinical improvement, cessation of febrile episodes

important role here.[12] Early diagnosis is crucial because limiting the progression of amyloidosis by treating the underlying disease is the cornerstone of the management strategy.

No directed therapy for HIDS is currently available. Recently a comprehensive review of the treatments of hereditary periodic fever syndromes was published by Ter Haar et al.[13] Specific data on the treatment of HIDS in this review suggest that colchicine is not effective.[13-15] Statins were a promising therapy due their blocking effect in the isoprenoid pathway but results were also poor.[13-15] NSAIDs and corticosteroids are commonly prescribed in clinical practice and are anecdotally reported to have positive results in HIDS.[14,15] Therapy with anakinra, an IL-1 inhibitor and etanercept, a TNF-α inhibitor, has shown overall positive results.[13-22] Recent publications with canakinumab, an IL-1 antibody, have also shown promising results.[15,23] The question remains what the therapy of amyloidosis secondary to HIDS should be. In *table 1* we summarise the results from previous case reports and small case series in the literature. Colchicine was found to be ineffective in one patient.[8] Two reports of treatment with anakinra were published, the clinical course was not described in one of the reports and no clear benefit was seen in the other.[6,10] Etanercept was reported to have good results in three patients.[6,7,9]

In the absence of a clear evidence-based treatment strategy we propose following a step-up plan for future cases. Stopping amyloidogenesis must be achieved by blocking the acute-phase response. Guidelines recommend initiating steroids but experts doubt their effectiveness. If the amyloidosis aggravates, the next step should be one of the biological drugs discussed above. Expert consensus is that anakinra may be more effective than TNF blockade, however this is based mainly on pathophysiological arguments and clinical experience. Anakinra has been the most effective biological drug for HIDS but has not been as effective in cases complicated by amyloidosis. Higher dosages of anakinra might be needed and timing of initiation of therapy is of major importance. The choice of a specific biological cannot be deducted from the literature and should be tailored to each patient based on individual characteristics. The key to limiting amyloid deposition and its target organ complications is early recognition and diagnosis.

DISCLOSURES

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

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PHOTO QUIZ

Not your average filling defect

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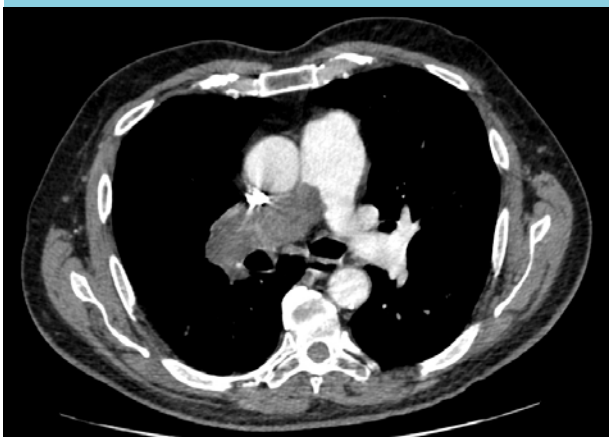
CASE REPORT

A 72-year-old man presented with progressive dyspnoea and weight loss for two months. He had a 20 pack-year tobacco history. He had not travelled recently. Vital signs were significant for a tachycardia of 102 beats/minute and an oxygen saturation of 95% on room air. The jugular venous pulse was elevated. Cardiopulmonary examination was normal. He had minimal lower extremity oedema. Laboratory evaluation revealed only mild normocytic anaemia. Brain natriuretic peptide was 54 ng/l. A clear chest radiograph prompted computed tomography angiography (CTA) of the chest *(figure 1)*.

WHAT IS YOUR DIAGNOSIS?

See page 48 for the answer to this photo quiz.

Figure 1. *Axial CTA at the level of bifurcation of the main pulmonary artery demonstrates a large filling defect occupying the entire luminal diameter of the right pulmonary artery with expansion of the artery in that area*



ANSWER TO PHOTO QUIZ (PAGE 47)

NOT YOUR AVERAGE FILLING DEFECT

DIAGNOSIS

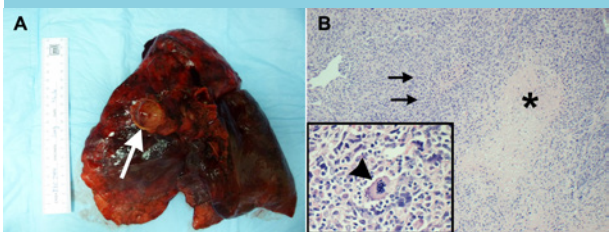
CTA demonstrated a large filling defect in the right pulmonary artery (RPA) compatible with pulmonary embolism. The patient's constitutional symptoms raised concern about malignancy as a predisposing factor for venous thromboembolism. ^{18}Fluorodeoxyglucose positron emission tomography (PET)/CT was performed, which revealed increased uptake (SUV_{max} 9.3) only in the RPA. This finding was consistent with a neoplasm arising from within the RPA itself.

After intraoperative frozen section confirmed malignancy, the patient underwent right pneumonectomy and sleeve resection of the RPA. Pathology demonstrated an 8.5 x 3.5 x 2.0 cm pulmonary artery intimal sarcoma (PAS) *(figure 2A)*. The tumour was composed of moderately pleomorphic spindle cells with abundant mitotic figures and scattered tumour giant cells as well as areas of necrosis *(figure 2B)*. Immunohistochemical stains were positive for vimentin, and fluorescence in-situ hybridisation to evaluate for murine double minute 2 (MDM2) amplification was likewise positive.

PAS is extremely rare. Men and women are equally affected and are usually between 45-55 years of age at disease onset. Nonspecific symptoms make delays in diagnosis common. Furthermore, since PAS appears as an intraluminal filling defect on CTA, these cases are often initially misdiagnosed as pulmonary embolism. Often, PAS is considered only when the patient does not respond to anticoagulation or even thrombolytic therapy.[1] CT findings suggestive of PAS rather than pulmonary embolism include filling defects occupying the entirety of the main pulmonary artery or its proximal branches and expansion of any segment of the pulmonary artery. Extraluminal extension also suggests PAS. On PET, PAS, unlike pulmonary embolism, will classically demonstrate increased uptake of ^{18} Fluorodeoxyglucose.[2]

In addition to the spindle cells and pleomorphic giant cells typical of mesenchymal tumours, a heterogeneous hypercellular pattern intermixed with varying degrees of necrosis and mitotic activity is characteristic of PAS. Immunohistochemical stains are usually positive for desmin, vimentin, cytokeratin, and smooth-muscle specific actin. Overexpression of the MDM2 oncogene, a negative regulator of p53, is a frequent finding.[2]

Figure 2. *(A) Gross pathology of the right lung demonstrates a large pulmonary artery intimal sarcoma (8.5 x 3.5 x 2.0 cm) in the right pulmonary artery. (B) Microscopic pathology shows moderately pleomorphic spindle cells (arrows) with areas of necrosis (asterisk) (H&E, 100x). Inset demonstrates a tumour giant cell (arrowhead) (H&E, 400x)*



Survival in PAS is poor: a mean of 1.5 months in patients treated without surgical intervention. A significant percentage of patients die of right ventricular failure secondary to outflow obstruction.[3] Histological subtype may also affect survival. Adjuvant chemotherapy, if tolerated, is considered standard of care and can increase survival to 12-18 months. Treatment regimens are extrapolated from other sarcomas and usually include anthracyclines, ifosfamide, and cisplatin. The role of radiotherapy is currently undefined.[4]

Our patient's postoperative course was uncomplicated. He declined adjuvant therapy. At three-month follow-up, he had no evidence of recurrent disease.

DISCLOSURES

No conflicts of interest for all authors.

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PHOTO QUIZ

Acute erythema of the face after methotrexate

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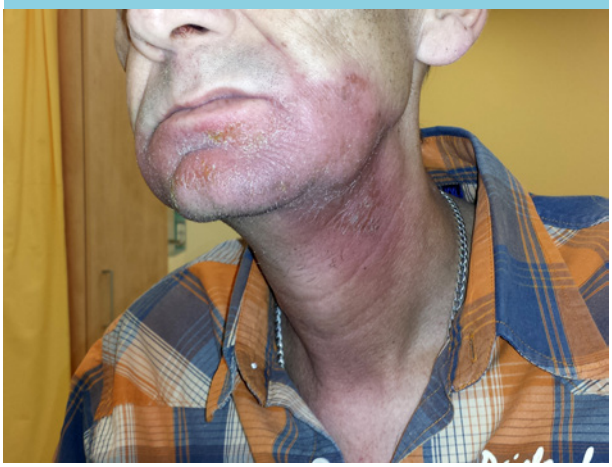
CASE REPORT

A 52-year-old man was treated with weekly 40 mg/m^2 methotrexate monotherapy as palliative treatment because of an irresectable recurrence of an oropharyngeal carcinoma. Five months before he received primary chemoradiotherapy, consisting of weekly cisplatin 40 mg/m^2 combined with radiotherapy to the tumour as well as the neck, with a maximum of 68G y, for a cT4aN2bM0 oropharyngeal carcinoma. He tolerated this therapy well, with only mild adverse events. The physical examination before starting the methotrexate revealed no abnormalities of the skin. After three doses of methotrexate a brisk and itchy erythema developed on the chin, which expanded rapidly to the whole neck (*figure 1* and *2*).

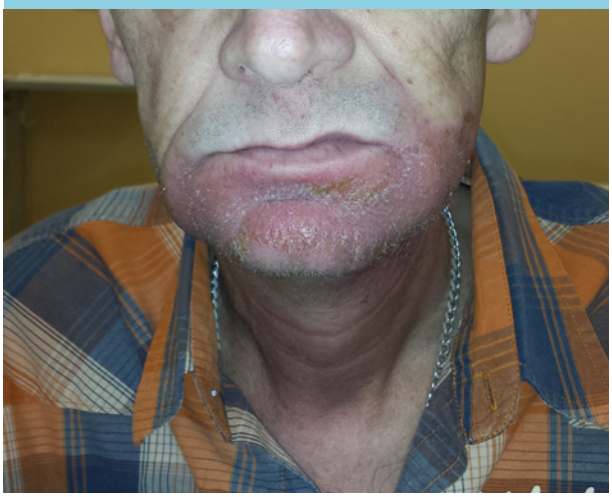
Figure 1. *Well demarcated erythema of the face and neck 21 days after administration of methotrexate*



WHAT IS YOUR DIAGNOSIS?

See page 50 for the answer to this photo quiz.

Figure 2. *Erythema of the chin*



ANSWER TO PHOTO QUIZ (PAGE 49)

ACUTE ERYTHEMA OF THE FACE AFTER METHOTREXATE

DIAGNOSIS

Erythema that looks like the acute radiation dermatitis seen during radiotherapy, which developed some time after the radiotherapy and is provoked by the administration of certain drugs, is called radiation recall dermatitis (RRD). This phenomenon was first described by D'Angio in 1959.[1] Most frequently RRD will occur, but a radiation recall mucositis, pneumonitis or enteritis have also been described.[2] The overall incidence of RRD is hard to estimate, because in the literature usually only case reports are described,[2] but Kodym found an incidence of 9%.[3] Causative agents can be chemotherapeutic agents, antibiotics, anti-hormonal therapy and statins as well.[2] RRD after methotrexate has already been described.[4] The exact aetiology is still not clear, but some hypotheses about the possible mechanism are vascular damage, epithelial stem cell inadequacy or sensitivity and drug hypersensitivity reactions.[2] The time between radiotherapy and development of the radiation recall phenomenon can range from seven days to 15 years.

Treatment of RRD consists of steroids and anti-inflammatory drugs, either systemically or topically, but what is most important is discontinuation of the causative drug. It is unclear whether rechallenge to the specific drug is possible, because this is performed infrequently. However, in some cases no new reaction occurred after rechallenge.[2]

In our patient the fourth gift of methotrexate was cancelled and topical corticosteroids were prescribed. After one week the erythema had almost totally disappeared. We decided to rechallenge with the same dosage of 40 mg/m^2 and after five weeks there was no evidence of recurrence of the RRD.

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LETTER TO THE EDITOR

Hepatitis E virus infection among blood donors in the South Caribbean: is screening warranted?

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Dear Editor,

Despite extensive screening measures to prohibit transfusion-transmissible infections, blood transfusion is not, and may never be, 100% safe. This is because new and re-emerging viruses are spreading more widely and rapidly and may pose a yet undefined risk to transfusion safety.[1,2] In order to be transmittable through blood, there should either be a period of asymptomatic viraemia, or the infection should be subclinical in a proportion of the infected population.[3,4]

Hepatitis E virus (HEV) is a member of the family *Hepeviridae* and predominantly transmitted by the faecal-oral route through contaminated water and food. However, HEV can also be transmitted through donation of HEV-infected blood.[3-6] Worldwide, HEV is not included in the standard screening programs in blood banks.

Patients usually recover spontaneously, although infection with HEV can be more severe in pregnant women and immune-compromised patients, especially those undergoing organ transplantation.[3-7] HEV is classified into four genotypes (1-4).[3,4] Genotype 3 is the main cause of human infections in the United States and Europe and can be transmitted to humans through ingestion of raw meat from infected animals, mostly swine.[8,9,10]

The global incidence of hepatitis E infection has increased, and is an important public health concern in developing countries.[1,3,4,8]

Several international studies have described the presence of HEV antibodies and HEV-RNA in the serum of healthy blood donors[1,6,10-12] with seroprevalences ranging between 2.3-32.6%.[1,8,10] Latin America, which is closely related to the South Caribbean, is considered to be an endemic region with seroprevalences between 1.5-20%.[8] In the Netherlands, Slot et al. showed that 27% of the donations tested positive for anti-HEV IgG, of which 3.5% also tested positive for HEV IgM; four of them were viraemic.[1] Based on their findings, the risk of HEV transmission from blood donors to blood recipients through blood transfusion is calculated to be around one per day.

The extent to which HEV circulates in Curaçao and Aruba in the South Caribbean is as yet unknown. The goal of this study was therefore to determine the HEV seroprevalence and potential risk of transmission via blood donors in the South Caribbean area.

Study setting

Curaçao and Aruba are two Caribbean islands, 40 miles north of the coast of Venezuela, with an estimated population of 150,000 and 107,000 people respectively. Donated blood from Aruba is stored in the blood bank in Curaçao. Both blood banks are certified yearly by Sanquin, which is the European Blood Bank Certification Organisation that works according to ISO standards.[13]

Data collection

A cross-sectional serosurvey was conducted in April and May 2011 in blood plasma of all blood donors. Informed consent was obtained at the moment of donation.

Blood donations of both islands, around 10,000 per year, are routinely screened for human immunodeficiency virus,

Table 1. *Seroprevalence of virus infections among blood donors in Curaçao and Aruba (n = 600)*

	Total (n = 600) N (%) CI 95%	Curaçao (n = 500) N (%) CI 95%	Aruba (n = 100) N (%)
Hepatitis E			
Anti-HEV IgG	25 (4.2%) CI 2.8-6.0%	19 (3.8%) CI 2.4-5.8%	6 (6%) CI 2.5-12.1%
Anti-HEV IgM	1 (0.5%) CI 0.008-0.82%	1 (0.2%) CI 0.01-0.1%	0 CI 0.0-3.0%
HEV-RNA PCR	0 (0%) CI 0.0-0.50%	0 CI 0.0-0.60%	0 CI 0.0-3.0%

HEV = hepatitis E virus; PCR = polymerase chain reaction; CI = confidence interval.

hepatitis B and C virus, human T-lymphotropic virus 1 and 2 and syphilis. Afterwards, samples are stored for two years at -80°C. Persons belonging to pre-defined risk groups for the transmission of viral diseases (e.g., men who have sex with men, people who have had a febrile episode < 6 months before donation) are not allowed to donate blood.

Diagnostics

A total of 1 ml blood plasma was collected from each donor. Samples were serologically analysed for anti-HEV IgG and anti-HEV IgM, with subsequent testing for HEV-RNA at the department of ViroScience of the Erasmus Medical Centre in Rotterdam. Sera were tested using the hepatitis E IgG-ELISA WE-7296 and hepatitis E IgM-ELISA WE-7196 (both Wantai Diagnostics, Beijing, China). Positive IgG-HEV samples were screened for the presence of HEV RNA by an internally controlled quantitative real-time polymerase chain reaction with primers detecting all four genotypes and validated according to International Standards Organisation guidelines 9001 and 15189.

Results

In total, 500 blood samples from Curaçao and 100 samples from Aruba were analysed. The mean age of donors from Curaçao was 55.1 years (range 19-75 years). Positive anti-HEV IgG donors were on average 55.3 years of age (30-73 years).

Overall, 25 (4.2%; 95% CI 2.8-6.0%) donor sera were reactive for anti-HEV IgG and one (0.17%; 95% CI 0.008-0.82%) tested positive for anti-HEV IgM. The IgG reactive samples were all HEV-RNA negative. An overview of the HEV prevalence is shown in *table 1*.

Discussion

In this combined cohort of blood donors from Curaçao and Aruba in the South Caribbean, 4.2% (95% CI 2.8-6.0%) and 0.17% (95% CI 0.008-0.82%) of the samples were found to be anti-HEV IgG and IgM seropositive, respectively. No samples were HEV-RNA positive. Based on these results, the potential risk of HEV transmission within this blood bank is very low.

The anti-HEV IgG seroprevalence and the 95% CI in our study is at the low end of the range compared with seroprevalences among blood donors in other high-income countries and surrounding regions, with ranges of 2.3-32.6%.[1,8,10,11] Genotype 3 is the main cause of human HEV infections in America and Europe and can be transmitted to humans from infected animals.[4,8,10] A major cause for human HEV infection is swine meat consumption; the relatively few pig farms and subsequently low swine consumption in the South Caribbean may explain the low seroprevalence.[4,8]

Our data may help to make a balanced decision as to whether HEV screening of blood donors should be indicated in the South Caribbean setting and whether HEV transmission among blood donors with a recent travel history to Curaçao or Aruba may be increased. Based on our findings, we do not believe that the blood banks in Curaçao and Aruba should extend their screening program for all donors to HEV. Besides that, our findings indicate that the risk of HEV transmission among Dutch donors with a recent travel history to the South Caribbean is not increased for Dutch blood recipients.

Roughly, one twentieth of blood donors have ever been infected with anti-HEV in the South Caribbean and none of the donations were viraemic. This number is not exceedingly worrying, especially since HEV infection, even in vulnerable patients, is usually self-limiting.[3,4] Thus, we believe that the risk of transmission of HEV through blood donation is very small in the South Caribbean. However, it can be considered to make exceptions for selected risk groups (e.g. immune comprised patients) to test donor blood for the presence of HEV-RNA.

Our study is the first to assess the seroprevalence of HEV among blood donors in Curaçao and Aruba in the South Caribbean, although there are some limitations to be discussed. First, only anti-HEV IgM and IgG positive samples were tested for the presence of HEV-RNA. Therefore, we may have missed some positive HEV-RNA samples. However, the serological response of anti-IgM only occurs about few days after presence of HEV-RNA.[3,5]

Another limitation is the limited access to epidemiological data. We recommend that future sero-epidemiological studies on viral infections among blood donors should also review the patient's past medical history, recent travel history, and lifestyle factors to determine the likelihood that test results are due to an infection with HEV. Notwithstanding these limitations, we believe that the results of our study provide a good indication of the seroprevalence and the potential risk of transmission of HEV among blood donors in the south-Caribbean.

In conclusion, the HEV seroprevalence in the present study is lower than seroprevalences among blood donors in other high income countries and surrounding regions. Globally, HEV is not included in the current standard screening programs for blood donors. Worldwide, it is debated whether screening for HEV should be performed routinely.[1,3] Based on our results, there is currently is no rationale for extension of blood donation screening programs to HEV for blood donors in the South Caribbean.

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LETTER TO THE EDITOR

Rabies prophylaxis for travellers

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Dear Editor,

I read the article by Wieten and colleagues[1] with great interest. The authors investigated risk factors of rabies exposure among travellers. However, I have some comments concerning this study.

In line with the recommendations of World Health Organization, postexposure prophylaxis (PEP) is not indicated for category I rabies suspected contacts.[2] However, ten persons in their study who received PEP had category I contact.

In their study, the median time between departure and animal-associated injury was found to be 9 days (IQR: 5-17 days). It is well known that protective antibodies against rabies vaccination begin to appear at postvaccination day 7.[3] So, departure time can be scheduled at least seven days after pre-exposure prophylaxis.

DISCLOSURES

Conflict of interest: none declared.

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REPLY TO LETTER TO THE EDITOR OF H.T. GOZDAS

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Dear Editor,

We appreciate Dr. Gozdas' interest in our work.

Regarding the point raised that a number of patients included in our study fell into WHO category I rabies suspected contacts, we explained the rationale behind our decision in the discussion of our paper:[1] 'Seven travellers with a type I incident received rabies immune globulin, in deviation from the current Dutch guidelines. The rationale for that was that four were children aged 12 years or less; and all seven cases had had contact with a pet dog proven to be rabid, imported from Poland or Morocco with unknown times or dates of exposure, explaining this more prudent approach.'[2]

Because the medical history in children is less reliable with regard to possible exposure, a more cautious approach was chosen.

Regarding the point-of-time of patients' visits to the travel clinics, we advise that all travellers should plan to pay their visit no less than four weeks prior to their planned departure. Practice tells us that this unfortunately does not always happen and that consequently, in the case of rabies immunisation, protection against exposure may not be effective during their first days of travels.

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LETTER TO THE EDITOR

Treatment restrictions and empirical antibiotic treatment of community-acquired pneumonia in elderly patients

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Dear Editor,

Community-acquired pneumonia (CAP) is a major health problem in the elderly, causing an estimated 5100 deaths in the Netherlands annually.[1] Treatment of CAP in elderly patients poses several challenges as a consequence of pre-existing comorbidities, quality of life and end-of-life decisions.[2] For a significant part of this specific patient population, optimal care may involve withholding treatment extension or even discontinuation of treatment. Adjustment in treatment can vary from specific restrictions such as do-not-resuscitate orders to providing palliative care only.

Previous studies found an association between treatment restrictions and mortality, and have also shown an association with less aggressive or inadequate care.[3,4] However, the presence of treatment restrictions is usually not reported in therapeutic clinical studies, such as studies evaluating treatment strategies for CAP. It is unknown if treatment restrictions are associated with non-related treatment choices in CAP patients as well.

We performed a prospective cohort study on hospitalised elderly CAP patients in the Netherlands. We aimed to determine whether treatment restrictions act as a confounder of the association between empirical antibiotic treatment and clinical outcomes defined as mortality on day 30 and day 90, as well as length of hospital stay.

We studied 1093 elderly CAP patients, of whom 296 patients (27.1%) had treatment restrictions within 48 hours of admission. Treatment restrictions were associated with 90-day mortality (crude HR 4.035, 95% CI 2.905-5.606; adjusted HR 2.636, 95% CI 1.912-3.634), which implicates that treatment restrictions are a good clinical marker for comorbidity and prognosis. An association with empirical antibiotic treatment, however, was not found (crude OR 0.962, 95% CI 0.729-1.269; adjusted OR 1.002, 95% CI 0.732-1.372). For determination of a possible confounding effect, we performed multivariate analyses with and without inclusion of treatment restrictions as potential confounders. For all analyses, treatment restrictions did not confound the association between empirical antibiotic treatment and clinical outcomes

In conclusion, in hospitalised CAP patients, treatment restrictions are frequently applied. They are a sensitive proxy for severity of comorbidity, frailty and prognosis. Treatment restrictions were not associated with empirical antibiotic treatment and did not confound associations between empirical antibiotic treatment and clinical outcome of CAP. However, given the strong and independent association with clinical outcome, documentation of treatment restrictions in future studies is recommended.

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