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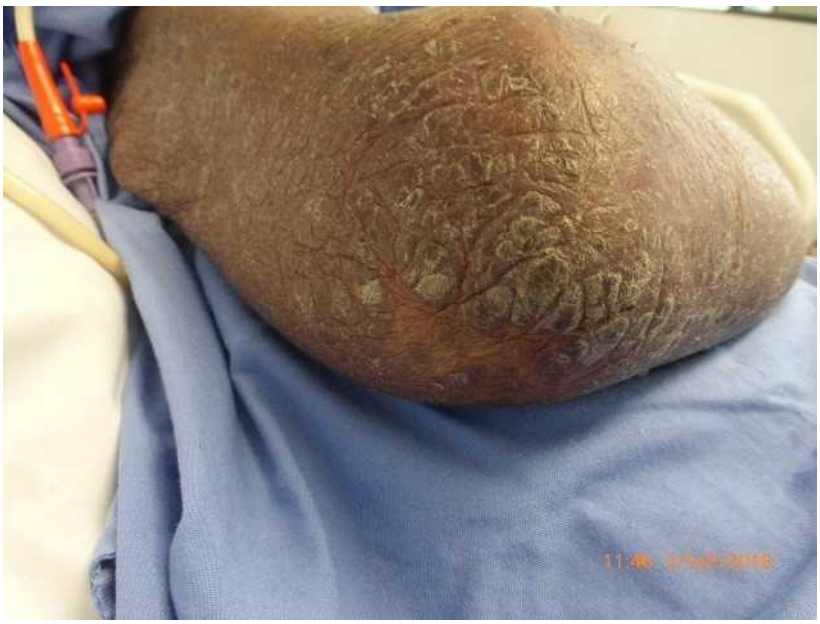

Brown-white hyperkeratotic plaques on the elbow: what is your diagnosis?

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EDITORIAL

Lithium: balancing mood, water, and renal function decline

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Lithia water was first marketed to consumers in the 1800s for its purported therapeutic merits for conditions ranging from gallstones to kidney disease.[1] Although later revealed to be homoeopathically dilute and curing little more than thirst, at that time, few could have predicted the use of lithium as a highly effective mood stabilizer, much less, its significant renal toxicity.

Lithium influences multiple elements in the renal urinary concentrating mechanism, potentially leading to nephrogenic diabetes insipidus (NDI). The pathophysiology of this condition includes entry of lithium into principal cells in the collecting duct by substituting for sodium on the epithelial sodium channel and accumulation in these cells, which dysregulates various downstream signaling pathways. One such pathway may involve the inhibition of glycogen synthase kinase type 3 (GSK3), which, paradoxically, may be protective in acute kidney injury.[2] Moreover, lithium-treated patients are characterized by elevated urinary prostaglandin E2 levels, likely the result of increased activity of cyclooxygenase-2. These, and possibly other events, reduce plasma membrane abundance of aquaporin-2 in affected cells, leading to impaired water reabsorption. In the longer term, lithium also lowers the ratio of principal to intercalated cells, resulting in augmentation of this effect.[3]

Prolonged exposition to lithium also places the kidney at risk for permanent injury via poorly defined pathways, in which inhibition of GSK3 again appears to be a cornerstone.[4] Lesions associated with chronic use include interstitial fibrosis and proximal tubular atrophy, and at a later stage, glomerulosclerosis.[5] The majority of patients with clinically evident lithium-induced nephropathy display microcyst formation, which is characteristic of lithium toxicity.[6]

Despite a large swathe of publications over the past decades, studies providing estimates of renal risks in unselected, well-monitored patients are still poorly aligned. In this issue of the *Netherlands Journal of Medicine*, Doornebal et al. report on a first cross-sectional baseline analysis of 98 lithium-treated patients recruited from two Dutch mental health centres for an ongoing prospective study.[7] They gave eligible patients a 40 µg intranasal dose of a vasopressin analogue (dDAVP) to determine maximal urine osmolality. After an average of eight years on lithium, 51 percent had a moderately decreased urinary concentrating ability, while 16 percent were diagnosed with NDI. As expected, defects in urinary concentrating ability became more prevalent the longer patients had been on lithium, appearing in up to 78 percent of those who had used it for over 15 years. Interestingly, it appears that patient-reported symptoms such as thirst and nocturia, which are frequently reported by lithium-treated patients,[8,9] are poorly correlated with the presence of NDI. In addition, in this population and other published reports, defects in urinary concentrating ability, which may become partly irreversible, occurred before a decrease in the estimated glomerular filtration rate (eGFR).

Most chronic kidney disease (CKD) appears only after at least a decade of lithium use.[10] Of note, toxicity-related discontinuation of lithium may have led to significant underreporting of such outcomes in this and previous cross-sectional studies. Data on predictors of the development of CKD during lithium treatment, in particular the relationship between baseline urinary concentrating ability and delayed eGFR decline, are lacking. Indeed, future data from the prospective study of this cohort will answer the question of whether more dilute urine in dDAVP-challenged patients may indeed be viewed as a presage to imminent kidney function decline.

REFERENCES

1. Shorter E. The history of lithium therapy. Bipolar Disord. 2009;11 Suppl 2:4-9.
2. Alsady M, Baumgarten R, Deen PM, de Groot T. Lithium in the Kidney: Friend and Foe? J Am Soc Nephrol. 2016;27:1587-95.

3. Christensen BM, Marples D, Kim YH, Wang W, Frokiaer J, Nielsen S. Changes in cellular composition of kidney collecting duct cells in rats with lithium-induced NDI. Am J Physiol Cell Physiol. 2004;286:C952-64.

4. Kjaersgaard G, Madsen K, Marcussen N, Christensen S, Walter S, Jensen BL. Tissue injury after lithium treatment in human and rat postnatal kidney involves glycogen synthase kinase-3beta-positive epithelium. Am J Physiol Renal Physiol. 2012;302:F455-65.

5. Presne C, Fakhouri F, Noel LH, et al. Lithium-induced nephropathy: Rate of progression and prognostic factors. Kidney Int. 2003;64:585-92.

6. Khan M, El-Mallakh RS. Renal microcysts and lithium. Int J Psychiatry Med. 2015;50:290-8.

7. Renal concentrating ability and glomerular filtration rate in lithium-treated patients. Neth J Med. 2019;77:139-49.

8. Lokkegaard H, Andersen NF, Henriksen E, et al. Renal function in 153 manic-depressive patients treated with lithium for more than five years. Acta Psychiatr Scand. 1985;71:347-55.

9. Bendz H, Andersch S, Aurell M. Kidney function in an unselected lithium population. A cross-sectional study. Acta Psychiatr Scand. 1983;68:325-34.

10. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379:721-8.

ORIGINAL ARTICLE

Retrieval of chronic hepatitis C patients. A manifesto for action to eliminate hepatitis C in the Netherlands: the CELINE project

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ABSTRACT

Chronic hepatitis C virus (HCV) infection is a global public health issue, which is associated with high rates of morbidity and mortality. The development of direct acting antivirals (DAAs) has transformed treatment: they offer us highly-effective therapy with superior tolerability compared to interferon-containing regimens. In 2016, the World Health Organization (WHO) therefore adopted several ambitious viral hepatitis elimination targets, aiming for a 90% reduction in new infections and a 65% reduction in mortality by 2030. The ultimate goal is to eliminate HCV completely. It is reasonable that these goals may be achieved in the Netherlands due to the low prevalence of chronic HCV, the availability of DAAs, and excellent healthcare infrastructure. This paper describes a national effort to curtail the HCV epidemic in the Netherlands through an HCV retrieval and linkage to care project (CELINE: Hepatitis C Elimination in the Netherlands).

KEYWORDS

HCV, chronic hepatitis C, elimination, retrieval

BACKGROUND

Chronic hepatitis C virus (HCV) infection targets the liver and, if left untreated, may lead to liver-related complications such as fibrosis, cirrhosis, hepatocellular carcinoma and ultimately death (liver and non-liver related). In 2015, an estimated 71 million people were living with chronic HCV globally and approximately 400,000 people died as a result of the infection.[1] For many years, pegylated interferon as combination therapy with ribavirin was standard therapy. Cure rates were low (40-60%) and adverse effects were serious and occurred in many patients. The discovery and development of direct acting antivirals (DAAs) has led to new perspectives as HCV infection can be completely eradicated in the majority of

patients with a treatment period of 8 to 12 weeks. Curing HCV infection leads to drastically lower mortality rates even in patients with advanced liver disease.[2] In 2016, the World Health Organization (WHO) adopted viral hepatitis elimination targets, aiming for a 90% reduction in new infections, and 65% reduction in mortality by 2030.[3] The WHO calls for action in five separate service domains: 1) presence of an up-to-date registration system with accurate data, 2) better testing and quicker access to treatment, 3) engagement of public health, 4) health coverage that is in line with this vision, and 5) innovation in the diagnostic and therapy pipeline. In the Netherlands, these conditions are partially met, which suggests that with targeted effort it is possible to envision a drastic reduction of HCV prevalence and possibly nationwide elimination within a decade. The current paper illustrates the situation of the HCV epidemic in the Netherlands and highlights the targeted efforts that have been taken, thereby reducing HCV-associated morbidity and mortality.

HCV IN THE NETHERLANDS

Historical aspects of the Dutch HCV epidemic

The worldwide epidemic of chronic HCV dates from the 1940s and is probably the result of nosocomial and iatrogenic factors, such as transfusion of HCV-infected blood and blood products and use of unsafe medical equipment.[4] These factors similarly fuelled the Dutch epidemic with an estimated 37% of the 1120 haemophilia patients testing HCV positive by the time HCV testing of blood products was introduced in 1992.[5] Another key contributor to the Dutch HCV epidemic is risk behaviour such as injection drug use and high risk sex, which was popular during the infamous "flower power" period in the 1960s and 70s. In the Netherlands, this wave of intravenous heroin use created a cohort of 30,000 heroin users in the early 1980s. Two political measures were highly efficient in reducing the risks of heroin use: wide availability and accessibility of opioid substitution therapy such as methadone, and the use of sterile injection equipment as a result of needle exchange programs. By the beginning of the 21st century, hazardous intravenous drug abuse had largely vanished, and along with it a major contributor of the HCV epidemic.[6,7] Injection drug use is still unpopular in the Netherlands, which is different from the situation in many other countries, including Europe.[8] Male-male sexual contact continues to be the most common mode of transmission in the Netherlands during the last decade.[9] Since 2000, sexually transmitted HCV infection outbreaks have been regularly reported in the Netherlands among HIV-infected men who have sex with men (MSM). These outbreaks are currently ongoing, although absolute numbers remain small.[10] Finally, HCV is also introduced into the country by first-generation migrants from HCV-endemic countries.

Overall, the HCV epidemic has led to excess mortality. Between 2002 and 2015, around 320 patients died annually due to HCV.[11]

The Netherlands: the ideal battleground for HCV elimination

The prevalence of HCV in the Netherlands is relatively low (0.16% in 2016),[5] compared to other European countries such as France (0.8%), Germany (0.4%), Italy (5.9%) and Romania (3.2%).[12] Based on data derived from major relevant risk groups, the number of Dutch chronic HCV carriers in 2016 was estimated at 23,000 people (8,461 – 37,809).[5] Group size estimates suggest that first-generation migrants from HCV-endemic countries account for more than half of all HCV-positive persons in the Netherlands (n = 13,819), followed by people who inject or have injected) drugs (PWID, n = 3,131), HIV-positive PWID (n = 303), HIV-positive MSM (n = 672), remaining HIV-positive patients (n = 327), haemophilia patients (n = 423), and individuals at low risk for infection (n = 4,210).[5] The absence of nosocomial transmission and controlled injection drug use has led to a very low incidence of acute HCV infections with a reported incidence rate of 0.26 infections per 100,000 in 2016.[9] This has resulted in a stationary HCV-infected population of a manageable size. It is likely that if this population is systematically targeted and treated, this will result in a decrease and eventual disappearance of HCV in the Netherlands. Arguments in favour of this may stem from a study that modelled HCV in the Netherlands.[13] Researchers tested various disease progression models to predict the future disease burden of HCV in the Netherlands. The study showed that the best and most realistic model of curtailing the HCV epidemic was the 'increased efficacy and treatment uptake' scenario, in which sustained virologic responses (SVR) were higher compared to those with the standard treatment regimen of that time (pegylated interferon/ribavirin) and in which a phased increase of treatment uptake was calculated based upon genotype and fibrosis stage. This strategy not only decreases the number of viraemic HCV patients in 2030 by 85%, but also decreases the number of liver-related deaths and hepatocellular carcinoma by 65% and 67%, respectively. These numbers are aligned with the WHO goals for 2030.[3] Obstacles in implementing this strategy in order to reduce prevalence of HCV and its complications include the high cost of DAAs and the lack of screening of risk groups for unidentified cases.

The first obstacle, high treatment cost, does not apply to HCV patients in the Netherlands due to the universal insurance system. The Netherlands has a compulsory and comprehensive insurance system with universal

coverage regardless of income, age, or employment status. Health insurance providers are legally required to provide a standard benefits package including care provided by general practitioners, hospitals and specialists, and prescription drugs without additional payment. This includes healthcare for chronic hepatitis patients in the 47 dedicated Dutch hepatitis centres, which is fully reimbursed with the exception of the standard non-refundable first payment of € 385.00 for all patients. Since 2015, all European Medicines Agency (EMA)-approved DAAs are available and are fully reimbursed for all HCV genotypes, independent of fibrosis stage, mode of transmission, or comorbidity. The new DAAs yield higher SVR rates than pegylated interferon/ribavirin combination therapy and they are generally much better tolerated, as is confirmed in real-world settings.[14-17] Even genotype 3 patients, previously considered to be difficult-to-treat patients, reach SVR in the majority of cases.[18] Since DAA costs became eligible for reimbursment in the Netherlands, an estimated 2,700 patients have been treated in the first year alone.[19] It has been estimated that more than 5,000 patients to date, have received DAA treatment. This exceeds the estimates of the model previously-mentioned and means that the current pool of chronic HCV carriers has been reduced from 23,000 to an estimated 18,000 people. This makes the Netherlands an ideal candidate for reaching the WHO viral hepatitis goals well before 2030.

National Hepatitis Plan

In order to achieve the goal of controlling and eliminating the HCV epidemic, the Dutch National Institute of Public Health and Environment (RIVM, Rijksinstituut voor Volksgezondheid en Milieu) has facilitated the development of a National Hepatitis Plan. This plan describes a strategy to control both the hepatitis B virus (HBV) and HCV epidemics and focuses on five areas or pillars: 1) awareness and vaccination, 2) identification of infected patients, 3) diagnosis and treatment, 4) improved organization of hepatitis care, and 5) surveillance systems. The National Hepatitis Plan may be viewed as the Dutch practical translation of the WHO goal towards elimination of viral hepatitis by 2030. The National Hepatitis Plan is endorsed by all relevant stakeholders in the field, including leading HCV experts in the Netherlands, representatives of the Dutch liver patient association (NLV, Nederlandse Leverpatiënten Verening) and the pharmaceutical industry.

Strategy for elimination

The first step in HCV elimination is treating as many patients as possible, a paradigm called 'treatment as prevention'. Two types of approaches seem feasible. First, identification of novel, unidentified cases as a result of screening specific risk groups and of active case finding by general practitioners (GP). Second, re-evaluation (retrieval) of patients with chronic HCV who have been cared for in the past but were lost to follow-up before they were cured. We will discuss both options below.

Screening

Screening strategies designed to eliminate HCV, depending on local prevalence and cost-effectiveness, can either be adopted as a national population screening program or can be used to specifically target high risk populations. The Dutch National Health Council concluded in 2016 that a population-based screening program is not feasible in the Netherlands in view of the relatively low prevalence of HCV and the fact that the majority of infected people will not develop symptoms as a result of the infection. The Council is in favour of case finding in risk populations (such as former and current PWID or migrants) and argues that identification of these cases is the responsibility of related healthcare, such as Community Health Services (GGD, Gemeentelijke Gezondheidsdienst), addiction centres, and prisons. Lastly, the Council recommended screening of HCV among healthcare workers.[20] The Minister of Health endorsed these recommendations for risk-based HCV testing as part of an overall strategy to prevent and control HCV infection and HCV-related disease.

Retrieval

Retrieval is the process of tracing patients through the assessment of medical records who have been previously diagnosed with HCV but were somehow lost to follow-up in the following years. These patients are either untreated (for instance, due to contraindications for pegylated interferon) or have been treated but not cured. There are also patients who tested positive for HCV but were not properly linked to care. The loss of follow-up from outpatient clinics of HCV patients who underwent liver biopsy during baseline evaluation has been estimated at 12% after three years,[21] and other studies showed a staggering 30% loss to follow-up among patients with HCV at tertiary care centres.[22,23] A number of reasons have been suggested for loss to follow-up, such as unawareness of follow-up appointments, or insufficient knowledge of the disease severity and treatment benefit. Prior to 2015, the standard of care for chronic HCV consisted of pegylated interferon combined with ribavirin. The expected side effects stopped many patients from starting therapy and in most cases were lost to follow-up.[24] The superior efficiency and safety profile of DAA treatment offers patients a new perspective: cure of chronic HCV without loss of quality of life.[25] The introduction of DAAs is the key development that spurred the initiation of HCV retrieval projects, which require cooperation between the primary care, secondary care, tertiary care, and public healthcare.

Several retrieval projects in the Netherlands have been executed. GGD are municipal health organizations for preventive healthcare among the general populations (such as vaccination campaigns) and among certain risk groups for diseases or infections. Several regional GGDs have executed retrieval projects, which identified some lost-to-follow-up HCV patients. However, hospital-based initiatives achieved a larger yield by screening medical records. For example, the "Chronic Hepatitis B and C Recall Northern Holland" aimed to retrieve lost-to-follow-up patients diagnosed with HVB and HVC between 2001 and 2016 by using data files of the public health system and microbiology laboratories. This approach identified 499 HCV-positive patients and registered 150/499 (30.1%) as lost-to-follow-up. Unfortunately, 126 patients (84%) were not eligible for retrieval due to unknown primary healthcare physicians, unknown home addresses, imprisonment, or relocation to a different region. Four of the 24 retrievable patients were evaluated at the outpatient clinic, resulting in a change of management in 3/4 (75%).[23] A general practitioner-based retrieval project in the region of Groningen-Drenthe included patients who tested hepatitis B surface antigen or anti-HCV-positive between 2003 and 2013 but were never referred to a hospital. This project yielded 515 patients, of whom 162 were HCV-positive. Ninety-three (57%) had false-positive HCV test results, died, or could not be traced. Twenty-five of the remaining 77 patients had a current indication for referral, of which 18 (72%) were actually referred to a hepatitis centre.[26] The larger "REtrieval And Cure of chronic Hepatitis C patients in the Utrecht region" (REACH) initiative detected HCV patients through screening of HCV-positive test results between 2001 and 2015. This project screened 2,487 HCV patients and filtering led to 269 patients (14.1% of total chronic HCV population in this region) who were eligible for retrieval and invited for screening. So far, 47/269 (17.4%) have visited the outpatient clinic.[27] Lastly, a retrieval project executed in the region of Nijmegen-Den Bosch (the Track Trace Treat project) also detected HCV patients through screening of HCV-positive test results between 2003 and 2017. So far, this project has resulted in identification of 175 HCV-positive patients of whom 81 (46%) were lost to follow-up. This study is still ongoing.

Treatment as prevention

In the interferon era, screening and retrieval were not regularly executed, since treatment was not promising due to side effects and suboptimal efficacy. However, treatment with novel DAAs gives screening and retrieval an entirely new ethical line of reasoning. Especially in lost-to-follow-up patients, caregivers have a certain ethical obligation to retrieve their patients to make them aware of the improved treatment options.

Besides preventing HCV complications, HCV treatment can limit further transmission. Two examples show that a systematic and targeted approach using treatment as prevention will reduce the HCV disease burden. A nationwide elimination program using DAAs in Iceland (TraP Hep C) suggests that treatment is a vital step in national elimination. In Iceland, the prevalence of chronic HCV is 0.3% (estimated 800-1,000 patients in a population of 330,000) and 15 months after launching the program, 479 patients had been evaluated, comprising 48-60% of the estimated total number of viraemic patients. At the time of writing, SVR rates were 96% in 188 of the 292 patients who had finished DAA therapy, and elimination of HCV from Iceland looks like a realistic prospect.[28] The second example is the ATHENA effort, which collects Dutch nationwide data from 98% of HIV-infected patients receiving care since 1998. The database contains 23,574 HIV-infected patients who have ever been linked to care, and 1,471 HCV/HIV co-infected patients (69% MSM, 15% PWID, and 15% unknown HIV transmission route). HCV treatment initiated between 2000 and 2017 reached 1,284 patients (87%), of which 1,124 (76%) were cured. In 6% (92/1471), DAA treatment results are pending.[29] When comparing incidence of acute HCV infections in the HIV-positive MSM part of this cohort before and after unrestricted access to DAAs, researchers found a 51% decrease.[30] These real-world data are consistent with the concept that HCV "treatment as prevention" averts new HCV infections in a population at risk for acute HCV infections.

HepNed and CELINE

HepNed is a Dutch research foundation supported by the Dutch Society of Hepatology that that is a collaboration between healthcare professionals who provide care for patients with viral hepatitis. As such, it is a consortium of gastroenterologists-hepatologists, internists-infectious disease specialists, hospital pharmacists, and microbiologists from all eight Dutch University Medical Centres. HepNed is the operational branch that coordinates patient-related viral hepatitis research in the Netherlands. The efforts of HepNed have led to joint studies demonstrating the added value of this collaboration.[31]

In view of the WHO viral hepatitis elimination targets, recent international developments, and encouraging pilot projects, HepNed designed a strategy that facilitates a nationwide retrieval project: "Hepatitis C Elimination in the Netherlands" (CELINE). CELINE aims to tackle the HCV problem by identifying lost to follow-up chronic HCV patients and giving them appropriate care according to the latest evidence-based guidelines (the online-only available Dutch HCV guidelines[32] and/or European Association

for the Study of Liver (EASL) Recommendations[33]). It is a three-year program which started in 2018. CELINE is financially supported through the HCV SCALE program (Screening Access and Linkage to CarE) from Gilead Sciences.

Structure of CELINE

The CELINE steering committee ensures successful delivery of the project, which include maximizing benefits, monitoring business and strategic issues, and providing advice for the project teams on issues that may endanger the project or impact project rationale or success. The Advisory Board is made up of three experts from the RIVM and the National Institute of Mental Health and Addiction (Trimbos Institute), with considerable experience in various aspects (clinical, epidemiological, and managerial) of human viral hepatitis research. The project teams consist of doctors and researchers in close collaboration with the HepNed group, who coordinate the day-to-day activities and execute the actual retrieval. The pilot REACH project has provided significant knowledge with respect to planning, flow of communication, and development of technical, managerial, and production procedures that will be used to execute and improve CELINE.

Deliverables

There are 4 measurable deliverables for CELINE:

1. Identification of traced patients and renewed access to healthcare.
2. Design of a structured compendium that describes design and execution of a sustainable, retrieval program that can be applied to other healthcare environments.
3. Mapping of the disease landscape through an HCV specific database that logs the data points of the retrieval effort.
4. Establishment of a uniform electronic platform (website) that allows effective information exchange.

Identification of cases & establishment of the cohort

CELINE aims to establish a cohort of chronic HCV-infected patients who fulfil the following criteria: 1) diagnosed with chronic HCV after the year 2000, 2) persistent viraemia at time of CELINE assessment, 3) lost to follow-up from regular clinical care, and 4) residence in the Netherlands. The investigator-initiated pilot studies (preliminary data) cover the geographical healthcare areas of 10 hepatitis centres. The focus of CELINE will be the 37 remaining hepatitis centres in the Netherlands.

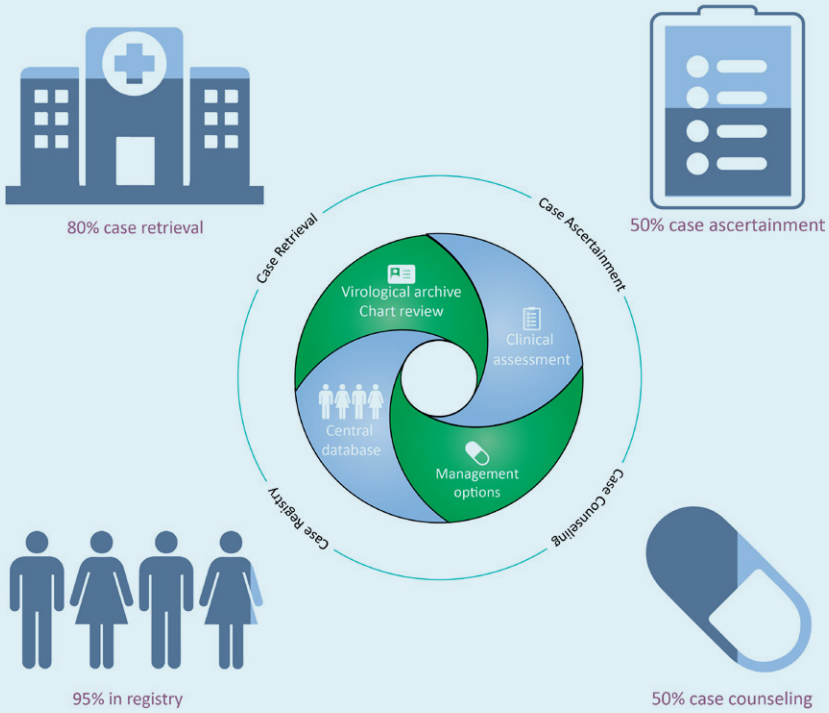
Based on the results from various Dutch pilot projects, the Centre for Infectious Disease Control (CIb, Het Centrum Infectieziektebestrijding) has issued a guidance directed to GGD on the most effective strategy to retrieve and re-evaluate chronic hepatitis patients. This lends governmental support to retrieval as a tool to reduce the burden of chronic HCV. The input of patients with every retrieval effort comes from various sources such as social and traditional media campaigns, general practitioners, laboratories, and the GGD.

Based on best practices, the most effective way to detect lost-to-follow-up patients is through reassessment of prior laboratory tests (positive anti-HCV and/or HCV RNA results) in all local and regional laboratories that perform virological testing for the hepatitis centre of interest. The virology laboratories in the Netherlands have filed their results digitally, which allow tracing of individual HCV test results performed up to 15 years ago. They are legally and ethically allowed to share data from all HCV-positive tested patients with clinicians, since they are seen as members of the treatment team.[34] The treatment team has the obligation to provide the best patient care possible and retrieval is seen as an integral part of this responsibility. Clinical chart reviews are performed to ascertain follow-up and retrieve patient and disease characteristics necessary for the cohort registry. Most hospitals in the Netherlands currently have an integrated electronic patient management system, which enable physicians to follow the patient easily through the healthcare system. Current address information is requested from the Municipal Records Database, if possible. All retrieved patients are clinically assessed in one of the participating hepatitis centres, according to previously established screening protocols including a detailed interview; blood tests, including virology and genotyping; and transient elastography (Fibroscan) to evaluate liver fibrosis stage. After the screening visit, patients receive their test results together with a patient-tailored management advice. The results and outcome of patient counselling are shared with the general practitioner and further management and/or treatment according to current guidelines (the Dutch[32] and/or EASL guidelines[33]) is planned. The choice of treatment regimen is dictated by the treating physician and will not be influenced by the researchers.

Registry

As part of CELINE, we built a dataset that includes data elements on routine demographics, such as route of transmission, co-morbidity, baseline viral load, HCV genotype, liver fibrosis assessments, prior treatment response (naïve, relapse, partial response, and non-response), virologic response to therapy, and therapeutic regimen. This is done as part of the HepNed nationwide registry for hepatitis C and is conducted in close collaboration with the Dutch HIV Monitoring foundation (SHM, Stichting HIV Monitoring).[35]

Figure 1. *Measurable endpoints of CELINE: the HCV elimination program in the Netherlands*



Expected outcome

In view of the pilot studies and the estimated size of the HCV population in the Netherlands, we estimate that CELINE will retrieve 4,000 patients and that ultimately 1,000 patients will commence DAA-based therapy (figure 1). CELINE has set a number of ambitious goals and indicates that in > 80% of 37 hepatitis centres, case retrieval will be completed as outlined in the working plan, and that in > 80% of the centres where the retrieval stage is completed, case ascertainment will be performed for > 50% of patients for whom a positive HCV laboratory test has been identified. Finally, the data of > 95% of patients who have been retrieved successfully will be entered into a central registry and > 50% of the patients who have had a complete case ascertainment will be provided case counselling.

CONCLUSION

The Netherlands is one of the countries with the lowest prevalence of chronic hepatitis C in Europe. There is a standard of healthcare, availability of DAAs, and the societal recognition to eliminate HCV; CELINE is well-positioned to perpetuate this momentum. Within the definitions set by the WHO, CELINE aims are to limit HCV complications, prevent new infections, and ultimately eliminate the disease. Modelling studies suggest that the Netherlands is an ideal battleground, giving us the opportunity to meet the WHO goals of 65% reduction in HCV-related mortality well before 2030. In doing do, we hope to become an example for other countries trying to reach this WHO goal. Achievement of HCV elimination (the ultimate WHO target) in Europe will require aligned regional and/or national strategies.

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REFERENCES

1. World Health Organization. Global Hepatitis Report 2017 [Internet]. Geneva, 2017 [cited: June 4th, 2018]. Available from: http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/.
2. Bang CS, Song IH. Impact of antiviral therapy on hepatocellular carcinoma and mortality in patients with chronic hepatitis C: systematic review and meta-analysis. BMC Gastroenterol. 2017;17:46. doi: 10.1186/s12876-017-0606-9.
3. World Health Organization. Combating hepatitis B and C to reach elimination by 2030 [Internet]. Geneva, 2016 [cited: June 4th, 2018]. Available from: http://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/.
4. Joy JB, McCloskey RM, Nguyen T, et al. The spread of hepatitis C virus genotype 1a in North America: a retrospective phylogenetic study. Lancet Infect Dis. 2016;16:698-702.
5. Koopsen J, Van Steenbergen J, Richardus J, et al. Chronic HBV and HCV infections in the Netherlands: Estimated prevalence in risk groups and the general population. Poster session presented at EASL, the International Liver Congress™; Apr 11-15, 2018; Paris, France.
6. Van Ameijden EJ, Coutinho RA. Large decline in injecting drug use in Amsterdam, 1986-1998: explanatory mechanisms and determinants of injecting transitions. J Epidemiol Community Health. 2001;55:356-63.
7. Lindenburg CE, Krol A, Smit C, Buster MC, Coutinho RA, Prins M. Decline in HIV incidence and injecting, but not in sexual risk behaviour, seen in drug users in Amsterdam: a 19-year prospective cohort study. AIDS. 2006;20:1771-5.
8. Van Laar MW, Van Gestel B, Cruts AAN, et al. Annual Report of the Netherlands National Drug Monitor 2017 [Internet]. Trimbos Institute; 2018 [cited: June 6th, 2018]. Available from: https://www.trimbos.nl/producten-en-diensten/webwinkel/product/af1568-jaarbericht-nationale-drug-monitor-2017.
9. Visser M, Van Aar F, Van Oeffelen AAM, et al. Sexually transmitted infections including HIV, in the Netherlands in 2016 [Internet]. RIVM; 2017 [cited: June 6th, 2018]. doi: 10.21945/RIVM-2017-0003. Available from: http://hdl.handle.net/10029/620872.
10. Urbanus AT, van de Laar TJ, Stolte IG, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS. 2009;23:F1-7.
11. Hofman R, Nusselder WJ, Veldhuijzen IK, Richardus JH. [Mortality due to chronic viral hepatitis B and C infections in the Netherlands]. Ned Tijdsch Geneeskd. 2016;160:D511.
12. European Centre for Disease Prevention and Control. Systematic review on hepatitis B and C prevalence in the EU/EEA [Internet]. Stockholm: ECDC; 2016 [cited: June 4th, 2018]. doi: 10.2900/24396. Available from: https://ecdc.europa.eu/en/publications-data/systematic-review-hepatitis-b-and-c-prevalence-eueea.
13. Willemse SB, Razavi-Shearer D, Zuure FR, et al. The estimated future disease burden of hepatitis C virus in the Netherlands with different treatment paradigms. Neth J Med. 2015;73:417-31.
14. Höner Zu Siederdissen C, Buggisch P, Böker K et al. Treatment of hepatitis C genotype 1 infection in Germany: effectiveness and safety of antiviral treatment in a real-world setting. United European Gastroenterol J. 2018;6:213-24.
15. Belperio PS, Shahoumian TA, Loomis TP, Mole LA, Backus LI. Real-world effectiveness of daclatasvis plus sofosbuvir and velptasvir/sofosbuvir in hepatitis C genotype 2 and 3. J Hepatol. 2018. doi 10.1016/j.jhep.2018.09.018 [Epub ahead of print].
16. Crespo J, Callega JL, Fernández I, et al. Real-world effectiveness and safety of oral combination antiviral therapy for hepatitis C virus genotype 4 infection. Clin Gastroenterol Hepatol. 2017;15:945-9.
17. Wong RJ, Nguyen MT, Trinh HN et al. Community-based real-world treatment outcomes of sofosbuvir/ledipasvir in Asians with chronic hepatitis C virus genotype 6 in the United States. J Viral Hepat. 2017;24:17-21.
18. Morisco F, Granata R, Camera S et al. Optimization of direct anti-viral agent treatment schedule: Focus on HCV genotype 3. United European Gastroenterol J. 2018;6:225-37.
19. Stichting Farmaceutische Kengetallen. [Use of HCV medication spiked after reimbursement by health insurers] [Internet]. Pharmaceutisch Weekblad. 2016;151(45) [cited: June 12th, 2018. Online summary (in Dutch) available from: https://www.sfk.nl/publicaties/PW/2016/gebruik-nieuwe-hcv-middelen-piekte-na-opname-basispakket.
20. Health Counsil of the Netherlands. [Screening risk groups for hepatitis B and C] [Internet]. The Hague, 2016 [cited: June 4th, 2018]. ISBN 978-94-6281-091-4. Available from: https://www.gezondheidsraad.nl/documenten/adviezen/2016/11/01/screening-van-risicogroepen-op-hepatitis-b-en-c
21. Toyoda H, Kumada T, Kiriyama S, et al. Markedly lower follow-up rate after liver biopsy in patients with non-alcoholic fatty liver diseases than those with viral hepatitis in Japan. BMC Res Notes. 2011;4:341.
22. Balkhy HH, El-Saed A, Sanai FM, et al. Magnitude and causes of loss to follow-up among patients with viral hepatitis at a tertiary care hospital in Saudi Arabia. J Infect Public Health. 2017;10:379-87.
23. Beekmans N, Klemt-Kropp M. Re-evaluation of chronic hepatitis B and hepatitis C patients lost to follow-up: results of the Northern Holland hepatitis retrieval project. Hepatol Med Policy. 2018;3:5.
24. Tsai SM, Kao JT, Tsai YF. How hepatitis C patients manage the treatment process of pegylated interferon and ribavirin therapy: a qualitative study. BMC Health Serv Res. 2016;16:247.
25. Younossi ZM, Stepanova M, Henry L, Nader F, Hunt S. An In-Depth Analysis of Patient-Reported Outcomes in Patients With Chronic Hepatitis C Treated With Different Anti-Viral Regimens. Am J Gastroenterol. 2016;111:808-16.
26. Spruijt AG, Wilting KR, Mithoe GD, Niessen WJ. [Tracing patients with chronic viral hepatitis]. Ned Tijdsch Geneeskd. 2016;160:D414.
27. Kracht PAM, Arends JE, Van Erpecum KJ, et al. REtrieval And Cure of chronic Hepatitis C patients in the Utrecht province (REACH). Poster session presented at EASL, the International Liver Congress™; Apr 11-15, 2018; Paris, France.
28. Olafsson S, Tyrfingsson T, Runarsdottir V, et al. Treatment as prevention for hepatitis C in Iceland (TRAP HEP C). A real-world experience from

a nationwide elimination program using direct acting antiviral agents. J Hepatol. 2017;66:S72.

29. Boerekamps A, Newsum AM, Smit C, et al. High Treatment Uptake in Human Immunodeficiency Virus/Hepatitis C Virus-Coinfected Patients After Unrestricted Access to Direct-Acting Antivirals in the Netherlands. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2018;66:1352-9.
30. Boerekamps A, van den Berk GE, Lauw FN, et al. Declining Hepatitis C Virus (HCV) Incidence in Dutch Human Immunodeficiency Virus-Positive Men Who Have Sex With Men After Unrestricted Access to HCV Therapy. Clin Infect Dis. 2018;66:1360-5.
31. Van Tilborg M, Lieveld FI, Smolders EJ, et al. Ribavirin steady-state plasma level is a predictor of sustained virological response in hepatitis C-infected patients treated with direct-acting antivirals. Aliment Pharmacol Ther. 2017;46:864-72.
32. The Dutch HCV Guideline [Internet]. 2018 [cited: Nov 30th, 2018]. Available from: www.hcvrichtsnoer.nl.
33. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66:153-194.
34. Centre for Infection Control. [Advice for retrieval and re-evaluation of patients ever diagnosed with hepatitis B and C] [Internet]. Bilthoven: LCI/RIVM, 2016 [cited: June 6th, 2018]. Available from: https://lci.rivm.nl/draaiboeken/hepatitis-b-en-c-opsporing-van-ooit-gediagnosticeerden.
35. European Union HCV Collaborators. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. Lancet Gastroenterol Hepatol. 2017;2:325-36.

ORIGINAL ARTICLE

Renal concentrating ability and glomerular filtration rate in lithium-treated patients

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ABSTRACT

Background. Lithium is the most effective drug for mood stabilization in bipolar disorder. However, lithium exposure has been associated with an impaired renal concentrating ability (RCA) and glomerular filtration rate (GFR). We examined RCA and estimated GFR in a cohort of patients treated with lithium.

Methods. 134 patients (≥ 18 years of age) with a mood disorder treated with lithium were screened; 100 patients were included. Demographic and clinical characteristics and blood and urine samples were collected. Additionally, a dDAVP-test was performed to determine maximal RCA.

Results. A dDAVP-test was performed in 98 patients (37 males, 61 females). Mean age was 51 years (SD: 12), median duration of lithium therapy 7 years (IQR: 4-15), mean maximal urine osmolality (U_{osmol}) 725 mOsmol/kg (SD: 153), and median eGFR 84 ml/min/1.73 m² (IQR: 68-95). Fifty patients (51%) had an impaired RCA and 17 patients (17%) had nephrogenic diabetes insipidus (U_{osmol} 600-800 and < 600 mOsmol/kg, respectively). Notably, clinical symptoms did not predict an impaired RCA. Nineteen patients (19%) had an eGFR ≤ 60ml/min/1.73 m². Multivariable regression analysis showed a significant association between the duration of lithium treatment and maximal U_{osmol} (B = -6.1, 95%-CI: -9.4, -2.9, p < 0.001) and eGFR (B = -0.6, 95%-CI: 0.2, -3.3; p < 0.01).

Conclusions. RCA is impaired in the majority of lithium-treated patients. Both RCA and eGFR are inversely associated with the duration of lithium therapy. Prospective follow-up will enable us to evaluate if abnormalities in RCA can be used to predict the development of lithium-induced chronic kidney disease.

KEYWORDS

Mood disorders, lithium, renal concentrating ability, nephrogenic diabetes insipidus, glomerular filtration rate, chronic kidney disease.

INTRODUCTION

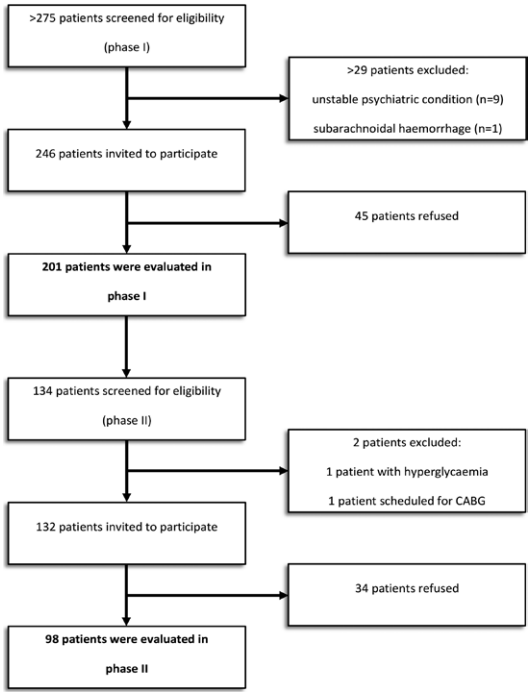
Bipolar disorder (BD) is a common mental illness that is characterized by recurrent episodes of major depression, mania, and hypomania.[1] The estimated lifetime prevalence of BD among adults worldwide is 1-3% and the mean age of onset is approximately 20 years.[2,3] Lithium has become the most effective and widely prescribed drug for mood stabilization in patients with mood disorders.[4] Until now, lithium remains a mainstay of treatment for BD, especially for acute mania and maintenance therapy. Furthermore, lithium has been shown to reduce the risk of suicide in patients with BD.[5] However, lithium exposure has been associated with several forms of renal injury. The most common renal side effect is nephrogenic diabetes insipidus (NDI). Although initially reversible, NDI can become irreversible with continued lithium use.[6] As a result, patients are not able to limit their urine output and must maintain a high fluid intake to avoid volume depletion. Since volume depletion increases proximal reabsorption and serum lithium levels, NDI places the patient at an

increased risk for acute lithium intoxication. Furthermore, long-term lithium therapy has been associated with chronic kidney disease (CKD).[7] However, available data do not allow firm conclusions of the magnitude and clinical relevance of lithium-induced CKD.

Aims of the study

The aim of our cross-sectional study is to evaluate the prevalence and severity of NDI and CKD in lithium-treated patients. This cohort will be followed prospectively and the results will be published separately to provide insight intp the association of renal concentrating ability and estimated glomerular filtration rate (eGFR) in patients on lithium maintenance therapy.

Figure 1. *Flowchart of patients participating in the study*



CABG = coronary artery bypass graft

In phase I of the study, patients with a mood disorder treated at the psychiatry outpatient clinic were screened and invited to participate in a prospective cohort study. In this article, the cross-sectional analysis of the baseline data are presented. In phase II of the study, a dDAVP test was performed in a subset of 98 patients to determine maximal urine osmolality as a measure of renal concentrating ability.

MATERIAL AND METHODS

Sample

The design of the study is shown in figure 1. The study was divided into two phases. For phase I, patients with a mood disorder treated at the outpatient psychiatry clinics of the Canisius Wilhelmina Hospital (CWZ), Nijmegen or GGZ inGeest Mental Health Center, Amsterdam, the Netherlands were screened between November 6th, 2012 and August 27th, 2013. Since we aimed to include 100 patients in phase II and estimated that 50% of patients would be willing to participate, the target population for phase I of the study was 200 patients.

Patient selection was performed based on the following inclusion criteria: 1) age ≥ 18 years, 2) diagnosis of BD or unipolar depression, and 3) current lithium treatment. Exclusion criteria included: patients 1) with a physical or psychiatric unstable condition, 2) who were hospitalized at the time of screening, or 3) who were unable to provide written informed consent. Two hundred forty-six patients were screened, provided with written information and invited by their treating psychiatrist to participate in phase I of the study. Informed consent was obtained from 201 patients (81%). Participants were asked to visit the outpatient clinic once for 30-45 minutes. Prior to this visit, they were asked to fill out a questionnaire including demographic characteristics (sex, age, race); psychiatric diagnosis; lifetime course of mood disorder; duration, dose and interruptions of lithium use; lithium intoxications; and alcohol and smoking habits. During the visit at the outpatient clinic, questionnaire information was discussed and the following additional data was collected: medical history, complaints of polyuria, thirst and polydipsia, micturition complaints, and current use of medication. This information was verified with the respective patient's medical and pharmacy records. Body height, weight, and waist circumference were recorded and blood pressure and heart rate were measured with an automatic blood pressure monitor (Omron 705IT). In addition, blood and urine samples were collected for measurements of serum urea, creatinine, sodium, potassium, calcium, phosphate, bicarbonate, osmolality, albumin, glucose, glycosylated haemoglobin (HbA_{1c}), total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, thyroid stimulating hormone and free thyroxin, 25-OH vitamin D, parathyroid hormone and urine dipstick (pH, glucose, erythrocytes, leukocytes, nitrite), creatinine, and albumin. Finally, additional blood and urine samples were collected and stored for future research.

Participants of this first phase were also invited to take part in phase II of the study, which included an additional 1-desamino-8-D-arginine vasopressin (dDAVP) test to determine maximal urine osmolality as a measure of renal concentrating ability. To this end, 134 patients participating in phase I were screened for eligibility to participate in phase II of the study between November 30th, 2012 and July 8th, 2013. The inclusion criteria were identical. The following additional exclusion criteria were applied: inability to comply with water restriction, moderate

to severe CKD (MDRD-eGFR ≤ 45 ml/min/1.73m²), hyponatraemia (sodium < 130 mmol/l), hypo- and hyperkalaemia (potassium < 3.0 or > 5.5 mmol/l), severe hypercalcemia (calcium > 2.80 mmol/l), hyperglycaemia (glucose > 10.0 mmol/l), established primary polydipsia or central diabetes insipidus, history of Sjögren syndrome, amyloidosis, sickle cell anaemia or previous treatment with ifosfamide, current treatment with desmopressin or demeclocycline, or pregnancy. Informed consent was obtained from 100 patients. The dDAVP test was performed during an additional 6-hour visit to the outpatient clinic. We followed the protocol of Tryding et al. with slight modifications.[8] Fluid intake was restricted from 22.00 hrs. the evening prior to the test. On the following morning, a fluid intake of 250 ml and a light breakfast were allowed. During the test, an additional fluid intake of 250 ml was allowed. At baseline, we recorded the presence of polyuria, thirst, polydipsia, micturition frequency and measured body height, weight, blood pressure, and heart rate. Blood samples were collected for measurements of serum creatinine, sodium, potassium, calcium, osmolality, glucose, and lithium levels. Additionally, urine samples were collected of measurements of creatinine, sodium, and osmolality. After voiding, 40 µg dDAVP was administered intranasally. Water intake, body weight, blood pressure, and heart rate were determined at six hours after administration of dDAVP and additional urine samples were collected at four and six hours after administration of dDAVP. Maximal renal concentrating ability was determined by measuring osmolality in the collected urine samples. The dDAVP test was not performed in two patients. One patient was scheduled for coronary artery bypass graft and another patient was excluded because of hyperglycemia and glycosuria.

Definitions

For the purpose of these analyses, the following definitions were used: *duration of lithium use* (total treatment duration with subtraction of periods of discontinuation of lithium); *hypertension* (systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg and/or treatment with antihypertensive drugs); *dyslipidaemia* (HDL cholesterol < 1.04 mmol/l, LDL cholesterol > 4.14 mmol/l, total cholesterol > 6.22 mmol/l, and/or treatment with lipid-lowering drugs);[9] *diabetes mellitus* (random plasma glucose ≥ 11.1 mmol/l, HbA_{1c} ≥ 48 mmol/l, and/or treatment with oral glucose-lowering drugs); *cardiovascular comorbidity* (history of cardiovascular events and/or treatment with acetylsalicylic acid, dipyridamole, or clopidogrel). Patients with a maximal urine osmolality 600-800 mOsmol/kg and < 600 mOsmol/kg were diagnosed as lithium-induced impaired renal concentrating ability and NDI, respectively. eGFR was calculated from serum creatinine values using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[10] To estimate the proportion of cases with different degrees of CKD, patients were classified according to the Kidney Diease: Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.[11]

Statistical analysis

Continuous variables are reported as median and inter-quartile range (IQR) or mean and standard deviation (SD). We compiled two separate directed acyclic graphs (DAGs), by using DAGitty software (http://www.dagitty.net), to select a minimal sufficient adjustment set of variables that would allow the identification of an unconfounded effect of duration of lithium treatment on our two outcome measures, e.g. maximal urine osmolality and eGFR. The DAGs were built by identifying all known factors affecting duration of lithium treatment, maximal urine osmolality, or eGFR. Variables in the minimal sufficient adjustment set blocked all non-causal but not the causal pathway between duration of lithium treatment and maximal urine osmolality or eGFR, and included current age, gender (male versus female), race (Caucasian versus other), centre (Amsterdam versus Nijmegen), psychiatric diagnosis (bipolar disorder versus other), and psycho-pharmacological comedication (anticonvulsants, antidepressants, antipsychotics, and sedatives). With linear regression analysis, we studied the independent effect of duration of lithium therapy on maximal urine osmolality or eGFR as dependent variables adjusted for all variables that were identified for the minimal sufficient adjustment set (age, sex, race, center, psychiatric diagnosis, and psycho-pharmacological comedication). Since cigarette smoking, body mass index, hypertension, dyslipidaemia, diabetes mellitus, maximal urine osmolality, or eGFR and cardiovascular comorbidity are likely intermediate variables in the pathway between duration of lithium treatment and maximal urine osmolality or eGFR, our multivariable models did not include these variables as potential confounders. Any association was considered statistically significant if the p-value was less than 0.05.

The study protocols were approved by the central ethics committee on research involving human subjects and the local ethics committees of the participating sites. All patients gave written informed consent before inclusion in the study. The study was performed in accordance with the Declaration of Helsinki.

RESULTS

See tables 1 - 6.

Table 1. *Clinical characteristics of study participants*

	Phase I	Phase II
Number of patients	201	98
Age, years (mean, SD)	51.2 (12.5)	51.5 (11.8)
Male sex (n, %)	86 (43)	37 (38)
Caucasian race (n, %)	190 (95)	89 (91)
Diagnosis		
Bipolar disorder (n, %)	178 (89)	84 (86)
Schizo-affective disorder (n, %)	10 (5)	7 (7)
Unipolar depression (n, %)	13 (7)	7 (7)
Lithium		
Serum lithium concentration, mmol/l (mean, sd)	0.71 (0.15)	0.72 (0.15)
Time on lithium, years (median, iqr)	8.0 (4.0-14.0)	7.5 (4.0-15.3)
Cardiovascular risk factors		
Obesity		
BMI, kg/m² (median, IQR)	26.7 (24.4-29.3)	27.1 (24.5-30.0)
> 30 kg/m² (n, %)	40 (20)	24 (25)
Smoking		
Former (n, %)	66 (33)	33 (34)
Packyears (median, iqr)	13 (3-24)	15 (5-26)
Actual (n, %)	62 (31)	26 (27)
Packyears (median, iqr)	21 (8-31)	15 (8-26)
Hypertension (n, %)	91 (45)	49 (50)
Systolic blood pressure, mm hg (mean, sd)	131 (18)	132 (22)
Diastolic blood pressure, mm hg (mean, sd)	77 (10)	77 (11)
Antihypertensive drugs (n, %)	54 (27)	30 (31)
Dyslipidaemia (n, %)	67 (33)	37 (38)
Total cholesterol, mmol/l (mean, sd)	5.2 (1.1)	5.2 (1.0)
Ldl cholesterol, mmol/l (mean, sd)	2.8 (0.9)	2.8 (0.9)
Hdl cholesterol, mmol/l (mean, sd)	1.5 (0.5)	1.6 (0.6)
Statins (n, %)	19 (10)	8 (8)
Diabetes mellitus (n, %)	12 (6)	3 (3)
Glucose, mmol/l (mean, sd)	5.1 (4.7-5.6)	5.1 (4.8-5.6)
Hba1c, mmol/mol (mean, sd)	35 (32-38)	36 (33-38)
Oral blood glucose-lowering drugs (n, %)	11 (6)	3 (3)
Cardiovascular history (n, %)	13 (7)	7 (7)

Numbers are in n and percentage (%), mean and standard deviation (SD) or median and interquartile range (IQR). BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; HbA1c = glycated haemoglobin

Table 2. *Medication use of study participants*

	Phase I	Phase II
Number of patients	201	98
Lithium		
Preparation		
Priadel (n, %)	118 (59)	59 (60)
Camcolit (n, %)	36 (18)	18 (18)
Lithium carbonate (n, %)	46 (23)	21 (21)
Dose, mg/day (mean, sd)	848 (281)	849 (296)
Schedule, once a day (n, %)	189 (94)	89 (91)
Psychopharmacological medication		
Anticonvulsants (n, %)	33 (16)	17 (17)
Antidepressants (n, %)	69 (34)	37 (38)
Tca (n, %)	22 (11)	11 (11)
Ssri (n, %)	46 (23)	24 (25)
Other (n, %)	4 (2)	3 (3)
Antipsychotics (n, %)	71 (35)	36 (37)
Typical (n, %)	14 (7)	5 (5)
Atypical (n, %)	61 (30)	32 (33)
Sedatives (n, %)	77 (38)	33 (34)
Benzodiazepine-agonists (n, %)	68 (34)	30 (31)
Other (n, %)	15 (8)	9 (9)
Antihypertensive drugs (n, %)	54 (27)	30 (31)
Beta blockers (n, %)	35 (17)	19 (19)
Propranolol (n, %)	20 (10)	10 (10)
Ace inhibitors/arb (n, %)	12 (6)	7 (7)
Calcium channel blockers (n, %)	11 (6)	6 (6)
Diuretics (n, %)		
Amiloride (n, %)	7 (4)	5 (5)
Thiazide diuretics (n, %)	17 (9)	10 (10)
Other (n, %)	2 (1)	1 (1)
Statins (n, %)	19 (10)	8 (8)
Oral blood glucose-lowering drugs (n, %)	11 (6)	3 (3)
Other		
Platelet aggregation inhibitors (n, %)	13 (7)	7 (7)
Nitrates (n, %)	3 (2)	1 (1)
Oral anticoagulants (n, %)	1 (1)	1 (1)

Numbers are in n and percentage (%). ACE inhibitors = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; SSRI = selective serotonin re-uptake inhibitors; TCA = tricyclic antidepressants

Patient characteristics

The patients screened, invited, participated, and evaluated in phase I and II of the study are shown in figure 1. Baseline demographic and clinical characteristics are shown in table 1. Ninety-eight patients participated in phase II of the study, 37 males and 61 females. The mean age was 51 years (SD: 12). The majority of these patients (86%) had a diagnosis of BD. Patients had been treated with lithium for median 7 years (IQR: 4-15). Twenty-two patients (22%) were on lithium for > 15 years. According to the questionnaire, medical records and examination at the psychiatry outpatient clinic, 24 patients (25%) were obese (BMI > 30 kg/m^2); 33 patients (34%) smoked cigarettes; 49 patients (50%) had hypertension, with 30 of them (31%) being treated with antihypertensive drugs; 37 patients (38%) had dyslipidaemia, with 8 of them (8%) being treated with statins; 3 patients (3%) had diabetes mellitus type 2, all of them being treated with oral blood-glucose lowering drugs; and 7 patients (7%) had experienced a cardiovascular event.

Table 3. *Subjective symptoms, renal concentrating ability, eGFR and albuminuria*

	Phase I	Phase II
Number of patients	201	98
Lithium		
Adverse effects		
Polyuria (n, %)	91 (45)	46 (47)
Micturition frequency at day-time (median, iqr)	NA	6 (5-8)
Micturition frequency at night-time (median, iqr)	NA	1 (0-2)
Thirst (n, %)	102 (51)	54 (55)
Polydipsia (n, %)	81 (40)	51 (52)
Renal concentrating ability		
Serum sodium concentration, mmol/l (mean, sd)		141 (2)
Serum osmolality, mosmol/kg (mean, sd)		294 (5)
Max. Urine osmolality, mosmol/kg (mean, sd)	NA	725 (153)
< 300 mOsmol/kg (n, %)	NA	1 (1)
300-599 mOsmol/kg (n, %)	NA	16 (16)
600-799 mOsmol/kg (n, %)	NA	50 (51)
> 800 mOsmol/kg (n, %)	NA	31 (32)
Renal function		
Serum creatinine, µmol/l (median, iqr)	77 (69-88)	80 (70-90)
eGFR, ml/min/1.73 m2 (median, IQR)	89 (74-100)	84 (68-95)
eGFR ≤ 60 ml/min/1.73 m2 (n, %)	17 (9)	12 (12)
Albumin/creatinine ratio, mg/mmol creatinine (median, iqr)	0.8 (0.5-1.4)	0.8 (0.5-1.4)
Micro-albuminuria (n, %)	23 (11)	9 (9)
Macro-albuminuria (n, %)	2 (1)	1 (1)
Chronic kidney disease (n, %)	32 (16)	19 (19)

Numbers are in n and percentage (%), mean and standard deviation (SD) or median and interquartile range (IQR). eGFR = estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation; chronic kidney disease, eGFR < 60 ml/min/1.73m2 and/or albuminuria; NA = not available

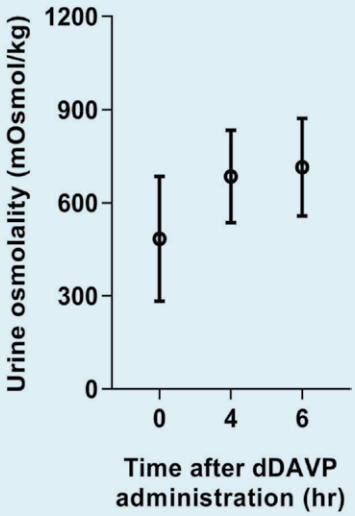
Table 4. *Max. Uosmol and eGFR in relation to duration of lithium use*

	0-5 yrs, n = 29	6-10 yrs, n = 30	11-15 yrs, n = 15	> 15 yrs, n = 23
Male sex (n, %)	11 (38)	11 (37)	4 (27)	10 (44)
Age (median, IQR)	45 (37-56)	48 (44-56)	53 (48-59)	61 (55-66)
Max. U_{osmol} (median, IQR)	802 (674-910)	727 (672-821)	638 (591-828)	679 (492-758)
< 300 (n, %)	0	0	0	1 (4)
300-599 (n, %)	2 (7)	4 (13)	4 (27)	6 (26)
600-799 (n, %)	12 (41)	18 (60)	7 (47)	12 (52)
> 800 (n, %)	15 (52)	8 (27)	4 (27)	4 (17)
eGFR (median, IQR)	91 (80-103)	93 (82-97)	73 (64-89)	63 (58-84)
> 90 (n, %)	15 (52)	17 (57)	3 (20)	2 (9)
60-89 (n, %)	12 (41)	11 (37)	10 (67)	13 (57)
45-59 (n, %)	2 (7)	0	2 (13)	7 (30)
30-44 (n, %)	0	2 (7)	0	1 (4)

Numbers are in n and percentage (%), mean and standard deviation (SD) or median and interquartile range (IQR). Max. U_{osmol} = maximal urine osmolality determined by a dDAVP test. eGFR = estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation

Table 2 shows the medication use of participants in both study phases. Focusing on phase II, participants had been treated with Camcolit (18%), generic lithium carbonate (21%), or Priadel (60%). Eighty-nine patients (91%) had been using lithium on a once-a-day schedule.

Figure 2. *Urine osmolality (mean and standard deviation) at baseline, 4 and 6 hours after intranasal administration of 40 ug 1-desamino-8-D-arginine vasopressin (dDAVP)*



The mean daily dose at the time of examination was 849 mg (SD: 296).

Adverse effects, urine osmolality and renal function

Table 3 shows that patients frequently reported complaints of polyuria (n = 46, 47%), thirst (n = 54, 55%), and polydipsia (n = 51, 52%). Patients who reported polyuria also reported a higher micturition frequency both during the day (median 5 vs. 6, p = 0.012) and night-time (median 1 vs. 2, p = 0.012) compared to patients who did not report polyuria. Patients reporting polyuria also more frequently reported thirst compared to patients who did not report polyuria (35 of 46 patients [76%] vs. 19 of 52 patients [37%], respectively; p < 0.01) and polydipsia (36 of 46 patients [78%] vs. 15 of 52 patients [29%], respectively; p < 0.01). Mean urine osmolality at baseline was 484 mOsmol/kg (SD: 201). Administration of dDAVP resulted in an increase of urine osmolality to 685 mOsmol/kg (SD: 149) at four hours and 715 mOsmol/kg (SD: 157) at six hours after administration of dDAVP (figure 2). Maximal urine osmolality (725 mOsmol/kg, SD: 153) was reached after four hours in 21 patients (21%) and after six hours in 77 patients (79%). The mean maximal urine osmolality in our study population was 725 mOsmol/kg (SD: 153). Fifty patients (51%) had an impaired renal concentrating ability (maximal U_{osmol} 600-800 mOsmol/kg) and 17 patients (17%) were diagnosed with lithium-induced NDI (maximal U_{osmol} F 600 mOsmol/kg). Patients with NDI had been longer on lithium therapy (median 14 vs. 7 years, p = 0.011). Table 4 shows that a disturbance in renal concentrating ability was

already observed within five years of lithium treatment. The prevalence of an impaired renal concentrating ability increased from 58% in patients treated with lithium for ≤ 5 years to 83% in patients treated for > 15 years. Patients with NDI had a slightly higher serum osmolality (median 298 vs. 294 mOsmol/kg, p = 0.045) and significant lower eGFR (median 64 vs. 86 ml/min/1.73 m², p = 0.005) compared to patients with a normal or impaired renal concentrating ability. Surprisingly, patients with NDI did not have significantly more complaints of polyuria (53% vs. 46%, p = 0.59), day or night-time micturition frequency (median 5 vs. 6, p = 0.23 and 1 vs. 1, p = 0.60), thirst (71% vs. 52%, p = 0.16), or polydipsia (71% vs. 48%, p = 0.09) compared to patients with normal or impaired renal concentrating. In addition, the urinary creatinine concentration measured in a urine sample collected in the morning after an overnight fluid restriction did not predict the renal concentrating ability.

The median eGFR in our study population was 84 ml/min/1.73 m² (IQR: 68-95). Twelve patients (12%) had an eGFR < 60 ml/min/1.73 m² and 10 patients (10%) had albuminuria. Of the total population, 19 patients (19%) had CKD. Patients with an eGFR < 60 ml/min/1.73 m² were older than patients with an eGFR ≥

Table 5. *Regression analysis of maximal urine osmolality at baseline*

	Beta	p-value	95% - confidence interval	
Univariable regression analysis				
Intercept	805		766	843
Years of lithium treatment	-7.4	< 0.001	-10.3	-4.6
Multivariable regression analysis				
Intercept	888		717	1058
Years of lithium treatment	-6.1	< 0.01	-9.4	-2.9
Current age	-0.9	0.54	-3.3	1.5
Gender (male versus female)	-4.7	0.88	-54.8	45.5
Race (caucasian versus other)	44.7	0.42	-47.8	137.2
Centre (amsterdam versus nijmegen)	-54.6	0.09	-106.8	-2.3
Diagnosis (bipolar disorder versus other)	5.8	0.90	-67.4	79.1
Psychopharm. Comedication	-14.5	0.65	-67.0	38.1

Table 6. *Regression analysis of estimated GFR at baseline*

	Beta	p-value	95% - confidence interval	
Univariable regression analysis				
Intercept	93.3		89.1	97.4
Years of lithium treatment	-1.0	< 0.001	-1.3	-0.7
Multivariable regression analysis				
Intercept	144.8		130.3	159.3
Years of lithium treatment	-0.6	< 0.01	-0.8	-0.3
Current age	-0.7	< 0.001	-0.9	-0.5
Gender (male versus female)	-2.8	0.28	-7.1	1.5
Race (caucasian versus other)	-3.2	0.50	-11.0	4.7
Centre (amsterdam versus nijmegen)	-9.0	< 0.01	-13.4	-4.5
Diagnosis (bipolar disorder versus other)	-2.2	0.56	-8.4	4.0
Psychopharm. Comedication	-1.8	0.50	-6.3	2.7

60 ml/min/1.73 m² (median age 65 vs. 50 years, p < 0.001), had been treated with lithium longer (median 21 vs. 7 years, p = 0.003), had hypertension more often (100% vs. 44%, p = 0.03), and had a lower maximal urine osmolality (median 542 vs. 745 mOsmol/kg, p < 0.001). As expected, both groups of patients had similar serum lithium concentrations (median 0.76 vs. 0.71 mmol/l, p = 0.64), but were treated with a lower lithium dose (median 600 vs. 800 mg/day, p = 0.007).

Association of lithium duration with U_{osmol} and eGFR

As shown in table 5, the univariable regression model showed a negative association between the duration of lithium therapy and maximal urine osmolality (B = -7.4, 95% confidence interval (CI) -10.3 to -4.6, p < 0.001). After correction for the confounding effects of age, sex, race, center, psychiatric diagnosis, and psycho-pharmacological comedication, duration of lithium therapy remained independently and inversely associated with maximal urine osmolality (B = -6.1, 95%-CI -9.4 to -2.9, p < 0.01). This means that after adjusting for the set of potential confounders, each additional year of lithium therapy results in a loss of maximal renal concentrating ability of 6.5 mOsmol/kg.

A similar model was built for the association between duration of lithium therapy and renal function (table 6). The univariable regression model showed a negative association between the duration of lithium therapy and eGFR (B = -1.0, 95%-CI -1.3 to -0.7, p < 0.001). After correction for the confounding effects of age, sex, race, center, psychiatric diagnosis, and psycho-pharmacological comedication, each year of lithium therapy leads to an additional decline of eGFR of 0.6 ml/min/1.73 m² (95%-CI -0.8 to -0.3, p < 0.01). Of note, in the multivariable analysis, centre was also associated with a lower eGFR (9.0 ml/min/1.73 m², 95%-CI -13.4 to -4.5, p < 0.01).

DISCUSSION

This study shows that a majority of lithium-treated patients had complaints of polyuria, thirst, and polydipsia. The data also demonstrate that almost one-fifth of patients did have a lithium-induced NDI. Surprisingly, polyuria, thirst, and polydipsia did not predict NDI as determined by a dDAVP test. Our study does add that a questionnaire of symptoms alone cannot be used to accurately identify patients with an impaired renal concentrating ability.[12-14] In addition, maximal urine osmolality could not be predicted by the urinary creatinine concentration measured in an urine sample collected after an overnight fluid restriction. Furthermore, duration of lithium therapy was independently and significantly associated with a decline in maximal urine osmolality. A disturbance in renal concentrating ability was already observed within five years of lithium treatment and the prevalence of an impaired renal concentrating ability increased with the duration of lithium maintenance therapy. These findings are in agreement with other studies which included patients with a comparable age, duration of lithium therapy, and renal function.[15-17]

In addition, we observed a prevalence of CKD exceeding 10%. Multivariable linear regression analysis showed that eGFR was associated with duration of lithium treatment. Several earlier studies reported no significant change[18-23] or only a slight deterioration in renal function with long-term lithium exposure.[13,17,24] In contrast, recent studies have shown a marked increase in the prevalence of CKD (eGFR < 60 ml/min/1.73 m²), especially in patients treated for many years.[7,25-28] Moreover, several authors have shown that long-term lithium therapy causes end-stage renal disease in a small proportion of patients.[29-34] One possible explanation for these apparently conflicting results is that earlier studies often relied on serum creatinine values alone which might have resulted in an underestimation of the prevalence of CKD. In addition, earlier studies predominantly reported on patients who were treated with lithium < 10 years. However, it may take decades before lithium-treated patients develop CKD. Our data show that duration of lithium treatment is independently, significantly and inversely associated with eGFR. This finding is more relevant, since CKD is associated with an increased risk of cardiovascular morbidity and mortality.[35] We therefore agree with Kripalani et al. that monitoring of cardiovascular risk factors is important to prevent cardiovascular events in this patient population.[36]

We studied the independent effect of duration of lithium therapy on maximal urine osmolality and eGFR as dependent variables adjusted for age, sex, race, center, psychiatric diagnosis, and psycho-pharmacological. However, our multivariable models did not include cigarette smoking, body mass index, hypertension, dyslipidemia, diabetes mellitus, maximal urine osmolality, or eGFR and cardiovascular comorbidity. We therefore performed an additional analysis including these potentially causal risk factors which confirmed that duration of lithium therapy was independently, significantly and inversely associated with maximal urine osmolality and eGFR.

It should be noted that a significant decline in renal concentrating ability was observed in 14 out of 29 individuals (48%) treated with lithium for ≤ 5 years. This observation is in accordance with findings of others who showed that lithium acutely and, with prolonged lithium exposure, progressively impairs renal concentrating ability. In healthy subjects, even a single oral dose of lithium carbonate has been shown to impair the antidiuretic response to hypertonic saline infusion, resulting in an

increased urine output (median 3.7 vs. 1.9 ml/min, p = 0.05).[37] In addition, a 4-week treatment of healthy volunteers with lithium carbonate also significantly reduced renal concentrating ability (mean maximal urine osmolality 960 vs. 1040 mOsmol/kg, p < 0.01).[38] In patients with mood disorders, longer exposure to lithium results in a progressive decline in renal concentrating ability.[39] Although this inability to adequately concentrate urine is initially reversible,[40-43] prolonged lithium exposure has been demonstrated to result in irreversible NDI.[44] It is not clear at which point lithium-induced NDI becomes irreversible. In most patients, a decrease in eGFR below 60ml/min/1.73 m² became apparent after treatment with lithium for at least 10 years. This observation suggests that a decline in renal concentrating ability likely precedes a decrease in eGFR. Our prospective study will enable us to investigate the predictive value of impaired renal concentrating ability with regard to the risk of developing lithium-induced CKD.

On the other hand, it can be argued that approximately half of patients had a normal renal concentrating ability after ≤ 5 years of lithium therapy. This suggests that there might be differences between individuals in sensitivity of the renal collecting ducts to lithium toxicity. We propose that future studies should focus on these differences.

Our study has several strengths. Besides lithium use and eGFR, we also report on albuminuria, prevalences of additional risk factors, and comorbidities like obesity, smoking, hypertension, diabetes mellitus, and cardiovascular morbidity and use of comedication. In addition, we report maximal renal concentrating ability determined by the current gold standard, a dDAVP test in a relatively large population. Only two similar studies have been published since 1990 reporting on renal concentrating ability in lithium-treated patients determined by a dDAVP test.[17,45] Our study also has some limitations. We performed a cross-sectional analysis and are therefore unable to ascertain causality between our covariates and renal concentrating ability or eGFR. Second, only patients currently treated with lithium were included in our study. Since lithium therapy may have been discontinued in patients who had developed a clinically significant reduction in renal concentrating ability or eGFR, bias towards including individuals with a more favourable course cannot be excluded. In this respect, the differences between the centres Amsterdam and Nijmegen are notable. This suggests unreported differences between the patient populations from both centers. Alternatively, we cannot exclude a difference between centres in back-referral to primary care. Furthermore, our study has a relatively small sample size resulting in an impaired statistical precision and lacks a control group.

CONCLUSION

In conclusion, our results demonstrate that both renal concentrating ability and eGFR are significantly and inversely associated with duration of lithium treatment. In addition, a significant decline in renal concentrating ability was observed in half of the individuals treated with lithium for ≤ 5 years, whereas in most patients, a decrease in eGFR below 60 ml/min/1.73 m² became apparent after treatment with lithium for at least 10 years. This observation suggests that a disturbance in renal concentrating ability precedes the development of CKD. Further research is needed to elucidate if abnormalities in renal concentrating ability predict the development of lithium-induced CKD. If so, renal concentrating ability can be used to select patients at high risk for CKD, which is not only worthwhile for selection of patients for increased surveillance, but also for future research, including placebo-controlled trials to investigate the benefit of amiloride to prevent lithium-induced CKD.

DISCLOSURES

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REFERENCES

1. DSM-5. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition DSM-5. American Psychiatric Association. 2013.
2. Pedersen CB, Mors O, Bertelsen A, et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. JAMA Psychiatry. 2014;71:573-81.
3. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. Arch Gen Psychiatry. 2011;68:241-51.
4. Miura T, Noma H, Furukawa TA, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: A systematic review and network meta-analysis. The Lancet Psychiatry. 2014;1:351-9.
5. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ. 2013;346:f3646.
6. Trepiccione F, Christensen BM. Lithium-induced nephrogenic diabetes insipidus: New clinical and experimental findings. J Nephrol. 2010;23(Suppl. 16):43-8.
7. Bocchetta A, Ardau R, Fanni T, et al. Renal function during long-term lithium treatment: A cross-sectional and longitudinal study. BMC Med. 2015;13:12.
8. Tryding N, Berg B, Ekman S, Nilsson JE, Sterner G, Harris A. DDAVP test for renal concentration capacity. Age-related reference intervals. Scand J Urol Nephrol. 1988;22:141-5.

9. NCEP. Third Report of National Cholesterol Education Program Expert Panel. Detection, Evaluation and Treatment of High Blood Cholesterool in Adults. Final Report. Circulation. 2002;106:3143-421.
10. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-12.
11. Paul E. Stevens AL. Evaluation and Management of Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline. Ann Intern Med. 2013;158:825-31.
12. King JR, Aylard PR, Hullin RP. Side-effects of lithium at lower therapeutic levels: The significance of thirst. Psychol Med. 1985;15:355-61.
13. Løkkegaard H, Andersen NF, Henriksen E, et al. Renal function in 153 manic?depressive patients treated with lithium for more than five years. Acta Psychiatr Scand. 1985;71:347-55.
14. Bendz H, Aurell M, Balldin J, Mathé AA, Sjödin I. Kidney damage in long-term lithium patients: A cross-sectional study of patients with 15 years or more on lithium. Nephrol Dial Transplant. 1994;9:1250-4.
15. Hetmar O, Bolwig TG, Brun C, Ladefoged J, Larsen S, Rafaelsen OJ. Lithium: long-term effects on the kidney I. Renal function in retrospect. Acta Psychiatr Scand. 1986;73:574-81.
16. Hetmar O, Clemmesen L, Ladefoged J, Rafaelsen OJ. Lithium: Long-term effects on the kidney: III. Prospective study. Acta Psychiatr Scand. 1987;75:251-8.
17. Kallner G, Petterson U. Renal, thyroid and parathyroid function during lithium treatment: laboratory tests in 207 people treated for 1-30 years. Acta Psychiatr Scand. 1995;91:48-51.
18. Johnson GFS, Hunt GE, Duggin GG, Horvath JS, Tiller DJ. Renal function and lithium treatment: Initial and follow-up tests in manic-depressive patients. J Affect Disord. 1984;6:249-63.
19. DePaulo JR, Correa EI, Sapir DG. Renal function and lithium: A longitudinal study. Am J Psychiatry. 1986;143:892-5.
20. Jensen SB, Rickers H. Glomerular filtration rate during lithium therapy: A longitudinal study. Acta Psychiatr Scand. 1984;70:235-8.
21. Waller DG, Edwards JG, Papasthatis-Papayanni S. A longitudinal assessment of renal function during treatment with lithium. QJM. 1988;68:553-8.
22. Schou M, Vestergaard P. Prospective studies on a lithium cohort: 2. Renal function. Water and electrolyte metabolism. Acta Psychiatr Scand. 1988;78:427-33.
23. Povlsen UJ, Hetmar O, Ladefoged J, Bolwig TG. Kidney functioning during lithium treatment: a prospective study of patients treated with lithium for up to ten years. Acta Psychiatr Scand. 1992;85:56-60.
24. Jorgensen F, Larsen S, Spanager B. Kidney function and quantitative histological changes in patients on long-term lithium therapy. Acta Psychiatr Scand. 1984;70:455-62.
25. Bassilios N, Martel P, Godard V, Froissart M, Grünfeld JP, Stengel B. Monitoring of glomerular filtration rate in lithium-treated outpatients - An ambulatory laboratory database surveillance. Nephrol Dial Transplant. 2008;23:562-5.
26. Bocchetta A, Ardau R, Carta P, et al. Duration of lithium treatment is a risk factor for reduced glomerular function: A cross-sectional study. BMC Med. 2013;11:33.
27. Janowsky DS, Soares J, Hatch JP, Zunta-Soares G, Hu Q, Davis JM. Lithium effect on renal glomerular functionin individuals with intellectual disability. J Clin Psychopharmacol. 2009;29:296-9.
28. Tredget J, Kirov A, Kirov G. Effects of chronic lithium treatment on renal function. J Affect Disord. 2010;126:436-40.
29. Roxanas M, Grace BS, George CR. Renal replacement therapy associated with lithium nephrotoxicity in Australia. Med J Aust. 2014;200:226-8.
30. Markowitz GS, Radhakrishnan J, Kambham N, Valeri AM, Hines WH, D'Agati VD. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. J Am Soc Nephrol. 2000;11:1439-48.
31. Presne C, Fakhouri F, Noel LH, et al. Lithium-induced nephropathy: Rate of progression and prognostic factors. Kidney Int. 2003;64:585-92.
32. Bendz H, Schön S, Attman PO, Aurell M. Renal failure occurs in chronic lithium treatment but is uncommon. Kidney Int. 2010;77:219-24.
33. Aiff H, Attman PO, Aurell M, Bendz H, Schön S, Svedlund J. End-stage renal disease associated with prophylactic lithium treatment. Eur Neuropsychopharmacol. 2014;24:540-4.
34. Wells JE, Cross NB, Savage RL, Parkin L, Horsburgh S, Richardson AK. Renal replacement therapy associated with lithium nephrotoxicity in New Zealand. N Z Med J. 2015;128:77-83.
35. Muntner P, He J, Hamm L, Loria C, Whelton PK. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol. 2002;13:745-53.
36. Kripalani M, Shawcross J, Reilly J, Main J. Lithium and chronic kidney disease. BMJ. 2009;339:166-9.
37. Pedersen RS, Bentzen H, Bech JN, Pedersen EB. Effect of an acute oral lithium intake on urinary Aquaporin-2 in healthy humans with and without simultaneous stimulation with hypertonic saline infusion. Scand J Clin Lab Invest. 2003;63:181-94.
38. Walker RJ, Weggery S, Bedford JJ, McDonald FJ, Ellis G, Leader JP. Lithium-induced reduction in urinary concentrating ability and urinary aquaporin 2 (AQP2) excretion in healthy volunteers. Kidney Int. 2005;67:291-4.
39. Boton R, Gaviria M, Batlle DC. Prevalence, Pathogenesis, and Treatment of Renal Dysfunction Associated With Chronic Lithium Therapy. Am J Kidney Dis. 1987;10:329-45.
40. Bucht G, Wahlin A. Renal Concentrating Capacity in Long-Term Lithium Treatment and after Withdrawal of Lithium. Acta Med Scand. 1980;207:309-14.
41. Bendz H. Kidney function in a selected lithium population: A prospective, controlled, lithium-withdrawal study. Acta Psychiatr Scand. 1985;72:451-63.
42. Wahlin A, Bucht G, Von Knorring L, Smigan L. Kidney function in patients with affective disorders with and without lithium therapy. Int Pharmacopsychiatry. 1980;15:253-9.
43. Vestergaard P, Amdisen A. Lithium treatment and kidney function: a follow-up study of 237 patients in long-term treatment. Acta Psychiatr Scand. 1981;63:333-45.
44. Bendz H, Sjödin I, Aurell M. Renal function on and off lithium in patients treated with lithium for 15 years or more. A controlled, prospective lithium-withdrawal study. Nephrol Dial Transplant. 1996;11:457-60.
45. Bendz H, Aurell M, Lanke J. A historical cohort study of kidney damage in long-term lithium patients: Continued surveillance needed. Eur Psychiatry. 2001;16:199-206.

CASE REPORT

Recognizing the zebra: a carboplatin-induced haemolytic anaemia

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KEYWORDS

Adverse events, carboplatin, chemotherapy, drug-induced haemolytic anaemia

What was known on this topic?
Carboplatin can lead to drug-induced immune haemolytic anaemia which can be a lethal adverse event.

What does this add?
Awareness for drug-induced immune haemolytic anaemia. Recognition is difficult while anaemia has a high incidence, especially in patients treated with chemotherapy, though drug-induced haemolytic anaemia is rare.

INTRODUCTION

Drug-induced immune haemolytic anaemia (DIIHA) is a rare condition affecting approximately 1:1,000,000 patients. DIIHA has been reported for several antimicrobials, non-steroidal anti-inflammatory drugs and some platinum-based chemotherapy agents.[1-4] While cisplatin is the most commonly reported platinum-based agent to cause DIIHA, some reports of carboplatin and oxaliplatin causing DIIHA are published.[5-10] The incidence of DIIHA due to carboplatin is unknown. Anaemia is a common finding in patients treated with carboplatin and even when haemolysis is considered, it may not be recognised due to its similarity to regular auto-immune haemolytic anaemia. The discriminative test for DIIHA is the direct antiglobulin test (DAT).[11] Several theories exist on the biochemical steps that lead to the formation of antibodies, but the exact pathophysiological mechanism behind DIIHA is still unclear.[2] We report a case of a patient developing haemolytic anaemia after the administration of carboplatin, despite previously having numerous successful treatments with this drug, and the course of action in our patient.

CASE REPORT

A 52-year-old woman with ovarium carcinoma was treated with neo-adjuvant chemotherapy, interval debulking, and adjuvant chemotherapy (carboplatin and paclitaxel) since 2010. In 2014, peritoneal metastases were discovered, which were treated with the same neoadjuvant, optimal debulking, and adjuvant schedule. Unfortunately, the patient relapsed in May 2016. She responded to carboplatin, gemcitabine, and bevacicumab, but relapsed again in December 2017 under bevacizumab monotherapy. She was still considered platinum-sensitive. Therefore, carboplatin was restarted. During these years, she came to the emergency room six times, all because of infections. Four of those emergency visits resulted in admission. When home after the 21st cycle, she experienced a fever and tingling sensation in all extremities and returned to the emergency room. In addition to her complaints, she mentioned a red discoloration of her

Table 1. *Results from urine dipstick analysis*

	Results	Reference values
pH	6.5	4.5-7.8
Leukocytes	+++	Negative
Blood	+++	Negative
Nitrite	Positive	Negative
Bilirubin	++	Negative
Urobilinogen	+++	Normal a
Bacteria	Positive	Negative

Table 2. *Laboratory test results for the first day of admission compared to earlier blood testing three days before admission/infusion*

	Results three days prior to admission	Results at admission	Reference values
Aspartate aminotransferase	25 U/l	107 U/l	< 31 U/l
Alanine aminotransferase	21 U/l	31 U/l	< 34 U/l
Alkaline phosphatase	76 U/l	81 U/l	< 98 U/l
γ-glutamyl transferase	67 U/l	68 U/l	< 38 U/l
Total bilirubin	7 µmol/l	26 µmol/l	< 17 µmol/l
Direct bilirubin	-	10 µmol/l	< 5 µmol/l
Lactate dehydrogenase	205 U/l	1464 U/l	< 247 U/l
Creatine kinase	-	114 U/l	< 145 U/l
Creatinine	55 µmol/l	58 µmol/l	44-80 µmol/l
Magnesium	-	0.58 µmol/l	0.75-0.95 mmol/l
C reactive protein	-	29 mg/l	< 5.0 mg/l
Haemoglobin	6.8 mmol/l	6.1 mmol/l	7.2-10.0 mmol/l
Reticulocytes	-	21.5 x 10^9/l	5.0-25.0 x 10^9/l
Thrombocytes	79 x 10^9/l	61 x 10^9/l	150-400 x 10^9/l
Ferritin	-	8018 µg/l	10-205 µg/l
Haptoglobin	-	< 0.08 g/l	0.3-2.0 g/l
Direct antiglobulin test	-	IgG 4+; C -	

urine without dysuria. Upon clinical examination, a visible tremor in all limbs was noticed and she was subfebrile. Results from urinalyis and laboratory test results are shown in tables 1 and 2, respectively. Based on these acute changes in lactate dehydrogenase and bilirubin, immeasurably low haptoglobin, and the presentation of symptoms almost directly after administration of carboplatin, drug-induced immune haemolytic anaemia (DIIHA) was suspected, but an autoimmune haemolytic anaemia and co-occurrence with a urinary tract infection could not be ruled out. Therefore, immediate treatment with antibiotics and high dose of prednisone (one milligram per kilogram body weight) was started. Carboplatin was not administered again. The tremor, tingling sensation and discoloration of the urine disappeared within a few days and the prednisone dose was tapered. Moreover, lactate dehydrogenase and haptoglobin slowly returned to normal during the following months (see table 3). The DAT turned out positive (IgG 4+, complement negative), confirming the diagnosis. Further diagnostic tests were run, including fragmentocytes, fibrinogen, blood coagulation tests, and parvovirus, all of which were negative, supporting the diagnosis DIIHA. For complete determination, blood was sent to the national reference laboratory to test for in vitro drug-dependent reactions. Unfortunately, no tests were performed as the laboratory considered this too high-risk due to the involvement of chemotherapy. While we were investigating whether the test could be performed abroad, our patient died due to pulmonary embolism and tumor progression, confirmed by autopsy.

Table 3. *Course of parameters for haemolysis over time*

	2 weeks after initiation of treatment	1 month after initiation of treatment	2 months after initiation of treatment
Lactate dehydrogenase (U/l)	479	539	411
Haptoglobin (g/l)	< 0.08	0.1	1.5
Haemoglobin (mmol/l)	4.5	4.7	6.7

DISCUSSION

DIIHA is a rare and life-threatening condition that can occur after administration of platinum-based chemotherapy.[2] While cisplatin is the most commonly reported platinum-based agent to cause DIIHA, reports of carboplatin and oxaliplatin causing DIIHA also exists.[5-10] More than half of these cases had lethal outcomes. It should be noted that DIIHA is often not recognized as the cause of anaemia, because platinum-based chemotherapy leads often to anaemia.[12]

Little is known about the development of DIIHA or the most optimal treatment. It is hypothesized that drugs interacting and loosely binding with red blood cells (RBCs) activate the immune system and lead to the formation of anti-drug immune complexes, leading to haemolytic anaemia. The initial treatment in this case is to stop the causative agent as soon as the DIIHA is recognized. Steroids or intravenous immunoglobulins are not recommended for drug-dependent DIIHA. There are also drug-independent antibodies that will react in vitro without the drug present. Garratty and Petz suggested a modification of the membrane, creating an epitope, which allows RBCs to bind the antibody without formation of the drug-RBC complex.[13] Moreover, sometimes non-immunological proteins (e.g. albumin) can bind due to the modification, and lead to prolonged increased haemolysis. Drug-independent DIIHA can benefit from treatment with steroids given the similarities to auto-immune haemolytic anaemia and has been shown to occur in carboplatin.[2,11,14] There is no clear consensus on the treatment of DIIHA caused by carboplatin or any other platinum-based agents. Most important is stopping the agent inducing the haemolysis. Whether or not to add a high dose of prednisone cannot be decided during the initial days, because it is too early for information on drug-dependency at presentation. Because our patient was seriously ill and the diagnosis of auto-immune haemolytic anaemia was also considered, we had no choice and treated her with prednisone. Recently an in vitro study was published showing that carboplatin-loaded nanoparticles using biodegradable polymer poly (ε-caprolactone) (PCL) enhanced the cellular uptake of carboplatin.[15] Normally larger doses of carboplatin need to be administered to achieve therapeutic levels due to poor cellular uptake of carboplatin, which causes harmful side effects including haemolysis. Carboplatin delivery as PCL nanoparticles was able to avoid every sign of haemolysis. These results suggest that carboplatin delivered in the form of PCL nanoparticles are biocompatible and a safer way to treat cancer compared to free carboplatin, avoiding carboplatin-induced DIIHA cases.[15] However, the clinical relevance of this PCL is limited because DIIHA is rare; however, carboplatin is widely used for the treatment of many types of malignancy. To conclude, in this case report, we want to create awareness of DIIHA and make it recognizable as a serious and lethal adverse event. Terminating drug administration is obviously the first step of treatment. While some patients were treated with prednisone, a standard plan of action remains unclear as it could depend partly on drug-independent antibodies. New improvements of carboplatin administration (such as the PCL-enhanced administration) could be an alternative for patients with a carboplatin-sensitive tumour, but in whom carboplatin leads to DIIHA. However, more research is needed before this can be safely implemented into clinical practice.

DISCLOSURES

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REFERENCES

1. Garbe E, Andersohn F, Bronder E, et al. Drug induced immune haemolytic anaemia in the Berlin Case-Control Surveillance Study. Br J Haematol. 2011;154:644-53.
2. Garratty G. Immune hemolytic anemia associated with drug therapy. Blood Rev. 2010;24:143-50.
3. Garratty G, Arndt PA. Drugs that have been shown to cause drug-induced immune hemolytic anemia or positive direct antiglobulin tests: some interesting findings since 2007. Immunohematology. 2014;30:66-79.
4. Mayer B, Bartolmas T, Yurek S, Salama A. Variability of Findings in Drug-Induced Immune Haemolytic Anaemia: Experience over 20 Years in a Single Centre. Transfus Med Hemother. 2015;42:333-9.
5. Betensky M, Witmer C, Fisher MJ, Nance S, Weiss MJ, Sesok-Pizzini DA. Immune hemolytic anemia with drug-induced antibodies to carboplatin and vincristine in a pediatric patient with an optic pathway glioma. Transfusion. 2014;54:2901-5.
6. Dacha S, Reddivari AK, Latta S, Devidi M, Iroegbu N. Carboplatin Induced Fatal Autoimmune Hemolytic Anemia: First Reported Case. World J Oncol. 2010;1:173-5.
7. Haley KM, Russell TB, Boshkov L, et al. Fatal carboplatin-induced immune hemolytic anemia in a child with a brain tumor. J Blood Med. 2014;5:55-8.
8. Leger RM, Jain S, Nester TA, Kaplan H. Drug-induced immune hemolytic anemia associated with anti-carboplatin and the first example of anti-paclitaxel. Transfusion. 2015;55:2949-54.
9. Maloisel F, Kurtz JE, Andres E, Gorodetsky C, Dufour P, Oberling F. Platin salts-induced hemolytic anemia: cisplatin- and the first case of carboplatin-induced hemolysis. Anticancer Drugs. 1995;6:324-6.
10. Marani TM, Trich MB, Armstrong KS, et al. Carboplatin-induced immune hemolytic anemia. Transfusion. 1996;36:1016-8.
11. Pierce A, Nester T, Education Committee of the Academy of Clinical Laboratory P, Scientists. Pathology consultation on drug-induced hemolytic anemia. Am J Clin Pathol. 2011;136:7-12.
12. Dufour P, Bergerat JP, Eber M, et al. Cisplatin-induced anemia: a potential interference with iron metabolism at erythroid progenitors level. Anticancer Drugs. 1990;1:49-54.
13. Garratty G, Petz LD. Drug-induced immune hemolytic anemia. The American Journal of Medicine. 1975;58:398-407.
14. Arndt P, Garratty G, Isaak E, Bolger M, Lu Q. Positive direct and indirect antiglobulin tests associated with oxaliplatin can be due to drug antibody and/or drug-induced nonimmunologic protein adsorption. Transfusion. 2009;49:711-8.
15. Karanam V, Marslin G, Krishnamoorthy B, et al. Poly (varepsilon-caprolactone) nanoparticles of carboplatin: Preparation, characterization and in vitro cytotoxicity evaluation in U-87 MG cell lines. Colloids Surf B Biointerfaces. 2015;130:48-52.

CASE REPORT

Acquired haemophilia A in a patient with breast cancer and lung carcinoma: a case report and literature review

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KEYWORDS

Acquired haemophilia A (AHA), malignancy

ABSTRACT

Acquired haemophilia A is a rare disorder caused by spontaneous formation of auto-antibodies (inhibitors) against coagulation factor VIII. This can lead to life-threatening haemorrhages. Six to twenty-two percent of patients with acquired haemophilia have an underlying malignancy. We describe a 69-year-old woman with metastatic breast cancer and non-small cell lung carcinoma who presented at the emergency room with spontaneous bruising, and who was using a vitamin K antagonist. She had a prolonged activated partial thromboplastin time (aPTT) due to a coagulation factor VIII deficiency caused by factor VIII antibodies. She was treated with prednisone and cyclophosphamide.

What was known on this topic?

Acquired haemophilia A is a rare disorder caused by spontaneous formation of auto-antibodies (inhibitors) against coagulation factor VIII. This can lead to life-threatening haemorrhages. Acquired haemophilia should be considered in patients with increased bleeding tendencies with a prolonged activated partial thromboplastin time, normal prothrombin time and platelet count, and a non-correcting mixing test. First-line treatment of acquired haemophilia A consists of prednisone and/or cyclophosphamide.

What does this add?

Acquired haemophilia A is a haematological emergency. When there is suspicion, the diagnosis should be made as soon as possible and a haemophilia treatment centre should be consulted. Six to twenty-two percent of patients with acquired haemophilia have an underlying malignancy. This is the first case described where there is acquired haemophilia A in a patient with two malignancies. Because it is a rare condition, registration of patients is of great importance to gain more insight into the etiology, treatment, and prognosis of the disorder.

INTRODUCTION

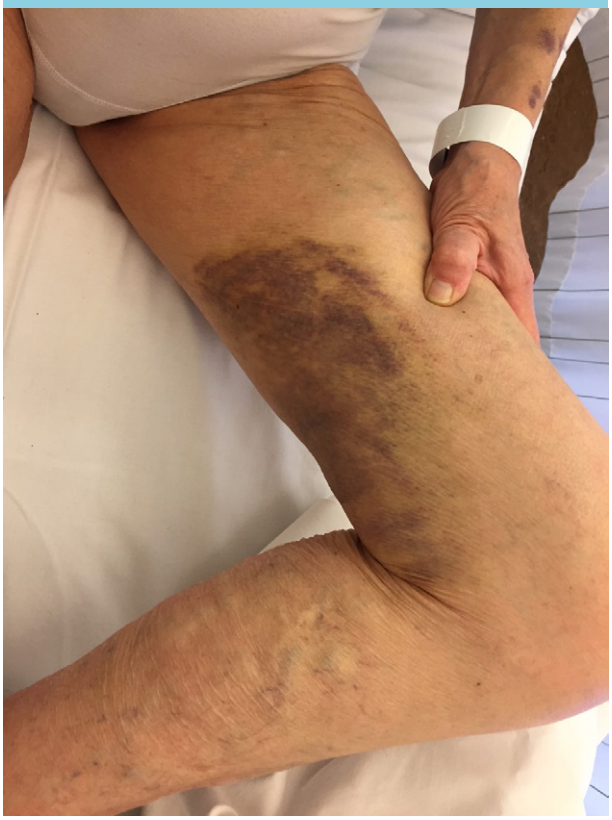
Acquired haemophilia A (AHA) is a disease caused by spontaneous formation of auto-antibodies (inhibitors) against coagulation factor VIII. This can lead to severe and potentially life-threatening haemorrhages.

AHA is rare, with a reported incidence of 1.48 million/year. Its frequency increases with age; the median age at diagnosis is 73.9 years.[1,2] Aan underlying condition can be identified in about half of all cases. The most commonly associated conditions are autoimmune disorders, postpartum period, and solid or haematological tumours. In literature, the incidence rates for the coexistence of AHA and malignancy varies between 6-22%.[3] Underlying malignancy is associated with worse prognosis of AHA.[2]

CASE REPORT

A 69-year-old woman presented at the emergency department with spontaneous bruising which started

Figure 1. *Extensive haematoma on the left upper leg*



a week prior. Her medical history included metastatic breast cancer, for which palliative hormonal therapy (letrozole) was started, and non-small cell lung carcinoma, for which she had received chemoradiation therapy with curative intention. In addition, she had chronic obstructive pulmonary disease (COPD) and a mechanical aortic valve for which she used a vitamin K antagonist (acenocoumarol). Furthermore, she taking chlortalidone, metoprolol, losartan, Lyrica®, and oxycodone.

At physical examination, she had a blue, swollen right hand and a big haematoma on her left upper leg (figure 1). Laboratory testing showed a prolonged prothrombin time (PT) of 25.4 seconds and aPTT of 141 seconds (reference values: PT 9.5-12.5s, aPTT 20-30s). Platelet count was normal. After correction of the PT with prothrombin complex and vitamin K, the aPTT remained considerably prolonged (83s). Plasma mixing studies failed to correct the aPTT (57.2s after mixing, normal control 29.7s). The Rosner Index was 20.7, which indicates the presence of an inhibitor. The diagnosis of AHA was confirmed when there appeared to be an undetectably low concentration of factor VIII (< 0.01 IU/mL, normal value > 0.5 IU/mL) with a high titre of factor VIII antibodies (100.7 Bethesda Units, BU).

The day after admission, she started with high-dose prednisone (1 mg/kg) and was transferred to a haemophilia treatment centre. Given the high titre, it simultaneous administration of prednisone and cyclophosphamide was considered. However, the patient had recently been treated with chemoradiation therapy and therefore was already susceptible to serious infections. Starting cyclophosphamide, with great chance of additional toxicity, was considered too risky. Because of the extensive haematomas, the vitamin K antagonist was stopped. Given the risk of thrombosis of her aortic valve, we refrained from administration of a bypassing agent (like activated protrombincomplex or recombinant factor VIIa) and carefully followed the bleeding, which fortunately stabilized without the need for a bypassing agent. A few weeks after starting prednisone, the bleeding tendency was clinically reduced and the antibody titre dropped to 27 BU. The aPTT, however, remained prolonged (around 70s) and the factor VIII activity immeasurably low. Therefore, cyclophosphamide (100 mg a day) was started. However, because of intensive care admission with respiratory insufficiency due to a viral infection and an exacerbation of COPD, the immunosuppressive therapy was discontinued shortly after initiation. She received recombinant factor VIIa because of persistent bleeding after central line removal. After recovery from the infection, the cyclophosphamide was restarted at a dose of 50 mg a day. Three months after starting treatment, she reached remission with unmeasurable antibody titre and normalization of factor VIII. At this point, her vitamin K antagonist was restarted. She did not experience any thrombotic complications related to her mechanic aortic valve.

DISCUSSION

There is a clear association between acquired haemophilia A and malignancy. The presence of factor VIII antibodies is considered a paraneoplastic phenomenon. Due to the rarity of the disease, there is insufficient data to make statements about haemophilia A in specific types of cancer, but there seem to be differences in prevalence. Previous studies show that about a quarter of patients with AHA and malignancy had a lung tumour and one-fifth to a quarter had prostate cancer or a gastro-intestinal malignancy.[1,4,5] In total, there are four known cases of patients with haemophilia A and breast cancer. There are no cases known of patients with a double tumour. If the diagnostic work-up of a new AHA patient shows evidence of malignancy, it is important to consider that tissue biopsy must be deferred until remission of AHA, as there is a high risk of bleeding complications.

Acquired haemophilia A should be considered in all patients with a recent onset of increased bleeding tendency and a prolonged aPTT with a normal PT and platelet count. Given the seriousness of the disease, additional tests

must be done as soon as possible to confirm (or reject) the diagnosis. If the aPTT does not correct with a mixing test, this indicates the presence of a circulating inhibitor directed against one of the coagulation factors (VIII, IX, XI or XII), but the presence of lupus anticoagulans can also lead to a non-correcting mixing test. To make the diagnosis, the activity of the coagulation factors must be measured. If there is a coagulation factor VIII deficiency, the antibodies can be quantified by the Bethesda assay (the Nijmegen modification of the assay). Recent studies demonstrate there is a significant association between the height of the antibody titre and factor VIII activity on the time to achieve remission and on overall survival.[6,7]

Because of the rarity and severity of the condition, a haemophilia treatment centre must always be consulted and transfer should be discussed. Based on retrospective cohort studies and clinical research, guidelines and recommendations have been developed for the treatment of acquired haemophilia A. First advice is to strive for adequate haemostasis by means of recombinant factor VIIa (NovoSeven®) and activated prothrombin complex (Feiba®).[8,9] No clinically relevant differences in efficacy and safety have been demonstrated and, if necessary, both products can be used simultaneously or sequentially if the effect of one product is insufficient.

As long as the antibody circulates in the blood, the risk of bleeding remains, and eradication of the inhibitor is therefore important. The development of antibodies against coagulation factor VIII is seen as an autoimmune phenomenon and is treated with immune suppressants. There are two treatment strategies: treatment with prednisolone only (1 mg/kg/day) or in combination with cyclophosphamide (1-2 mg/kg). Meta-analyses focusing on treatment results suggest that combination therapy is superior to prednisolone alone in achieving complete remission and disease-free survival. However, overall survival was not significantly better, probably because cyclophosphamide is associated with many severe and life-threatening side-effects like neutropenia-related infections.[6,7,10] Therefore, the requirement to reduce the risk of severe bleeding always needs to be balanced with the risk of side effects, especially in the elderly and in patients with comorbidity that makes them more susceptible to infection. Treatment is monitored by determining aPTT, factor VIII activity and antibody titre. Meanwhile, attention should also be paid to the treatment of an underlying condition, if present.

In recent years, rituximab has been given more and more as second-line treatment. There are no randomized prospective studies comparing rituximab with other immunosuppressive treatments. Therefore, rituximab cannot yet be recommended as first line treatment.[6,8,11]

In conclusion, AHA is a rare disorder that should be considered as a haematological emergency. It is idiopathic in half of all patients, and in the other half, there is a clear association with an underlying condition, for instance a malignancy. Since few data are available on treatment and prognosis, registration of patients is of great importance to gain more insight into this disorder, and its etiology, treatment, and prognosis.

REFERENCES

1. Collins PW, Hirsch S, Baglin TP, et al. Acquired haemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood. 2007;109:1877.
2. Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired haemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost. 2012;10:622-63.
3. Franchini M, Castaman G, Coppola A, et al. Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management. Blood Transfus. 2015;13:498-513.
4. Sallah S, Wan JY. Inhibitors against factor III in patients with cancer. Analysis of 41 patients. Cancer. 2001;91:1067-74.
5. Napolitano M, Siragusa S, Mancuso S, Kessler CM. Acquired haemophilia in cancer: A systematic and critical literature review. Haemophilia. 2018;24:43-56.
6. Collins PW, Baudo F, Knoebl P, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Blood. 2012;120:47-55.
7. Tiede A, Klamroth R, Scharf RE, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. Blood. 2015;125:1091-7.
8. Hamulyák K, van der Linden PWG. Hoofdstuk 10: Verworven hemofilie-A en de ziekte van von Willebrand K. Richtlijn Diagnostiek en behandeling van hemofilie en aanverwante hemostasestoornissen: Van Zuiden Communications B.V.; 2009. p. 127.
9. Collins P, Baudo F, Huth-Kühne A, et al. Consensus recommendations for the diagnosis and treatment of acquired haemophilia A. BMC Research Notes. 2010;3:161.
10. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. Br J Haematol. 2003;121:21-35.
11. D'arena G, Grandone E, Di Minno MN, Musto P, Di Minno G. The anti-CD20 monoclonal antibody rituximab to treat acquired haemophilia A. Blood Transfus. 2016;14:255-61.

CASE REPORT

Waterpipe smoking: not as innocent as it may seem

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ABSTRACT

Introduction. Waterpipe (hookah) smoking is popular; in Dutch surveys, 26% of the respondents have smoked a waterpipe at least once. However, waterpipe smoking is not without risk. We present a series of carbon monoxide (CO) poisonings after waterpipe smoking and discuss the etiology and treatment of CO intoxication after waterpipe smoking.

Case descriptions. We present three patients who presented with syncopial episodes and a variety of other neurological and circulatory symptoms after smoking a waterpipe. All patients had significantly elevated carboxyhaemoglobin levels (26%, 19% and 26%). Patients were treated with oxygen, following Dutch guidelines; one patient was admitted for eight hours of oxygen therapy. The other two patients were observed shortly, diverging from the guidelines because symptoms passed and the carboxyhaemoglobin normalised.

Discussion. Reviewing combustion chemistry, the formation of CO is a logical consequence of using burning coals as a heat source. This is due to CO_2 reduction with carbon. This chemical process has not previously been related to waterpipe smoking. Dutch guidelines advise eight hours of oxygen therapy. The research this guideline is based on, justifies therapy directed at symptom relief and carboxyhaemoglobin normalisation. This strategy may prevent unnecessary hospital admissions and exposure to high-dose oxygen.

Conclusion. We described three cases of CO intoxication after waterpipe smoking and argue why this may not be an incidental finding. Greater awareness of this risk is urgently needed. We conclude that the literature does not firmly support a fixed treatment duration.

KEYWORDS

Carbon monoxide, intoxication, hookah, toxicology, waterpipe, emergency

What was known on this topic?

Previous publications have reported carbon monoxide intoxications after waterpipe smoking. It is important to recognise this, often subtle, presenting intoxication because of possible serious complications and simple effective treatment possibilities. Most cases are best treated with high flow (normobaric) oxygen.

Waterpipe users and primary care clinicians should be aware that due to the process of CO_2 reduction, carbon monoxide is formed with a burning coal as a heat source and therefore is forming a risk of CO intoxication.

What does this add?

There is little evidence supporting a fixed duration of O_2 treatment. Taking into account the possible adverse effects of high flow oxygen and necessity to admit patients, we advise treatment aimed on symptom relief and normalization of HbCO levels.

INTRODUCTION

Waterpipe (hookah) smoking is very popular, and the number of hookah lounges is growing. Studies in the United States show that waterpipe smoking is almost as popular as regular cigarette smoking.[1] A survey in the Netherlands showed that, even though a small fraction (2-8%) of the population uses the waterpipe more than once a month; 26% of responders had experienced smoking a waterpipe at least once.[2] Previous publications have described the risks of waterpipe smoking, in particular carbon monoxide (CO) intoxication.[3] In this paper we describe a series of CO intoxications after waterpipe smoking and why this problem is likely to be a logical consequence. Furthermore, we discuss the

treatment of CO intoxication and the rationale behind fixed treatment duration as described in the Dutch guidelines.

CASES

Patient A

Patient A, an 18-year-old male with mild asthma had smoked the waterpipe for one hour. After getting up from his seat, he lost consciousness for approximately two minutes, where after he managed to get up. When he collapsed a second time, bystanders called emergency services. Evaluation by ambulance personnel showed a widened gait and he was transported to the hospital. On assessment in the emergency department, the patient complained of mild dyspnea and a vibrating sensation throughout his body. Physical examination showed normal vital parameters, and pulse oximetry showed a saturation of 100% with no supplemental oxygen. Further physical examination, including neurological evaluation, showed no abnormalities. An echocardiogram (ECG) was unremarkable, and a venous blood gas analysis (VBG) was performed to screen for electrolyte disorders. The VBG showed a carboxyhaemoglobin (HbCO) concentration of 26% (normally ≤ 10% in smokers).[4] The patient was treated with oxygen (O_2) at 15L/min via a non-rebreathing mask (NRM). A VBG 90 minutes later showed a HbCO of 10% and after two hours, the patient was free of complaints. Further treatment was initiated according to Dutch guidelines in "het Acute Boekje";[5] the patient was admitted for eight hours of treatment with high-flow oxygen, where after he was discharged in good condition.

Patient B

Patient B, a 17-year-old male with no relevant past medical history, collapsed three times after smoking a waterpipe. In between the syncopal episodes, he felt lightheaded and vomited twice. On evaluation in the emergency department, he felt general weakness. Physical examination showed a tachycardia of 115/min, an O_2 saturation of 97%, and an occipital haematoma. The ECG and head computed tomography scan were unremarkable and the VBG showed a HbCO of 19%. Treatment with high-flow oxygen was started. After 1 hour and 45 minutes, the patient was symptom-free and the HbCO was normalized to 7%. Because of complete resolution of symptoms, normalisation of HbCO and patient's strong objection to admission, the patient was discharged home.

Patient C

Patient C, a 24-year-old female with no relevant past medical history, presented after sitting in a hookah lounge for several hours, while only smoking for a brief period of time. After getting up from her seat she felt unstable, weak, and subsequently collapsed. She had had no complaints of dyspnea, palpitations, or headache. In the emergency department, she was free of symptoms. Vital parameters, physical examination and ECG showed no abnormalities. VBG showed a HbCO of 26% and high-flow oxygen was started. After 90 minutes, the HbCO declined to 9% and the patient was free of complaints. The treating physician diverged from the Dutch guidelines and decided to discharge the patient home. He did so because the initial symptoms were only mild and completely resolved; importantly, HbCO levels were normalised.

DISCUSSION

All three described patients had a different presentation of an intoxication with CO after smoking a waterpipe. Previous publications have described how a waterpipe works and emphasised the fact that waterpipe smoking is more harmful than cigarette smoking.[3,6] The best-known source of CO is incomplete combustion; this process plays a role in inhalation of smoke or exhaust fumes or gases from a malfunctioning heater. Yet, during waterpipe smoking another important CO-forming process, known as the Boudouard reaction, may play a role.[7]

According to this reaction, reduction of CO_2 with the hot carbon leads to the formation of CO:

CO_2 (g) + C (s) → 2CO (g)

This reaction is temperature-dependent, and CO formation starts around 600°K (327°C) and exponentially increases at higher temperatures. Although no reports in medical literature exist on exact burning temperatures of hookah coals, hookah coal manufacturers report burning temperatures up to 650°C. Even though CO production starts dominating the reaction at temperatures exceeding 700°C, the fraction of CO formed may well be relevant in causing CO intoxication.[8]

In China, the formation of CO in burning coals is so widely known that many suicide attempts are done by burning coals in a sealed room.[9]

Taking into consideration both CO-forming processes, the chance of exposure to CO while inhaling over a glowing piece of coal is considerable. In electric waterpipes, the reduction of carbon will not play a role considering the absence of hot carbon.

After inhalation, CO has an affinity for haemoglobin 200-300x that of oxygen. Furthermore, the oxygen affinity of CO-free haem groups is increased, thus impairing oxygen delivery. Consequently, CO impairs both oxygen uptake and delivery capacity. Besides the effects on oxygen transport, studies have also shown evidence that CO

Table 1. *General staging of CO intoxications.[11] Please note no clear correlation between HbCO level and symptom severity exists and clinical symptoms are leading in determining intoxication severity*

	Mild	Moderate	Severe
Suggested carboxy-haemoglobin (HbCO) %	< 10%	10-25%	20-25%
Symptoms	None	Headache, lethargy, tiredness	Loss of consciousness, confusion, signs of cardiac ischemia

interferes with the electron transport chain by impairing cytochrome C oxidase function.[10]

Other experimental (*ex vivo* and animal) studies show evidence for CO-related oxidative stress and leukocyte mediated-inflammatory changes causing neuronal injury. Although incompletely understood, these non-HbCO-dependent mechanisms may explain why symptoms at specific HbCO levels vary widely between patients. Therefore, interpretation of HbCO values alone does not provide a good estimation of the severity of the intoxication. Severe intoxications may present with relatively low HbCO levels, thus clinical symptoms should be leading.

Table 2. *Late and persisting sequelae of CO intoxications[12]*

Neurologic	Cognitive/psychologic
Parkinson-like syndromes	Concentration disorders
Walking and movement disorders	Memory loss
Bradykinesia	Cognitive disorders
Intention tremor	Dementia
Myoclonia	Personality changes
Dyspraxia	Anxiety
Dysphasia	Emotional lability
Ataxia	Psychosis
Postural instability	Depression
Vertigo	Mania
Cortical blindness	Insomnia
Loss of hearing	
Chorea	
Electroencephalography (EEG) abnormalities	
Epilepsy	
Peripheral neuropathy	
Recurrent headaches	
Incontinence	

Table 1 describes general staging as described in recent literature.[11] Aside from the acute symptoms, CO intoxication leads to persisting or later developing neurologic sequelae in 10-32% of patients. These late symptoms usually occur within days but may take months to develop. A diversity of symptoms has been described ranging from headache to impaired concentration (table 2).[12]

As soon as the clinical suspicion of CO intoxication rises, high-flow oxygen over a non-rebreather mask should start immediately. Diagnostics should consist of a VBG; arterial blood gas has no diagnostic superiority.[13] Normal values for HbCO vary from 0-5% in non-smokers to just over 10% in heavy smokers. Thus, HbCO values over 5% in non-smokers and 10% in smokers, in combination with symptoms should be considered a CO intoxication.[4,11] Pulse oximeters are not reliable in patients with CO intoxication because they cannot discriminate oxyhaemoglobin from carboxyhaemoglobin. This means the oxygen saturation value indicated reflects the sum of HbCO plus the true oxygen saturation (HbO2).[4]

Oxygen therapy displaces the CO from the haemoglobin; the half-life of HbCO is hereby reduced from approximately 320 minutes to approximately 75 minutes.[9] In some cases, hyperbaric oxygen therapy (HBOT) may be indicated. Using HBOT, it is possible to dissolve an amount of free oxygen in the plasma that meets tissue needs, regardless of the amount of haemoblogin blocked by CO. Moreover, HBOT has also been shown to inhibit leukocyte-mediated inflammatory changes and oxidative stress in the brain.[14,15] Several studies have shown a positive effect of HBOT on preventing neurologic sequelae.[14] However a systematic review on the efficacy of HBOT in CO intoxication showed conflicting results. The pooled data from the six trials showed an odds ratio for neurologic sequelae of 0.78 (95% CI: 0.54 to 1.12) compared to normobaricoxygen.[16] Considering the possible harmful effects (barotrauma, oxygen toxicity) and limited availability, this therapy is only indicated for a limited category of patients. HBOT can be indicated in case of a high-risk intoxication including patients with ECG changes, coma, severe lactic acidosis,

or pregnancy. For these patients, early consultation with a hyperbaric centre is essential.

One of our patients was admitted for oxygen therapy; this treatment strategy was chosen based on Dutch guidelines. These guidelines state that any patient with a CO intoxication (with no contra indications for treatment and no indication for hyperbaric treatment), treatment should consist of eight hours of high-flow oxygen. However, evidence for this treatment strategy is weak. The recommended eight hours originate from a study analysing the average time to diminishing of symptoms and normalising of HbCO, during treatment with normobaric high-flow oxygen and HBOT. In the normobaric oxygen group (n = 30), an average of 4.2 hours (SD 3 hours) was found in this study.[14] Treatment until symptom resolution and HbCO normalisation seems just as effective in both short and long-term.[4] Using this strategy, which is recommended by authorities such as the United States' Centers for Disease Control and Prevention (CDC), unnecessary admission and exposure to high concentrations of oxygen can be prevented.[17] In patients with sepsis, traumatic brain injury, and cardiac ischaemia, hyperoxygenation has been related to adverse effects including increased formation of reactive oxygen species that cause reperfusion injury and worse outcomes.[18] These outcomes justify prudence in using high-flow oxygen for an extended period of time.

CONCLUSION

Waterpipe smoking and using hot coals as a heat source is popular but more harmful than one might consider due to the risk of CO intoxication. A broader awareness of this risk in both waterpipe users and primary and emergency care providers is essential. In patients presenting with altered mental status or atypical neurological complaints, CO intoxication should be included in the differential diagnosis. Informing about waterpipe use and VBG analysis are rapid and simple but essential in diagnosing CO intoxication.

We advise that patients should be treated with high-flow oxygen until symptoms resolve and HbCO normalises. Standard treatment duration is not strongly supported by studies and treatment with high-flow oxygen may well have harmful effects.

REFERENCES

1. Singh H, Arrazola RA. et al. Tobacco Use Among Middle and High School Students United States, 2011–2015. CDC Morbidity and Mortality Weekly Report. 2016;64:381-5.
2. Rijksinstituut voor Volksgezondheid en milieu. Waterpijp: Risico op koolmonoxidevergiftiging bij gebruik [Internet]. Bilthoven(NL); 2016 [cited April 24th, 2018]. Available from: http://www.rivm.nl/dsresource?objectid=a139503a-3be4-41bc-802b-7ac130aa3dde&type=org&disposition=inline.
3. Bens BW, ter Maaten JC, Ligtenberg JJ. Koolmonoxidevergiftiging na roken van een waterpijp. Ned Tijdschr Geneeskd. 2013;157:A6201.
4. Hampson NB, Piantadosi CA, Thom SR, Weaver LK. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. Am J Respir Crit Care Med. 2012;186:1095-101.
5. Nederlandse internisten vereniging. Acute boekje – Richtlijnen voor de diagnostiek en behandeling van aandoeningen op het gebied van inwendige specialismen [Internet]. 5th edition 2017. [Cited April 24th, 2018]. Available from: https://www.hetacuteboekje.nl/hoofdstuk/intoxicaties/bewustzijnsdaling.html.
6. Misek R, Patte C. Carbon Monoxide Toxicity after Lighting Coals at a Hookah Bar. J Med Toxicol. 2014;10:295-8.
7. Whitten KW, Davis RE, Peck L, Stanley GG. Chemistry. 8th edition, Cengage Learning, 2006: p 851.
8. Hunt J, Ferrari A, Lita A, Crosswhite M, Ashley B, Stiegman AE Microwave-Specific Enhancement of the Carbon?Carbon Dioxide (Boudouard) Reaction. J Phys Chem C. 2013;117:26871-80.
9. Li CK, Tsui KL, Hung CY, Yau HH, KAM CW. A retrospective study on carboxyhaemoglobin half-life in acute carbon monoxide poisoning in patients treated with normobaric high flow oxygen. Hong Kong J Emerg Med. 2006;13:205-11.
10. Akyol S, Erdogan S, Idiz N, et al. The role of reactive oxygen species and oxidative stress in carbon monoxide toxicity: an in-depth analysis. Redox Report. 2014;19:180-9.
11. Smollin C, Olson K. Carbon monoxide poisoning (acute). BMJ Clinical Evidence. 2010;2010:2103.
12. Pepe G, Castelli M, Nazerian P, et al. Delayed neuropsychological sequelae after carbon monoxide poisoning: predictive risk factors in the Emergency Department. A retrospective study. Scand J Trauma Resusc Emerg Med. 2011;19:16.
13. Van Exsel JAJM, Simons SO, Kramers C, Heijdra YF. Wanneer volstaat een veneuze bloedgas op de SEH? Ned Tijdschr Geneeskd. 2017;161:D785.
14. Thom SR, Taber RL, Mendiguren II, et al. Delayed Neuropsychologic Sequelae After Carbon Monoxide Poisoning: Prevention by Treatment With Hyperbaric Oxygen. Ann Emerg Med. 1995;4:474-80.
15. Thom SR. Leukocytes in carbon monoxide-mediated brain oxidative injury. Toxicol Appl Pharmacol. 1993;123:234-47.
16. Buckley NA, Juurlink DN, Isbister G, Bennett MH, Lavonas EJ. Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database of Systematic Reviews. 2011;4:CD002041.
17. Center for Disease control. Clinical guidance for carbon monoxide poisoning [Internet]. Update September 2017 [Cited May 24th, 2018]. Available from: https://www.cdc.gov/disasters/co_guidance.html.
18. Vincent J-L, Taccone FS, He X. Harmful Effects of Hyperoxia in Postcardiac Arrest, Sepsis, Traumatic Brain Injury, or Stroke: The Importance of Individualized Oxygen Therapy in Critically Ill Patients. Can Respir J. 2017;2017:2834956.

PHOTO QUIZ

To diagnose from scratch: crusted scabies mimicking a T-cell lymphoma

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Figure 1A. *Brown-white hyperkeratotic plaques on the elbow*

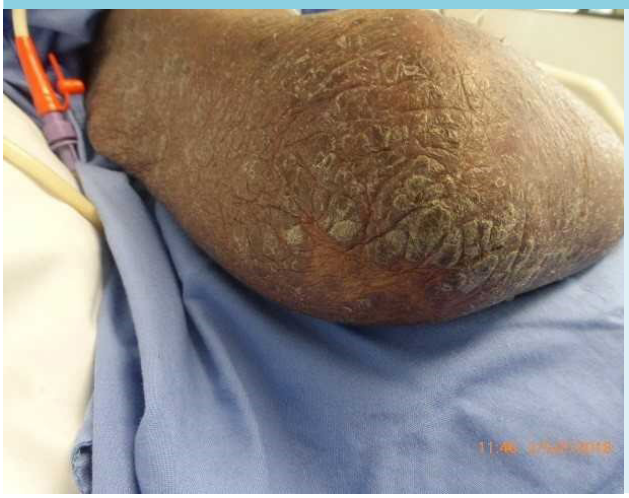
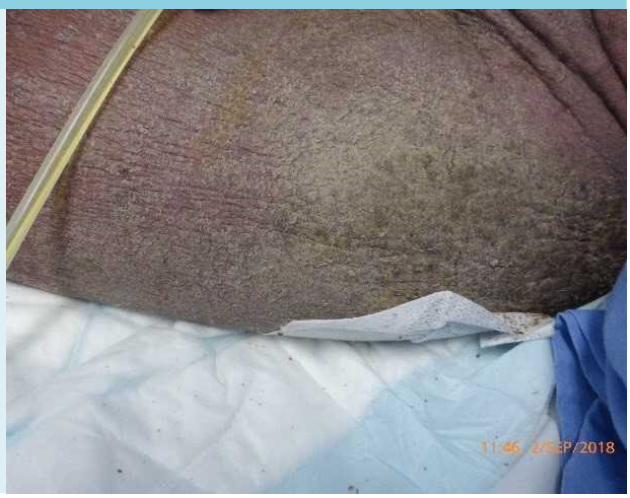


Figure 1B. *Erythaema with fine white scaling and yellow-white plaques*



CASE REPORT

A 68-year-old male from Suriname was admitted to our intensive care unit (ICU) with progressive respiratory failure with a cavitating lung lesion. On admission, a *de novo* HIV infection with a CD4 count of 370 cells/µl and a viral load of 2.132.715 copies/ml was diagnosed. Cachexia was present (body mass index 16.9 kg/m^2) with a blood pressure of 100/60 mmHg, pulse 124/min and a temperature of 39.4°C. The patient was erythroderm and covered with brown-white plaques and profound white-yellowish scaling (figures 1A and B). His whole body, including his face and scalp was affected. His nails were discoloured, thickened and some were dystrophic. He continuously experienced pruritus, despite daily washing of his skin and twice daily applying Vaseline or indifferent ointment on his skin by nurses or family members. Severe scaling of the skin necessitated his bedsheets to be replaced frequently. A skin biopsy (from the elbow, see figure 1A) showed an orthokeratotic keratinizing epidermis, also slightly acantholytic thickening with an influx of lymphocytes. Immunohistochemical additional colouring did not identify *herpes simplex*, *herpes zoster*, or *Borrelia*. The intra-epidermal and peri-vascular lymphocytes were positive for marker CD3 and particularly CD4. Markers CD20 and CD30 were negative.

WHAT IS YOUR DIAGNOSIS?

See page 161 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 160)

TO DIAGNOSE FROM SCRATCH: CRUSTED SCABIES MIMICKING A T-CELL LYMPHOMA

DIAGNOSIS

The pathologists concluded an atypical population of T cells suspicious for mycosis fungoides or Sezary-syndrome (cutaneous T-cell lymphoma). To confirm this diagnosis, blood samples were sent to a reference centre for immunophenotyping. However, this showed a more reactive T-cell population with CD8+ cells with an effector phenotype, activated HLA-DR (Human Leukocyte Antigen - DR isotype) and normal expression of CD2,3,4,5,7 and 8; only a small number of CD8+ cells expressed CD30. Hence, the diagnosis of cutaneous T-cell lymphoma was not confirmed. Treatment of this T-cell lymphoma was postponed because of his critical illness. During his stay in the ICU, his skin condition somewhat improved after systemic antibiotics (meropenem and ciprofloxacin) were started for a pulmonary infection. Anti-retroviral therapy with dolutegravir, emtricitabine and tenofovir was initiated almost directly after admission but did not affect his skin lesions. Two weeks after the start of systemic antibiotics, steroid cream (class 4) was advised by the dermatologist and applied twice daily for treatment of his T-cell lymphoma. The patient experienced less itching, the crusted skin lesions disappeared slowly, and the non-crusted skin became darker. However, the skin lesions did not disappear completely, still affecting the face, armpits, elbows, legs, and abdomen.

Approximately two months after ICU admission of our patient, a nurse was diagnosed with scabies by his general practitioner. This fact alarmed the staff that the patient could have unrecognized crusted or "Norvegian scabies". A skin-scraping and microscopy examination was then performed on the patient, which identified countless mites and mites eggs (figures 2A and B) and thus confirmed the diagnosis of crusted scabies. Treatment consisted of ivermectin orally on days 1, 2, 8, 9, 15, 22, and 29. Permetrin 50 mg/g cream was applied on the skin daily. After a few days, his crusted skin lesions completely disappeared. With the diagnosis of scabies in mind, the histopathology was revised and sent out for second opinion; in addition to scabies, there was still a strong suspicion of a cutaneous T-cell lymphoma (CD8-positive mycosis fungoides). Unfortunately, the patient died due to other complications before receiving treatment for this suspected T-cell lymphoma.

Crusted or disseminated scabies is a diagnosis that is frequently missed and can lead to hospital outbreaks.[1] It can occur in patients that have compromised cellular immunity, e.g. HIV-infection, human T-cell lymphotropic virus type 1 (HTLV-1) infection, lymphoma, and Hansen' disease (leprosy). A high number of scabies mites are present, and it is therefore very contagious. In our hospital, the Outbreak Management Team identified approximately 400 health workers who had some form of contact with the patient. They all received, according to Dutch national guidelines a prophylactic treatment of a single dose of ivermectin. Four individuals who nursed the patient intensively in the ICU department were diagnosed with

Figure 2A. *Scabies mite*

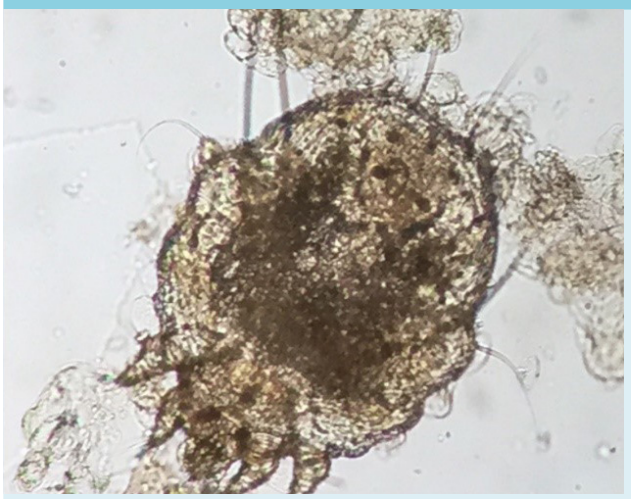
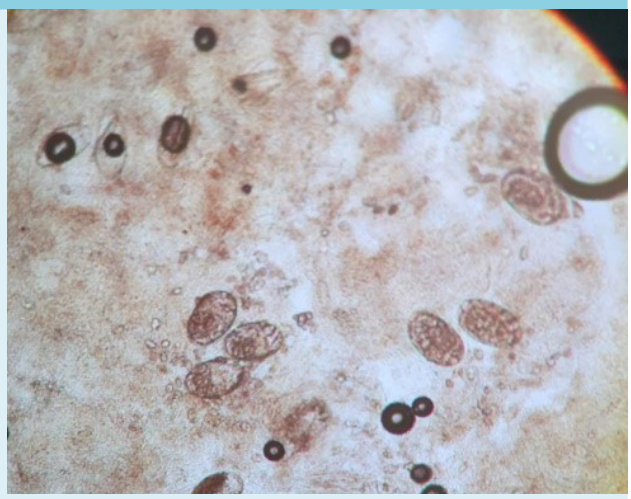


Figure 2B. *Scabies eggs*



(Both photos from patient)

scabies. The high-level standard hygienic measures (strict hand hygiene, wearing gloves and medical gowns at all patient-related activities) probably explains the low number of health workers infected, compared to other previous hospital outbreaks.[2] Retrospectively, the skin lesions significantly improved and the skin was less discoloured 2-3 days after starting meropenem and ciprofloxacin. There are no similar reports published, except for a 7-day course of co-trimoxazol which was not effective against scabies.[3] The most plausible explanation in our opinion, is that these systemic antibiotics treated unrecognised secondary bacterial infections of the skin (e.g. cellulitis), which are common in crusted scabies but more difficult to diagnose in dark skin. The effects of topical corticosteroids are known to diminish hyperkeratotic skin lesions and reduce the pruritus, and is therefore often described as "scabies incognito". It is known that a skin biopsy in crusted scabies can mimic other cutaneous diseases, such as Langerhans cell histiocytosis.[4] The revised histopathology showed a strong suspicion of a T-cell lymphoma; however, several diseases can mimic CD8+ T-cell lymphoproliferative disorders.[5] This emphasizes the indispensability of clinical-pathological correlation in pathology requests.

This case illustrates that we, as physicians, are prone to several forms of cognitive bias. We relied too heavily on the presumptive diagnosis of the pathologist and we failed to make a proper list of differential diagnosis. This is a form of "anchoring", a cognitive bias when a person relies too heavily on the initial piece of information he/she receives when making a diagnosis. Here, anchoring resulted in premature closure in the diagnostic process and delay in appropriate treatment.

REFERENCES

1. Hardy M, Engelman D, Steer A. Scabies: A clinical update. Aust Fam Physician. 2017;46:264-8.
2. Leistner R, Buchwald D, Beyer M, Philipp S. Scabies outbreak among healthcare workers in a German acute care hospital.J Infect Prev. 2017;18:189-92.
3. Shashindran CH, Gandhi IS, Lal S. A trial of cotrimoxazole in scabies. Br J Dermatol. 1979; 100:483.
4. Drut R, Peral CG, Garone A, Rositto A. Langerhans cell hyperplasia of the skin mimicking Langerhans cell histiocytosis: a report of two cases in children not associated with scabies. Fetal Pediatr Pathol. 2010;29:231-8.
5. Mitteldorf C, Plumbaum H, Zutt M, Schön MP, Kaune KM. CD8-positive pseudolymphoma in lues maligna and human immunodeficiency virus with monoclonal T-cell receptor-beta rearrangement. J Cutan Pathol. 2018 Nov 8.

PHOTO QUIZ

A spleen like you've never seen?

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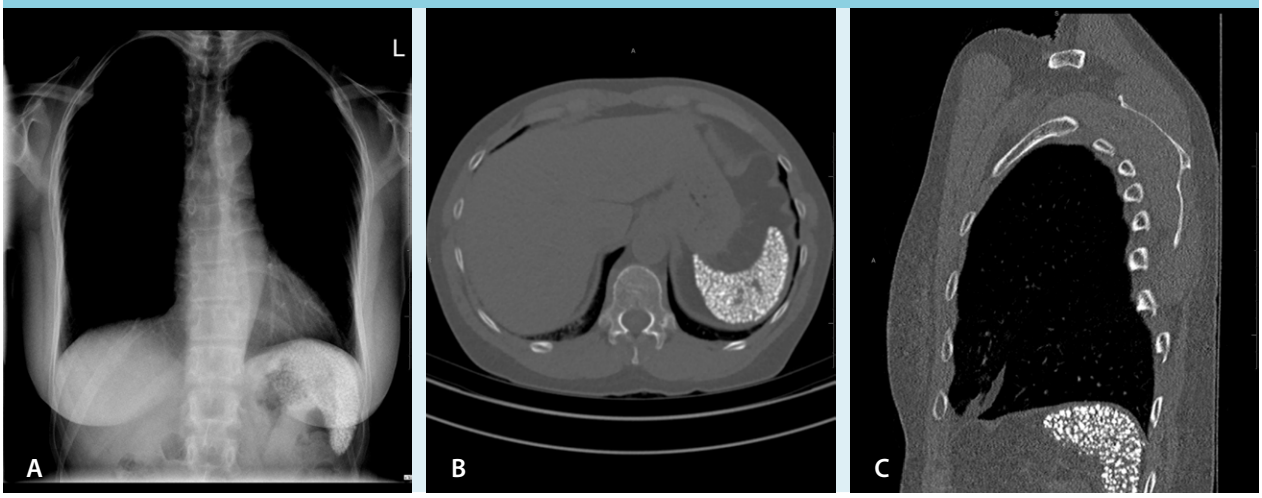
Figure 1A-C. *X-ray and CT scan of the chest, showing an odd and interesting image directly under the left hemidiaphragm. Panel A: chest X-ray; panel B: CT scan chest axial view; panel C: CT scan chest sagittal view)*



CASE REPORT

A 59-year-old female was admitted to the Intensive Care Unit (ICU) in respiratory distress. She was admitted to the general ward three days before with misery and fatigue, and became rapidly dyspnoeic at day three. Influenza A virus testing was positive, despite her annual preventive influenza vaccination.

Medical history revealed proven systemic lupus erythematosus (SLE), nephritis with slow progressive kidney failure, living related kidney transplant in 1995 resulting in chronic allograft nephropathy, living unrelated kidney transplant in 2015, mild mitral valve and moderate aortic valve insufficiency with left ventricular hypertrophy, and interstitial lung disease since 2018. Known prescribed medications were omeprazole, prednisolone, tacrolimus, everolimus, irbesartan and montelukast.

Physical examination showed a very tachypnoeic patient with use of accessory respiratory muscles, respiratory rate 40/minute, $SatO_2$ 68% with 15 litres/minute oxygen on a non-rebreather-mask, blood pressure of 190/105 mmHg, heart rate of 155/minute and tympanic temperature of 37.4°C. Blood gas analysis showed a non-compensated metabolic acidosis (pH 7.27, pCO_2 6.1 kPa, HCO^{3-} 21.0 mmol/l, base excess -5.9 mmol/l) and hypoxia (pO_2 8.1 kPa, $SatO_2$ 88%). We started respiratory support with non-invasive ventilation. Laboratory results showed no leukocytosis, elevated C-reactive protein of 116 mg/l, lactate of 3.0 mmol/l and n-terminal prohormone of brain natriuretic peptide (NT-proBNP) of 34847 pg/mL. Chest X-ray showed extensive bilateral infiltration of lower lung fields and pleural effusion. CT scan of the chest was performed to exclude pulmonary emboli, which were not present. We suspected cardiogenic pulmonary oedema and started treatment with furosemide, nitroglycerine, milrinone, and hydrocortisone stress scheme. Moreover, we treated her with oseltamivir and cefotaxime, later on switched to ceftazidime because of a sputum culture showing *Pseudomonas*. With this treatment, our patient recovered rapidly, and we waived further diagnostics (on for instance *Aspergillosis*).

While reviewing the X-ray and CT scan (figure 1), we noticed an odd and interesting image directly under the left hemidiaphragm.

WHAT IS YOUR DIAGNOSIS?

See page 164 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 163)

A SPLEEN LIKE YOU'VE NEVER SEEN?

DIAGNOSIS

X-ray and CT scan of the chest showed extensive small-sized calcifications of the spleen (figure 1).

Various autoimmune disorders can cause splenic abnormalities, like splenomegaly and splenic infarction. SLE is a chronic multisystemic autoimmune disease, in which several organs and tissues are damaged by pathogenic autoantibodies and immune complexes. Abdominal involvement of SLE can occur in virtually any organ within the abdominal cavity, although only renal involvement integrates diagnostic criteria.[1] Rupture, splenomegaly, infarction, infections, and atrophy of the spleen have been recognized in patients with SLE. Rapid enlargement of the spleen in a lupus patient should raise concern for the possibility of lymphoma.[2]

Splenic calcifications have been reported in SLE and in various other diseases such as rheumatoid arthritis, systemic sclerosis, amyloidosis, sickle cell anaemia, anthracosilicosis, lymphoma, infections (histoplasmosis, tuberculosis, brucellosis, candidiasis, *Pneumocystis jirovecii*), trauma and coeliac disease.[3-5] Despite this wide range of causes, splenic calcifications still remain rare and reports on prevalence are not available. In our case, these other causes of splenic calcifications like infections (negative HIV testing, interferon gamma-release assay – tuberculosis negative), sickle cell anaemia, lymphoma and environmental causes were ruled out from the history, clinical examination and laboratory findings. Segmental splenic infarction associated with lupus anticoagulants and anti-cardiolipin antibodies can also result in splenic calcification, however were negative in our patient. Whether splenic calcification can predispose to hyposplenism remains unclear.[3] It may precede autosplenectomy and hyposplenism, possibly emphasizing the importance of pneumococcal vaccination.[6]

The guideline on hyposplenism from the 'Dutch National Institute for Public Health and the Environment' recommends vaccination and antibiotics for patients with sickle cell disease, splenic infarction and radiation of the spleen. In other diseases able to cause functional hyposplenism (table 1) like SLE, this is less clear. Peripheral blood smear without Howell-Jolly bodies does

Table 1. *Diseases with risk of functional asplenia (adapted from the guideline Asplenia, Dutch National Institute for Public Health and the Environment)*

	Diseases
Cardiac	Congenital cyanotic heart diseases
Intestinal	Celiac disease* Inflammatory bowel diseases (mainly colitis ulcerosa)
Liver	Cirrhosis, with or without portal hypertension* Chronic active hepatitis
Haematological	Sickle cell disease* Other haemolytic anaemia with extreme haematopoiesis Primary thrombocythemia
Auto-immune	Vasculitis (splenic infarction)* Systemic of discoid lupus erythematosus* Rheumatoid arthritis
Infiltrating	Amyloidosis Sarcoidosis
Vascular	Splenic artery occlusion Splenic vein thrombosis Coeliac artery thrombosis
Other	Graft versus host disease Stem cell transplantation* High dosed steroids Radiation of spleen (Hodgkin's disease)* HIV infection with low CD4-cell count

* One of more common causes of functional asplenia

not exclude functional hyposplenism, and ultrasound and CT imaging is inefficient to judge splenic function. Spleen scintigraphy could be conclusive, but is invasive. So, in these cases, the advice to treating medical specialists is to not routinely provide vaccination and antibiotics to all patients with potential hyposplenism, but to individually assess each case in consultation with an infectious diseases consulant.[7]

DISCLOSURES

The authors have no conflicts of interest to declare.

REFERENCES

1. Kirby JM, Jhaveri KS, Maizlin ZV, et al. Abdominal manifestations of systemic lupus erythematosus: spectrum of imaging findings. Can Assoc Radiol J. 2009;60:121-32
2. Lee LK, Hahn PF. Beyond splenomegaly: An image-based review of infectious and inflammatory diseases of the spleen [Internet]. July 2017 [cited March 13th, 2019]. https://appliedradiology.com/articles/beyond-splenomegaly-an-image-based-review-of-infectious-and-inflammatory-diseases-of-the-spleen.
3. Vaiopoulos AG, Kanakis MA, Katsouri K, et al. Diffuse calcifications of the spleen in a woman with systemic lupus erythematosus. Case Rep Med. 2015;2015:414102.
4. Topin J, Mutlu GM. Images in clinical medicine. Splenic and mediastinal calcifications in histoplasmosis. N Engl J Med. 2006;354:179.
5. Fyfe AJ, Gallipoli P. Multiple splenic calcifications. Br J Haematol. 2009;144:808.
6. Elzein FE, Elzein S, Albalawi R. Splenic calcification in systemic lupus erythematosus. BMJ Case Rep. 2017 sep 21;2017. pii: bcr-2017-222206. doi: 10.1136/bcr-2017-222206.
7. Richlijn Asplenie: Rijksinstituut voor Volksgezondheid en Milieu, 2019. (Accessed April 10, 2019, at https://lci.rivm.nl/richtlijnen/asplenie).