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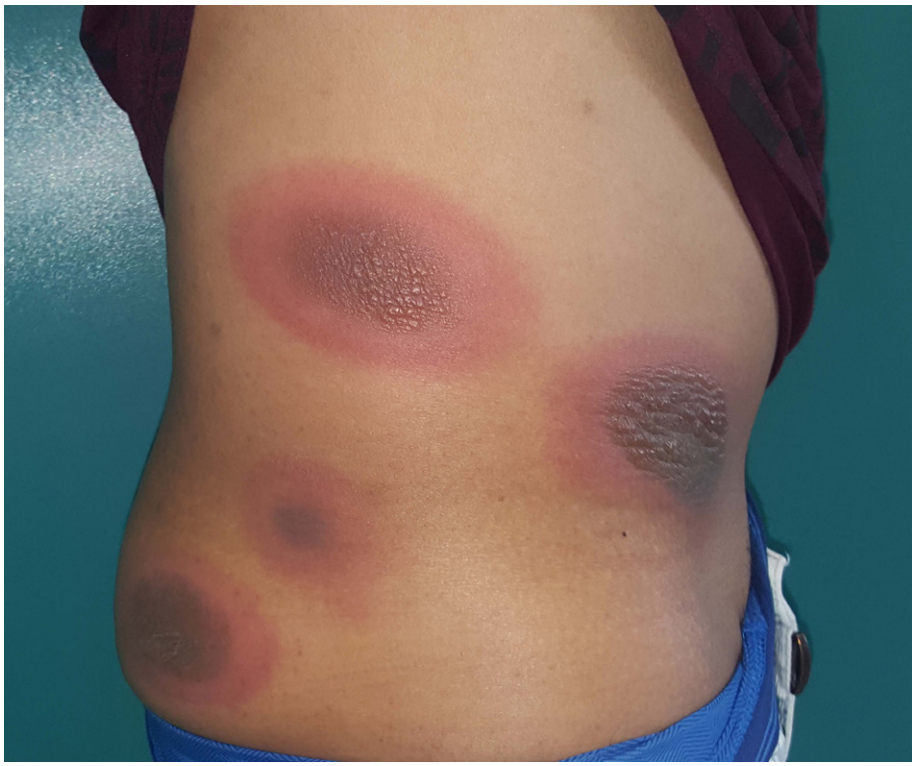

Recurrent skin lesions after medication intake; what is your diagnosis?

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EDITORIAL

Perspectives in allergy

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Over the last decades, the prevalence of allergic diseases is rising. Numerous studies have demonstrated an increase in rhinitis, asthma, atopic dermatitis, food allergy and anaphylaxis. The availability of better diagnostics and increased awareness is not the main cause of this rise. Western lifestyle and particularly a decrease in microbial burden in early childhood appears to skew the immune system to a T-helper 2 cell domination resulting in an increase in the production of IgE antibodies. Particularly, helminth infections and infections from microbes such as *Helicobacter pylori* may be protective in the development of allergic diseases. As the increase in allergic diseases does no fully coincide with the hygienic measures taken in the early 20th century, factors such as obesity, less physical activity, less outdoor activities with increased exposure to indoor allergens as a result and the progressive use of antibiotics have been put forward as lifestyle factors contributing to the rise of allergic diseases.[1] Whereas the Western world is reaching a level of saturation, the prevalence of allergic diseases is still increasing in developing countries. It has been estimated that allergic rhinitis affects approximately 400 million people around the world, whereas asthma affects 300 million subjects. A dramatic increase in allergy to peanuts has been observed from 1990 to the present in the USA and the UK. Factors such as differences in peanut preparation, delayed oral consumption of peanut products, changes in skin due to daily bathing thereby facilitating penetration of allergens through the skin, with subsequent sensitisation, have been put forward.[1]

The high prevalence of allergic diseases has a major socioeconomic impact. Rhinitis and asthma interfere with school, work and leisure. Allergic rhinitis affects school performance and the results of examinations. Whereas asthma results in absence from work, rhinitis may substantially decrease work productivity. In addition, many studies point to impaired quality of life in patients with food allergy. Instruments have been developed to estimate this burden of disease.[2] The high prevalence of allergic disease is also mirrored by the substantial level of health care costs and indirect costs. A review[3] reported that annual costs for rhinitis and asthma may increase to more than € 1000 and € 2000, respectively, per patient, depending on the country. The extra costs for households with members with self-reported food allergy have been estimated at € 3933 per year in the Netherlands, whereas the total costs of cow milk allergy in the Netherlands for new cow milk allergy sufferers up to the age of 1 year were estimated to be € 11.28 million. In addition, a French study estimated the costs for food- or drug-associated anaphylaxis at € 1895 per case.

In recent years, the diagnosis of allergic diseases has been improved. Major developments have been made, particularly in the field of food allergy. The key role of IgE antibodies in type I allergic reactions is well established. The diagnosis of food allergy has traditionally been based on clinical history and food specific IgE testing, including skin prick testing. These tests are characterised by a high sensitivity but the specificity is limited: positive test results to foods that are tolerated are common.

The golden standard in the diagnosis of food allergy is the double blind placebo controlled food challenge (DBPCFC).[4] This test is time consuming, expensive and not without side effects. Therefore, additional diagnostic tests are needed to make the correct diagnosis. During the last two decades significant progress in biochemistry and molecular biology enabled the detection and quantification of specific IgE antibodies to allergen protein components and epitope-emulating peptides, also called molecular allergy diagnosis or component resolved diagnosis.

This new methodology in clinical food allergy diagnosis is improving the ability to identify specific clinical phenotypes. Component resolved diagnosis measures specific IgE against individual allergens, utilising native or recombinant allergens. Native allergens are purified from allergen extracts and recombinant allergens are biotechnologically produced by bacteria or yeasts.

Component resolved diagnosis can, for instance, distinguish between genuine sensitisation and that based on cross-sensitisation of food allergens mutually

or food allergens and inhalation allergens (pollen-food syndrome) and consequently gives insight into the sensitisation pattern and the risk of a mild or more severe allergic reaction. There are relatively harmless, unstable allergens, such as profilins, and potentially dangerous allergens that are extremely resistant to proteolysis, heat denaturation and pH changes, such as the allergens of the Prolamin superfamily including lipid transfer proteins and 2S albumins. Pathogen-related proteins, such as PR-10 proteins, play an important role in the pollen-food syndrome and usually cause mild to moderate symptoms such as 'oral allergy'. Furthermore, diagnostic cut-off values have been difficult to determine for allergens where component testing has been demonstrated to be beneficial. Consequently, there is a growing number of studies measuring predictive values of specific allergen components for food allergy.[5] The recently published European Academy of Allergy and Clinical Immunology Molecular Allergology User's Guide provides comprehensive information on important allergens and describes the diagnostic options using component resolved diagnosis. The User's Guide documents the rapid progression of molecular allergology from basic research to its integration into clinical practice, a quantum leap in the management of allergic patients.[6] However, we should take into account that, for example, age and geographic differences affect the results of component resolved diagnosis and it should always be utilised in the context of clinical history. Therefore, component resolved diagnosis is not ready to replace the DBPCFC and evaluations of component testing for a number of major food allergens are lacking. So, in conclusion, DBPCFCs are as yet indispensable, and well-described guidelines on the performance and interpretation of the DBPCFC are much needed.

Recently, a Dutch national multidisciplinary guideline was published under the auspices of the Dutch Society of Allergology, which aims to standardise the indications and performance of the food challenge in the Netherlands. The merit of this guideline is that allergists, paediatricians, dieticians and dermatologists reached consensus. Patient organisations were involved in a survey to identify the barriers and bottlenecks in food allergy. This guideline advises not to replace food challenges by sensitisation tests or component resolved diagnosis to establish the diagnosis of food allergy, in patients who have never eaten the tested food, who did not react with convincing symptoms, who reacted more than one year before presentation, or who did not react to a clearly identifiable allergenic food.[7]

The growing demand of allergic patients on health care services asks for measures to prevent disease. However, large and long-lasting studies with a focus on allergen avoidance in early childhood have failed to prevent the development of allergic diseases. In recent years the paradigm of early allergen avoidance was challenged by observations that introduction of peanut in the first months of life protects against the development of peanut allergy.[8] Other preventive studies try to address the effectiveness of early introduction of egg. It remains, however, a matter of debate how to translate the findings of these studies to general measures at a population level.

Dietary restriction of food allergens is, however, still the hallmark of treatment for those individuals with well-established allergy to specific foods. As food avoidance may be a burden interfering with social life and accidental exposure resulting in anaphylactic reactions may occur, attempts have been made to induce tolerance by different forms of immunotherapy. Most studies focus on oral immunotherapy. Until now, 12 studies with peanut, five with egg and ten with milk have been published.[9] In general, oral immunotherapy induces desensitisation during treatment. Patients are able to tolerate food challenges with the culprit allergen at the end of the trial. However, sustained tolerance to food after the end of treatment has only been evaluated in a few studies. Egg and milk allergy recurred in 70% of the children after discontinuation of treatment leading to the question whether oral immunotherapy should be given life-long.[9] Finally, oral immunotherapy is being hampered by common adverse events and drop-outs, which makes it difficult to position this treatment in daily practice.

In contrast, for more than a century sustained efficacy has been achieved with inhalant allergen immunotherapy. Subcutaneous immunotherapy is being considered a treatment modality that can change the natural course of allergic disease. Attempts to find more patient-friendly and safe ways to administer allergens led to the introduction of sublingual immunotherapy. Ineffective sublingual immunotherapy products hindered the acceptance of this treatment, but currently the efficacy of grass pollen and house dust mite tablets is well established in large randomised trials. The long-term treatment, problems with adherence and safety aspects of immunotherapy have been the starting point for a search for effective, safe and less demanding forms of immune-modulation. These new developments can be divided into different routes of administration (intralymphatic or epicutaneous), use of allergens in combination with anti-IgE, allergen fusion with immune response modifiers, use of allergens coupled with adjuvants, use of recombinant allergens or modified allergens or the administration of allergen peptides.[10] Finally, the availability of biologicals such as anti-IgE (omalizumab) for severe asthma and spontaneous urticaria, anti-IL5 (mepoluzimab) for severe eosinophilic asthma and new biologicals in the pipeline will broaden the therapeutic arsenal for the allergic patient.

In conclusion, allergy is an evolving field in science and patient care. Improvement and standardisation of diagnostic procedures, as illustrated by the paper by Van Maaren et al.,[7] and the availability of new therapeutic possibilities will clearly benefit the allergic patient.

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SPECIAL REPORT

Dutch guideline on food allergy

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ABSTRACT

The diagnosis of food allergy is established in cases where an immediate allergic reaction has occurred in the last year to a clearly identifiable allergenic food combined with sensitisation to this allergenic food. In all other cases, a food challenge test is required to establish or reject the diagnosis of food allergy. Although the double-blind placebo-controlled food challenge (DBPCFC) test is considered the gold standard, false-positive and false-negative outcomes occur. The incidence of false-positive outcomes is unknown because the results of DBPCFC tests cannot be further confirmed by other tests. If possible, it is important to perform double-blind challenges with recipes that have been validated for blinding and to use challenge procedures that have been proven safe in clinical practice, in order to reduce the risk of unwanted false-positive and false-negative outcomes and severe challenge reactions. The national guideline of the Dutch Society of Allergology describes when challenges are indicated and contraindicated, how food challenges are best conducted and how patients could best be managed and followed-up after the challenge tests have been completed.

KEYWORDS

Double blind placebo controlled food challenge, Dutch guideline, food allergy

INTRODUCTION

If the patient's history concerning the ingestion of a particular allergenic food or information about the symptoms following ingestion or the time interval between ingestion and the beginning of the symptoms are lacking, not clear cut or not specific for an allergic reaction, determination of specific immunoglobulin E (IgE) may help to rule out an allergic cause. Absence of specific IgE in these cases indicates that the patients are probably not allergic to the ingested food because the specificity of this sensitisation test is very high. If, on the other hand, the patient has specific IgE to an allergen, the chance the patient is allergic to this allergen is more likely but yet not confirmed because the sensitivity of this test is in itself very low. This is because many people have specific IgE that is of no clinical relevance. In these cases a challenge test is the only way to ascertain the clinical relevance. The double-blind placebo controlled challenge (DBPCFC) is the best test available to establish the diagnosis of food allergy. Although the DBPCFC is the gold standard, false-positive, false-negative and inconclusive results, and undesired severe reactions do occur. A false-positive result indicates that the patient reacts convincingly during the challenge but is not allergic to the challenged food.

A false-negative result indicates that the patient does not react during the challenge but is allergic. Whether the test result is false-negative or false-positive will only be known if patients report that they reacted during (re)introduction of the challenged food or that they did not react following accidental ingestion. Because patients have reported such reactions and because placebo reactions have been documented during placebo-controlled challenges, it is known that these unwanted results do exist. However, the incidence of these undesired results is not known.

A false-positive challenge test has a negative impact on the quality of life.[1] A patient who avoids food has a poorer quality of life and may have a diet that lacks essential nutrients.[2] Additionally, increasing scientific evidence suggests that delayed introduction of foods or unnecessary avoidance may increase the risk of acute allergic reactions on (re)introduction to these foods in atopic children.[3] The danger of a false-negative test is obvious: the patient runs the risk of an allergic reaction during introduction when they may not be carrying emergency medication.

By adjusting the number of challenge steps, the start dose and last dose, the time intervals and the stop criteria for termination of the challenge test or the proportion of open to double challenges, the numbers of false-positive results, false-negative results and undesired reactions change. The goal of this guideline is to explain how to minimise the risk of these adverse results while keeping the challenge test acceptable as a routine test.

PLACE OF SENSITISATION TESTS IN DIAGNOSING FOOD ALLERGY

Sensitisation tests aim to detect specific IgE directed against an allergen. Specific IgE can be determined indirectly by a skin prick test or directly by a serological test. The result of a sensitisation test can be compared with the results of the gold standard, the DBPCFC. In this way the specificity and sensitivity can be determined. In general, the sensitivity of specific IgE tests with allergens is low, especially when the results are not combined with information from the patient's history.

Allergenic foods contain a mixture of different allergens. Skin prick tests with food or specific determinations of IgE give no information on which allergen the patient is sensitive to in this mixture. The individual allergens that are present in one food are called components by the manufacturer of a test to determine specific IgE to increasing numbers of individual allergens. This test is called component resolved diagnosis. With this test, one can discriminate between food-specific allergens that are associated with systemic reactions and some highly cross-reactive food-plant allergens such as those belonging to the pathogen-related family of proteins 10 (PR10) and profilins that are associated with tolerance or relatively mild symptoms as itchy mouth confined to the oral cavity and throat (so called 'oral allergy complaints'). As a result, component resolved diagnosis testing has a higher specificity and sensitivity when used to diagnose allergy to foods that contain both types of allergens such as peanut and tree nuts, as compared with skin prick tests and serological tests with these foods, but not in e.g. milk that contains milk specific components.[4]

The cut-off values of serological tests that can predict the negative or positive outcome of the food challenge test are of more clinical use than sensitivity and specificity of tests. If these positive and negative predictive values (PPV and NPV) can predict the outcome of the challenge test with high probability, a challenge test may not always be needed to establish presence or absence of allergy. If one could predict the negative outcome of a challenge test with 100% certainty in patients that have specific IgE equal or below a certain cut-off value, challenges may no longer be needed in these patients. An NPV of 95% indicates that 5% of the patients who have a value equal to or below the cut-off value would react in a food challenge test. Advising patients who have a 5% chance of being allergic to introduce food based on a sensitisation test alone is usually not acceptable because some of them run a risk of a severe reaction in an unsupervised setting.

High specific IgE cut-off values associated with a post-test probability of a positive outcome of a challenge test of 100% are desirable but are likely to be applicable to only a relatively small number of patients. If a PPV of 95% is considered acceptable, a larger proportion of challenge tests would be redundant. However, even more modest cut-off values associated with correspondingly more modest PPVs have been found to differ between populations of different ages, and even from different centres. There are many possible explanations for these differences including differences in age and sex composition, geographical region, proportion of sensitised patients, all of which may influence prevalence and thus PPV. Moreover, the prevalence of food allergy can vary over time and therefore cut-off values associated with certain PPVs may change.

As mentioned above, a new approach to serological testing is the component resolved diagnosis test, or determination of specific IgE to single allergens contained in foods. This has proved most successful in peanut allergy. Positive specific IgE tests to Ara h2, a major peanut specific allergen, is associated with an increased risk of clinical peanut allergy and, to a lesser extent, an increased risk of relatively severe reactions to peanuts. In several studies, PPVs of specific IgE against Ara h2 may be associated with PPVs as high as 95%. As expected, the cut-off value of Ara h2 with a PPV of 95% differs from one study to another. Published specific IgE cut-off values to different

allergens associated with high PPVs are thus of limited generalisability and as a result cannot currently replace challenge tests.[5-7]

Aside from establishing the diagnosis of food allergy, the challenge test gives the patient some experience in recognising symptoms and improves health-related quality of life. Reactions and the amount of food protein eliciting them may not be extrapolated to accidental reactions because in real life other factors are operational that can influence the threshold level, such as the way the consumed food has been processed and the matrix in which it is present, the use of medication, the presence or absence of illness and co-factors such as exertion and alcohol.

The Dutch guideline Task Force advises not to replace food challenges by sensitisation tests or component resolved diagnosis testing to establish the diagnosis of food allergy in patients who have never eaten the tested food, who did not react with convincing symptoms, who reacted more than one year before presentation, or who did not react to a clearly identifiable allergenic food.

INDICATIONS AND CONTRAINDICATIONS

Challenge tests are indicated in the following cases:

- To establish the diagnosis of food allergy
- To evaluate if a patient has outgrown a food allergy that was established in the past
- To establish the clinical relevance of specific IgE to an allergenic food if patient history is indeterminate
- To educate a patient on which symptoms he may expect if he accidentally ingests the food and how to respond.

Absolute contraindications are:

- Uncontrolled asthma
- Unstable angina pectoris
- Severe chronic lung disease
- Pregnancy
- Fever.

Relative contraindications are present when factors associated with severe reactions or complications during challenge tests that negatively interfere with the treatment of a reaction or that hamper the interpretation of the challenge test are operational. There is no direct medical evidence that these factors truly prohibit a challenge procedure because in challenge studies patients who have a medical condition or use medication that could negatively affect the severity or treatment of a reaction (beta-agonists, ACE inhibitors and NSAIDs) or interpretation of the challenge test (systemic corticosteroids and antihistamines) are always excluded. Indirect evidence concerning potential risk factors of severe reactions during challenge tests are derived from studies of patients seen in the emergency room because of anaphylactic reactions or who have been treated with allergen immunotherapy and reacted severely to a subcutaneous injection.[8,9] Because risk-augmenting medication can often temporarily be stopped or switched, or unfavourable conditions may often be treated prior to challenge or are of a temporary nature, it is rarely acceptable to undertake an oral food challenge when such risk factors are present, even if direct evidence of the increase in risk is lacking.

If an unfavourable condition persists or medication cannot be stopped or switched, it is advised to consult or refer to a centre where an allergist who has extensive experience with food challenges under difficult circumstances and with high-risk challenges can supervise the procedure. Official criteria for these 'allergy specialist centres' have not been formalised, but the Task Force considers centres that meet the following criteria as such:

- Challenges are supervised by recognised allergists/ paediatric allergists
- In these centres large numbers of challenge tests are performed
- The food challenge procedures are protocolised
- Tasks and responsibilities before, during and after the challenge test are clearly assigned
- All amenities are present to treat anaphylaxis including intensive care facilities.

OPEN VS DOUBLE-BLIND CHALLENGES

The challenge test can be done in an open (open food challenge: OFC) or double-blind fashion (double-blind placebo-controlled challenge: DBPCFC). In an open challenge test the food may be administered in its native form. In a double-blind challenge, the challenge material is administered incrementally on two occasions. On one day, the food to be tested is given while being masked in a matrix food (for example in a slice of cake or drink), while on the other day only a matched placebo is given. The order of the days is randomised so that neither the patient nor anyone in contact with the patient knows on which day the placebo or the suspected food is given.

Studies in which DBPCFCs are performed show that placebo reactions occur regularly. Generally these reactions consist of subjective symptoms or symptoms that appear more than two hours after the end of procedure, but sometimes they also consist of acute reactions with objective symptoms. In clinical practice, if we only use OFCs the outcome would be that a small unknown percentage of challenges ending with acute objective symptoms would be considered positive while actually being false-positive. Consequently some patients would be

incorrectly diagnosed as being allergic. If open challenges ending with subjective symptoms are also considered positive, it would result in a considerably larger percentage of false positive results.

The potential negative influence of several of these factors can be minimised by blinding the procedure. The result from the administration of the suspected food is compared with that of the placebo before making the diagnosis. The test is considered positive if the patient reacts to the suspected food with symptoms constituting the agreed stop criteria and clearly more severe than to the placebo. Patients not reacting on either test day or with atypical or relatively mild reactions on the placebo day are considered test negative.[10-12]

It is advised to choose an open challenge test if it is very likely that the patient is not allergic. If subjective or late symptoms are to be expected, if the patient has eczema, if the patients fears a severe reaction, or symptoms following an ingestion are different from what would be usually expected (e.g. urticaria instead of oral allergy complaints after eating an apple) the double-blind food challenge should always be the first choice.

RISK OF SEVERE REACTIONS AND SAFETY PRECAUTIONS

The percentage of a near-fatal or fatal anaphylaxis during oral food challenges is probably negligible in daily practice. In the literature no fatal reactions have been documented. The percentage of severe allergic reactions published in the literature reaches a maximum of 10% depending on how a severe reaction is defined and the characteristics of the patients who are challenged. It is believed that the percentage of anaphylaxis in the clinics where the members of the Task Force work is much lower than 10%. This low percentage is likely due to the fact that challenges are performed with carefully selected patients by skilled and experienced personnel, and with procedures and up-dosing schedules that have been proven safe and reliable in clinical practice.

In the Netherlands, allergists tend to categorise challenge tests into high- and low-risk challenges and take extra precautions when a high-risk challenge is performed. Despite this fact, no consistent predictors of a severe reaction during a challenge can be derived from published food challenge studies.[13,14] All authorities agree that any patient with a previous life-threatening reaction to a food is a high-risk patient unless there is evidence of tolerance subsequent to the severe reaction. Nevertheless the majority of high-risk patients have only experienced mild reactions, and the Task Force felt the need for uniform criteria that would discern high- and low-risk challenges in patients without previous life-threatening reactions. Criteria were thus derived from retrospective studies in which the characteristics of patients visiting an emergency room because of accidental (near) fatal anaphylaxis were analysed.[15] Patients in these studies have similar characteristics in different studies and these criteria are the same as those used to decide who needs to be prescribed an epinephrine auto-injector.[16]

The following criteria apply for high-risk challenges:

- If any combination of two of the following is present:
  - Challenges with adolescents and young adults (≥ 12 years of age)
  - Challenges in patients with asthma or a previous asthmatic reaction to the food to be challenged
  - Challenge in a patient who has reacted to traces of the food to be challenged
  - A challenge test with a peanut or tree nut.
- A challenge test with a food to which the patient reacted severely in the past regardless the degree of sensitisation.

As a result of these criteria, a challenge test with a peanut or tree nut is a high-risk test if only one other criteria applies, while a challenge test involving other foods is considered high risk if two criteria are applicable. Challenge tests with fruit are considered low risk even if two risk factors are applicable. Challenge tests with a food to which the patient has had an anaphylactic reaction in the past are always considered high risk even if no other criterion is applicable and even if a fruit is challenged.

If these criteria are used in daily practice, the chance of severe reactions during low-risk challenge tests is probably low but can never be completely excluded. For this reason the setting in which the challenge is performed must always be suitable to care for patients who have an anaphylactic shock and the supervising personal should always be prepared for such an event. Furthermore it is advised to only perform high-risk challenge tests in allergy specialist centres as indicated above.

RECIPES AND LOGISTICS OF CHALLENGE MATERIAL

To guarantee that the challenged food has been blinded appropriately, recipes should be used that have been validated for blinding. To validate recipes is a labour intensive procedure and in most studies that use 'double-blind' challenge tests the recipes used are not validated. The recipes that are validated are summarised in the full text version of the guideline as are the other requirements for these recipes to make them acceptable to use them in challenge tests.[17]

Recipes that are validated for blinding for double-blind challenge tests are available for the following allergenic

foods: cow's milk, hen's egg, soy milk, hazelnuts, peanut, cashew nut and wheat. Unfortunately, there are none for fish, shell fish, legumes other than soy and peanut, and seeds. These allergenic foods can thus only be challenged in an open fashion. Open challenges are usually best performed with food in its native form.[18-20]

CHALLENGE DOSING SCHEDULE

The optimal challenge schedule meets the following criteria:

- The challenge procedure should be performed in half a working day so that sufficient observation time is left.
- The lowest dose administered is about the same as the lowest threshold dose on which an allergic patient is able to react to prevent large numbers of patients reacting (severely) to the first dose.
- The highest dose is similar to the amount of food an adult or child could consume at one time in daily life to prevent false-negative results due to an inadequate final dose.
- The incremental doses and time intervals in between two following doses should be chosen in such a way to prevent severe reactions because the time interval is too short or a dose gap is too large.

The first-mentioned criterion could conflict with the last if a safe procedure cannot be completed within office hours. Fortunately, a lot of experience has been acquired with recipes and up-dosing schedules that meet the criteria above. An interval between doses of 30 minutes has proven to be safe and practical, even though there is evidence showing that many patients probably react to cumulative rather than discrete doses. One of the limitations of the schedules currently in use may be that the last dose is not always high enough to rule out false-negative outcomes.

Dosing schedules that have proven to be safe and practical have been shown to be quite similar for different foods when each dose step is expressed as the amount of protein of the allergenic food. As a result the same up-dosing schedule is advised for both open and double blind challenges independent of the food challenged. The ideal incremental dose sequence is mentioned in the full text version as are the adjustments that could be made depending on the food that needs to be challenged.[17,21-23]

Even when the last dose is similar to an age-appropriate portion of the food, false-negative results are possible. This is known because some patients fail to successfully introduce the food because of reactions during introduction. The reasons for this are only partially known and include occurrence of enhancing co-factors during introduction, induction of short lived tolerance by the challenge procedure and matrix effects. Therefore, open challenges should be carried out to confirm negative DBPCFCs and are especially important following high-risk negative double-blind challenges or those where the final dose was less than a possible daily portion, or when the double-blind test is unexpectedly negative.

STOP CRITERIA AND INTERPRETATION

It is generally felt that early termination of challenges with minimal symptoms will result in a greater number of false-positive test results. Conversely, late termination of challenges with clear objective symptoms will result in a greater number of severe reactions. Stop criteria for termination of the challenge test should be defined in such a way that the number of false-positive results and severe reactions can be kept to a minimum. Unfortunately it is not known which stop criteria are optimal because no studies exist in which the challenge tests with different stop criteria are compared. Therefore stop criteria are generally based on consensus and optimal stop criteria appropriate to the goals of the test centre should be ascertained in daily practice. Currently, it is deemed that objective stop criteria result in the lowest number of false-negative results and are still safe when used in studies. However, in daily practice it may not always be feasible to continue challenges until objective symptoms occur.

In 2012 the PRACTALL Task Force published a set of stop criteria that are advocated by the American and European Societies of Allergology. The Task Force of the present guideline adopted and translated these stop criteria into Dutch to promote their implementation. Using uniform stop criteria will promote the comparability of the results of challenge tests wherever they are performed. The symptoms in the PRACTALL list are ordered according to organ system, e.g. gastrointestinal or lower airways, and the severity of the symptoms is graded (mild, moderate, severe).

The PRACTALL stop criteria are not absolute. Based on the presence of a certain combination of specific symptoms and their severity it is more or less likely that the cause of the symptoms is allergic. This advice on when to stop and when to continue leaves room for the supervising allergist to decide if the challenge test day is positive or not (yet). If symptoms occur that are not enough to terminate the challenge it is advised to extend the time interval or to repeat the last administered dose. If an OFC ends with subjective, mild or moderate objective symptoms, or with other symptoms than what would be expected from the patient's medical history, it is advised to perform a DBPCFC to confirm the allergy.[8,24]

FOLLOW-UP AFTER THE CHALLENGE

Performing challenge testing is only of value if such tests are followed up by successful reintroduction of foods which tested negatively or continued elimination of the challenged foods following positive tests. In case of a positive challenge result, the challenge is successful if the patient manages to avoid the food he reacted to and/or is capable of treating him/herself adequately following accidental exposures while maintaining a diet that is still varied and not lacking in essential nutrients. A negative challenge is successful if the patient manages to (re)introduce the food into the diet. From five published studies in which patients were asked by means of a questionnaire or an interview if they had introduced the tested food permanently it is known that up to a third do not manage to introduce the food for various reasons.[25] From a questionnaire sent by the Task Force to patients who underwent a food challenge test, it is known that 37% wished they had been followed up more effectively after the challenge test. From these data it may be concluded that follow-up after a challenge test may be improved and that good follow-up probably leads to better long-term results.

Although there are no studies on the optimal form of follow-up for patients after a challenge test, the Task Force offers advice based on expert opinion and consensus. Following a negative challenge test it is advised to (re) introduce foods with the help of an introduction schedule for home use. Such introduction schedules include an explanation on how a patient can introduce the food over the course of a few days so that ultimately he or she feels confident eating a normal portion. In the event the patient experiences symptoms attributable to ingesting the food being introduced, contact with an allergist, dietitian or an experienced allergy nurse should be sought to discuss if the introduction should be continued with or without an adjustment of the schedule, or stopped. It is also advised to contact the patient a few months after the introduction to ask if the food is now being eaten regularly. If consumption of the food has been stopped, the reason for this may be ascertained and assistance offered to solve the problem.[26]

Patients in whom the food allergy has been confirmed should be instructed how to read labels, how to deal with advisory labelling (i.e. 'may contain') and be prescribed an epinephrine auto-injector where appropriate. Such a prescription should be accompanied by written and repeated oral instructions on how to treat a reaction in the event of accidental ingestion. Especially if the allergenic food cannot be easily avoided and/or if the food is part of the staple diet, such as wheat or milk, it is advised to refer the patient to an experienced dietitian. The dietitian can instruct the patient on the correct interpretation of food labels, find alternative ingredients for recipes and prescribe supplements if the diet lacks essential nutrients. The dietician may also support the patient and family members in dealing with the food allergy.

INSTRUCTION AND PRACTICAL ADVICE

In the last chapter of the guideline some practical advice is given on topics for which no evidence exists. This advice is based on expert opinion and consensus of the members of the Task Force.

The Task Force deems it important that one supervisor is appointed to be responsible for the decision to continue or terminate the challenge test and determine and administer the treatment in the event of a reaction. This supervisor should be an experienced paediatrician specialised in allergies for challenges that are performed in children and an experienced allergist or dermatologist for challenges performed in adults. During the challenge test the patient should always be monitored by healthcare providers who are trained to recognise allergic symptoms and are capable of starting treatment and supporting advanced treatment of a severe anaphylactic reaction.

The full text of the guideline provides information on how to instruct the patient, and how long the patient should be observed depending on if the patient reacted and the severity of the reaction.

DISCLOSURES

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REVIEW

Peritoneal dialysis underscores its merits in portal hypertension-related and nephrogenic ascites

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ABSTRACT

In the Western world, peritoneal dialysis (PD) is less frequently applied as substitute therapy in end-stage renal disease (ESRD). In the Netherlands the use of PD has decreased from 30.3 to 13.5% due to several factors, but not due to lower PD-related outcome. The lower penetrance of PD diminishes experience with and exposure of young professionals to this treatment modality. This does not enhance a free and motivated choice among renal replacement therapies for patients who cannot be transplanted pre-emptively. To rejuvenate interest in PD and to underscore its merits, we would like to share the use of PD on two extraordinary occasions, where PD was the only way out. Ascites due to portal hypertension with profound gastrointestinal haemorrhage and nephrogenic ascites poses major management challenges in ESRD patients. In conclusion, PD came to the rescue and tremendously increased quality of life in the patients presented. To be readily available, a certain penetrance of and expertise in PD as renal replacement therapy is warranted.

KEYWORDS

Ascites, peritoneal dialysis, dialysis, nephrogenic ascites, portal hypertension, quality of life

INTRODUCTION

For patients requiring renal replacement therapy because of end-stage renal failure, dialysis and renal transplantation are the treatment options available. Peritoneal dialysis (PD) is complementary to haemodialysis with at least comparable survival, better preservation of residual renal function, lower healthcare costs and improved quality of life and patient satisfaction.[1,2] Despite this, the percentage of patients performing PD has declined in most Western countries.[1] In the Netherlands PD use has decreased from 30.3 to 13.5% in the past 15 years.[3] This has been ascribed to increased living related and unrelated organ donation and more investments in haemodialysis chairs, but not to a lower PD-related outcome. Training in and exposure to PD is a major concern with the decreasing numbers of PD patients, both for young nephrologists and for nurses. This hampers the free and motivated choice of patients requiring renal replacement therapy between the available options. To rejuvenate interest in PD and to underscore its merits, we present two extraordinary cases where PD was the only option: one with portal hypertension-related ascites and profound gastrointestinal bleeding, and one with nephrogenic ascites. They pose difficult management problems that were favourably resolved by PD.

CASE 1

A 52-year-old Afro-American female presented in 2003 with nephrotic syndrome due to systemic lupus erythematosus nephritis class V complicated by portal vein thrombosis. Her renal disease responded well to treatment with glucocorticoids and azathioprine. A liver biopsy performed later that year revealed disturbed microcirculation due to portal vein thrombosis. An uneventful period followed. However, from 2013 onwards, she was frequently admitted because of profound haematemesis and tense ascites, which required multiple rubber band ligation sessions and percutaneous drainage, respectively. A transjugular intrahepatic portosystemic shunt was impossible because all major branches of the portal vein were occluded and surgical intervention was too risky in

view of her comorbidity. Ascites and oedema formation were treated with high doses of diuretics, large-volume paracenteses, and intravenous infusions of albumin. Her kidney function deteriorated intermittently and her quality of life steeply (Karnofsky score 20-30). On physical examination the patient showed normal blood pressure but tense ascites with collateral circulation reflected in abdominal wall veins. Apart from this, her physical examination was unremarkable.

Laboratory investigation showed normal liver function and enzymes, creatinine 5.7 mg/dl, and urea 70 mg/dl. Endogenous creatinine clearance was 12 ml/min with a proteinuria of 0.5 g/24 h. Serum albumin was 37 g/l, ascites albumin 9 g/l, and the serum ascites albumin gradient (SAAG) was 28 g/l. The ascites white blood count was 0.1 x 10^9/l. Abdominal echography showed portal vein thrombosis with collateral vasculature, a hepatopetal flow and ascites. Endoscopy revealed bleeding varices that were treated by multiple banding sessions. Echocardiography revealed no cardiac failure or cardiac inflow obstruction.

Because of refractory ascites, the need for frequent large volume paracenteses, deteriorating renal function, low quality of life and frequent hospitalisation PD was started.

After drainage of ascites a Swan-neck Tenckhoff catheter was laparoscopically placed without complications. Initially, drainage of the ascites was started and gradually PD fluid was introduced to achieve a negative fluid balance. No episodes of hypotension or peritoneal fluid leakage were observed. A schedule with four exchanges a day of 1.5 litres of 1.36% glucose-containing peritoneal dialysis fluid was initiated. A peritoneal equilibration test performed after 4-6 months of dialysis disclosed a high ultrafiltration and a high solute transport pattern. The 24-hour dialysate protein content was 1 g/l.

In the following year she had no peritonitis or other PD-related complications. There were no episodes of oedema, and she presented less frequently with bleeding episodes. Endoscopic studies showed diminishing gastric and oesophageal varices. Liver function tests remained normal. At present, the patient maintains a residual diuresis of 1100 ml, a renal creatinine clearance of 7 ml/min, and an adequate Kt/V (measure of dialysis dose) of 2.2. Her serum albumin is stable at 37 g/l. Hospitalisation rate decreased tremendously (from 55 days/year in the year prior to PD to 14 and 0 days/year in the two consecutive years with continuous ambulatory PD, respectively) and her clinical condition as well as her quality of life increased favourably (Karnofsky score improved from 20-30 to 70).

CASE 2

A 61-year-old Afro-American man with diabetes mellitus type 2 was treated with intermittent haemodialysis three times weekly because of end-stage diabetic nephropathy since 2002. In 2006 he presented with collapse and hypoxaemia. A pulmonary embolism was ruled out by CT scan, which showed pericardial and pleural effusion. In addition, ascites, hypalbuminaemia and hypotension were noted. His Kt/V was adequate (1.3 per dialysis), but daily haemodialysis and isolated ultrafiltration were necessary because of overhydration. Echocardiography revealed a good left and right ventricular function, no valve abnormalities, and pericardial effusion of 1 cm all around without inflow obstruction.

Ascites culture and cytology were negative, including a polymerase chain reaction for typical and atypical mycobacteria. The ascites was a straw-coloured exudate, had a white blood cell count of 0.1 x 10^9/l and a SAAG of 1 g/l. Liver function tests, iron studies, thyroid-stimulating hormone, and parathyroid hormone were normal. No evidence was found of portal hypertension, cardiac or pericardial disease, peritoneal infection or malignancy. Nephrogenic ascites was diagnosed. Because of refractory ascites and inability to continue or intensify haemodialysis due to hypotension, a PD catheter was placed laparoscopically following intermittent drainage of ascites. A peritoneum biopsy was performed, which showed minor nonspecific chronic inflammation.

PD was started in the supine position with low intraperitoneal volumes that were gradually incremented. Protein loss in 24-hour dialysate decreased from 24 g/l to 1 g/l.

He became anabolic and normotensive (120/70 mmHg) with a desired dry weight gain of 5 kg. His Karnofsky score increased from 20 to 70. After two months a peritoneal equilibration test was performed, which showed a high average transport pattern that remained stable over the years. His Kt/V was 1.8. He continued on PD for eight years, his clinical course was not uneventful (amputation of both lower legs in 2008, peritonitis due to *S. aureus* in 2013). He died due to myocardial infarction following peritonitis in 2014.

DISCUSSION

PD was successful in both cases for a number of reasons: the patients felt much better because the mechanical problem of ascites was no longer present, caloric and protein intake increased with a subsequent rise in lean body mass. In addition it ensured continuous control of salt, water balance and uraemia.

There are a few things to keep in mind when considering PD in patients with ascites. First, if there is significant abdominal wall oedema, it may result in delayed wound healing. It is prudent to have a longer break-in period. Secondly, not all the ascites fluid should be drained at once. Thirdly, distended abdominal wall veins must be taken into

account when choosing the placement site of ports and of the PD catheter.

In our first patient the ascites was due to portal hypertension subsequent to portal vein thrombosis with a SAAG of 28 g/l. Patients with portal hypertension requiring dialysis for acute or chronic renal failure pose management challenges.[4,5] PD offers several advantages over haemodialysis (no anticoagulation, normalised bleeding time). Excessive bleeding following catheter placement and excessive protein loss have been mentioned as possible drawbacks, but this has not been well documented in the literature. The protein content of ascitic fluid in patients with portal hypertension is generally low and the contribution of protein losses with dialysis fluid to malnutrition in such patients is uncertain at best. The high ultrafiltration and solute removal rate corresponds to a high peritoneal permeability, which can be attributed to an increase in the peritoneal surface area related to portal hypertension.[4] Our patient did not show hepatic failure and was successfully controlled with a progressively negative fluid balance during PD. Insertion of foreign bodies in the abdominal cavity including peritoneovenous shunts has been abandoned by the hepatology community due to the high risk of catheter occlusion and infection. Fortunately our patient did not sustain any peritonitis and protein losses decreased (from 9 g/l in ascites to 1 g/l in dialysate) during follow-up, maintaining serum albumin levels. At present she feels well. PD appears cost-effective with respect to hospitalisation rate, morbidity and quality of life.

Our second patient suffered from nephrogenic ascites. This is a rare and poorly understood condition characterised by refractory ascites in a patient with end-stage renal disease, where portal hypertensive, infectious and malignant processes have been excluded.[6-8]

Pathophysiological factors associated with nephrogenic ascites include chronic fluid overload, changes in peritoneal permeability and impaired lymphatic peritoneal resorption in uraemia.[7-10] Contributing factors may be hypoproteinaemia, hyperparathyroidism, congestive heart failure, constrictive pericarditis, pancreatitis or cirrhosis with portal hypertension.[11]

Diagnosis is made by exclusion of other causes. The ascitic fluid (high protein content, low SAAG, and low leukocyte count) is typically an exudate.[7] This narrows the aetiological possibilities to tuberculous peritonitis, pancreatitis, malignancy, and nephrogenic ascites. Histological examination of the peritoneum often reveals chronic inflammation and mesothelial cell proliferation with variable degrees of fibrosis.[8,9,12,13] A peritoneal biopsy in our patient showed chronic nonspecific inflammation.

In the treatment of nephrogenic ascites salt and water restriction, vigorous haemodialysis with isolated ultrafiltration and intravenous albumin infusion has been advocated,[14] but this is not always effective[11] and severe hypotension may become the limiting factor,[9] as was the case in our patient. A peritoneovenous shunt has been shown to improve nephrogenic ascites,[15] but is not free of complications.[8,15] PD relieved the ascites and favourably improved the condition of our second patient. The reduction of protein loss in both patients, but especially in the second case, remains unexplained but is of clear benefit. PD has been shown to resolve ascites by reducing the intraperitoneal fluid protein concentration which draws fluid into the peritoneal cavity by oncotic forces.[12]

Renal transplantation is the most effective treatment for nephrogenic ascites: almost all reported cases had complete resolution of the ascites within 2-6 weeks.[7,8] This observation argues for a disturbed fluid balance as the primary cause. Our patient was not willing to accept a kidney transplant, and at presentation there were medical contraindications to transplantation.

The appearance of nephrogenic ascites was believed to indicate an extremely poor prognosis.[6,8,13] One year after the development of nephrogenic ascites a third of patients have died.[11] Today, however, the prognosis is certainly much better. Though renal transplantation appears the cure, PD is a readily available, effective treatment that relieves ascites and improves both the clinical condition of patients with nephrogenic ascites and their quality of life.

In conclusion, two challenging refractory ascites cases are presented: one with hepatorenal disease and one with nephrogenic ascites. They posed difficult management problems that for a prolonged period were favourably resolved by PD. Also for less extraordinary cases, initiating renal replacement therapy on PD was associated with favourable survival outcomes when compared with starting on haemodialysis treatment.[16] In the absence of medical or social contraindications, PD can offer other important benefits, including patients' autonomy and lower costs.[16] Furthermore, for the growing group of elderly patients, PD has a number of advantages and most of the perceived barriers to PD may be overcome.[17] In addition, for the rising numbers of those suffering from end-stage heart failure refractory to available therapies, PD may be an effective, cost-effective and safe therapeutic option for fluid control, improving heart function while preserving residual renal function with less hospitalisations and better quality of life.[18] To be readily available, a certain penetrance of and expertise in PD as renal replacement therapy is warranted. Increasing collaboration between different centres to keep a high level of knowledge in PD and to explore the reasons for not selecting PD as initial dialysis modality will be needed. In this way the adagium of a free and motivated patient choice among all renal replacement modalities can better be met.

DISCLOSURES

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ORIGINAL ARTICLE

Regional variation in the practice of euthanasia and physician-assisted suicide in the Netherlands

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ABSTRACT

Background: The practice of euthanasia and physician-assisted suicide has been compared between countries, but it has not been compared between regions within the Netherlands. This study assesses differences in the frequencies, characteristics, and trends of euthanasia and physician-assisted suicide between five regions in the Netherlands and tries to explain the differences by demographic, socioeconomic, and health-related differences between these regions.

Methods: Data on the frequencies, characteristics, and trends of euthanasia and physician-assisted suicide for each region and each year from 2002 through 2014 were derived from the annual reports of the Regional Review Committees. Averages and trends were determined using a regression model with the regions and years as independent variables. Demographic, socioeconomic, and health-related variables for each region and each year were derived from the Central Bureau for Statistics and added to the model as covariates.

Results: The frequencies, characteristics, and trends of euthanasia and physician-assisted suicide differed between the regions, whereas the frequencies of non-assisted suicide did not differ. Euthanasia and physician-assisted suicide were most frequent and were performed most often by general practitioners, in patients with cancer, in the patient's home, in North Holland. The regional differences remained after adjustment for demographic, socioeconomic, and health-related differences between the regions.

Conclusion: More detailed research is needed to specify how and why the practice of euthanasia and physician-assisted suicide differs between regions in the Netherlands and to what extent these differences reflect a deficiency in the quality of care, such as other forms of regional variation in health care practice.

KEYWORDS

Demography, euthanasia, physician-assisted death, physician-assisted suicide, regional variation

INTRODUCTION

Euthanasia and physician-assisted suicide – together physician-assisted death – were legalised in the Netherlands in 2002, after having been permitted in ethical debates, law cases, and medical practice since the 1980s. A physician who provides euthanasia or assists in suicide is exempted from prosecution under several legally prescribed conditions. The physician should be convinced that the patient has made a voluntary and well-considered request and that his suffering is unbearable without a prospect of improvement. He should, additionally, inform the patient about the situation and prospects, conclude with the patient that no reasonable alternatives exist, consult at least one independent physician, and perform the euthanasia or assisted suicide with due medical care. The physician should report each case of euthanasia or assisted suicide to a Regional Review Committee, which consists of a physician, a jurist, and an ethicist and assesses whether the conditions have been met. The decision of a Regional Review Committee that the physician has complied with the conditions is final. If a Regional Review Committee decides that the physician has not complied with the conditions, the case is transferred to the Public Prosecutor, who decides about prosecution.[1]

The number of reported cases of euthanasia and physician-assisted suicide in the Netherlands has risen from 1882 in 2002 to 5306 in 2014, which is 1.3% to 3.8% of all deaths.[2] The practice of euthanasia and physician-assisted suicide and the developments in their practice in the Netherlands have been compared with those in other countries.[3-5] However, possible regional differences in the practice and the developments within the Netherlands have not been studied.

The Netherlands has been divided into five regions, in each of which a Regional Review Committee attends to the reported cases of euthanasia and physician-assisted suicide. The five Regional Review Committees jointly publish annual reports which describe and discuss the cases of euthanasia and physician-assisted suicide that have been assessed and count the numbers and characteristics of these cases per region. The annual reports thereby enable the comparison of the practice of euthanasia and physician-assisted suicide between the regions. In this study, we use these data to regionally compare the frequencies, characteristics, and trends of euthanasia and physician-assisted suicide since their legalisation in the Netherlands. We try to explain regional differences by demographic, socioeconomic, and health-related differences between the regions.

METHODS

Regions of the Regional Review Committees

The five regions of the Regional Review Committees correspond to groups of provinces. Region 1 includes the provinces Groningen, Friesland, and Drenthe. Region 2 includes Overijssel, Gelderland, Utrecht, and Flevoland. Region 3 includes only North Holland. Region 4 includes South Holland and Zeeland. Region 5 includes North Brabant and Limburg. Since 2012, the Dutch legislation on euthanasia and physician-assisted suicide also applies to the Dutch Caribbean islands Bonaire, Saba, and Saint Eustatius. Cases from these islands are assessed by the Regional Review Committee of Region 1. These islands were not included in the analyses, because only one case has been reported from there.

Euthanasia, physician-assisted suicide, non-assisted suicide, and other deaths

Data on the frequencies, characteristics, and trends of euthanasia and physician-assisted suicide in the five regions have been made publicly available in the annual reports of the Regional Review Committees.[2] From these reports we derived, for each year and each region, the numbers of reported cases of euthanasia and physician-assisted suicide, the numbers of specialties of the reporting physicians, the numbers of the locations where the reported cases were carried out, and the numbers of the disorders underlying the reported cases.

We derived the numbers of non-assisted suicide, for comparison, and the numbers of all deaths, as totals and stratified per underlying disorder, for each year and each province, from the StatLine Databank of the Central Bureau for Statistics.[6] We summed these numbers for each group of provinces that constitute one of the five regions of the Regional Review Committees.

Demographic, socioeconomic, and health-related data

We derived demographic, socioeconomic, and health-related data for each year and each province from the StatLine Databank.[6] We averaged each variable for each group of provinces that constitute one of the five regions of the Regional Review Committees weighed by the numbers of inhabitants, households, or voters in the provinces. We categorised the variables in eight groups. One group contained the percentages of women and of inhabitants aged 45 to 65, 65 to 80, and 80 years and older. A second group contained the percentage of divorced inhabitants, the percentage of widowed inhabitants, the percentage of households consisting of one person, the percentage of households with children, and the average number of inhabitants in a household. A third group contained the percentage of non-Western immigrants. A fourth group contained the percentages of inhabitants who were unemployed, who were disabled from employment, who were on social welfare, the average income standardised for differences in household composition, the number of legal bankruptcies, the percentages of inhabitants with intermediate education, and with higher education. A fifth group contained the average distances to the nearest general practitioner, hospital, library, cinema, and swimming pool. A sixth group contained the percentages of Roman Catholics, Protestants, and Muslims. A seventh group contained the percentages of votes for political parties in the national parliament, whereby Christian parties apart from the Christian Democratic Appeal, parties for elderly, and right-wing protest parties were categorised jointly and other parties that never obtained parliamentary seats were excluded. An eighth group contained the number of hospital admissions per 10,000 inhabitants per ICD-10 category of disorders.

We derived additional data from the StatLine Databank[6] for each province on self-reported health collected by the population-sample Health Questionnaire Study spanning the years from 2008 through 2011. These data include prevalences of lifestyle-related risk factors, physical and psychological complaints, medical disorders, health care use, medication use, and general health experience. We averaged each variable for each group of provinces that constitute one of the five regions of the Regional Review Committees weighed by the numbers of inhabitants in the provinces.

Analyses

To calculate the frequencies of euthanasia, physician-assisted suicide, a combination of both, and non-assisted suicide we divided these numbers by the numbers of all deaths for each region and each year. To determine the averages and trends of these numbers we used a linear regression model with the percentages logarithmically transformed as outcomes, the five regions as a categorical independent variable, the calendar years 2002 through 2014 as a continuous independent variable, and the interaction between the regions and the calendar years as an independent variable. We did not separately determine the averages and trends of cases with a combination of euthanasia and physician-assisted suicide, because they constituted less than 0.1% of all cases in each region and each year. We likewise determined the averages and trends stratified per underlying disease relative to the numbers of all deaths due to the same disorder. To determine the averages and trends of the characteristics of the cases of euthanasia and physician-assisted suicide we used the same model, only with the logarithmically transformed percentages of the characteristics relative to the numbers of all cases of euthanasia and physician-assisted suicide as outcomes.

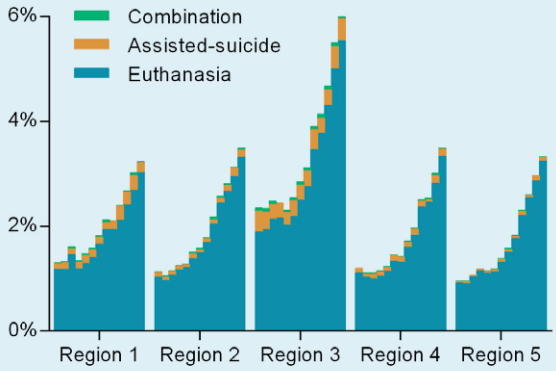
To determine whether the differences in the averages and trends of the numbers of euthanasia and physician-assisted suicide between the five regions could be explained by differences in demographic, socioeconomic, and health-related data between the regions, we separately added each aforementioned group of variables as covariates to the regression model and determined the adjusted averages and trends for each region. We imputed missing values of covariates using linear regression with respect to the calendar years, as linear trends were observed. When the analyses were repeated without these imputed values, similar results were obtained. We separately added each aforementioned variable on self-reported health as a covariate to the regression model, with the numbers of euthanasia and physician-assisted suicide, like these variables, averaged over the years from 2008 through 2011 to determine the adjusted averages for each region.

We did not calculate confidence intervals or statistically test the differences between regions, because the data were derived from the entire populations of all regions. The averages and trends had very narrow confidence intervals and differed between regions with $p < 0.001$.

RESULTS

Figure 1 shows the numbers of cases of euthanasia, physician-assisted suicide, and a combination of both reported from 2002 through 2014 in the five regions in the Netherlands relative to the numbers of all deaths in the same years and same regions. The total numbers of euthanasia and physician-assisted suicide increased in all regions.

Figure 1. *Frequencies of euthanasia and physician-assisted suicide from 2002 through 2014 in the different regions in the Netherlands*



Numbers of cases of euthanasia, physician-assisted suicide, or a combination of both are given as percentages relative to the numbers of all deaths in the same years and same regions. Each bar represents a year, ordered per region from 2002 at the left to 2014 at the right.

Table 1 quantifies the averages and trends of the numbers of euthanasia and physician-assisted suicide – with those of non-assisted suicide for comparison – from 2002 through 2014 in the five regions in the Netherlands relative to the numbers of all deaths in the same years and same regions. The averages and trends of the numbers of euthanasia and physician-assisted suicide differed up to 1.7% and 5.6%, respectively, whereas those of non-assisted suicide differed up to 0.2% and 1.0%. The average numbers of euthanasia and physician-assisted suicide were highest in Region 3.

Table 2 quantifies the averages and trends of the numbers of euthanasia and physician-assisted suicide per underlying disorder from 2002 through 2014 in the five regions in the Netherlands relative to the numbers of all deaths due to the same disorder in the same years and the same regions. As observed without stratifying per underlying disorder, the averages and trends differed between the regions, but the differences in the averages were smaller for disorders other than cancer and the differences in the trends were smaller for cancer. The averages were highest in Region 3 for all disorders.

Table 3 shows the averages and trends of the characteristics of the cases of euthanasia and physician-assisted suicide from 2002 through 2014 in the five regions in the Netherlands relative to all cases of euthanasia and physician-assisted suicide in the same years and same regions. As observed for the averages and trends in the

Table 1. *Frequencies of euthanasia, physician-assisted suicide, and non-assisted suicide from 2002 through 2014 in the different regions in the Netherlands*

	Averages					Trends				
	Region 1	Region 2	Region 3	Region 4	Region 5	Region 1	Region 2	Region 3	Region 4	Region 5
Euthanasia	1.8	1.8	3.0	1.7	1.6	+8.0	+10.8	+9.3	+10.4	+11.1
Assisted suicide	0.2	0.1	0.3	0.1	0.1	+7.2	+6.2	+1.6	+4.1	+6.9
Total of euthanasia and assisted suicide	2.0	1.9	3.4	1.8	1.7	+7.9	+10.5	+8.4	+10.0	+10.9
Non-assisted suicide	1.2	1.1	1.2	1.0	1.2	+1.6	+1.5	+1.3	+2.3	+1.4

Average numbers of euthanasia, physician-assisted suicide, and non-assisted suicide are given as percentages relative to the numbers of all deaths from 2002 through 2014. Trends are given as percentages by which these numbers have annually increased (+) or decreased (-) from 2002 through 2014.

Table 2. *Frequencies of euthanasia and physician-assisted suicide per underlying disorder from 2002 through 2014 in the different regions in the Netherlands*

	Averages					Trends				
	Region 1	Region 2	Region 3	Region 4	Region 5	Region 1	Region 2	Region 3	Region 4	Region 5
Cancer	5.3	5.1	9.1	5.0	4.5	+5.2	+7.9	+5.4	+7.1	+7.9
Cardiovascular disorder	0.2	0.2	0.4	0.1	0.2	+25.8	+25.1	+21.0	+23.4	+29.7
Neurological disorder	3.3	2.8	3.4	2.8	3.1	+9.3	+6.6	+12.1	+7.9	+9.7
Pulmonary disorder	0.5	0.6	1.3	0.5	0.7	+15.1	+17.3	+13.8	+19.0	+22.5
Psychiatric disorder	0.1	0.4	0.6	0.2	0.3	NA	NA	NA	NA	NA

Average numbers of euthanasia and physician-assisted suicide are given per underlying disorder as percentages relative to the numbers of all deaths due to the same underlying disorder from 2002 through 2014. Trends are given as percentages by which these numbers have annually increased (+) or decreased (-) from 2002 through 2014. Because data on euthanasia and physician-assisted suicide with an underlying psychiatric disorder or underlying dementia are only available from 2012 onward, estimates of trends are not available (NA) for this disorder.

numbers of euthanasia and physician-assisted suicide, the averages and trends of their characteristics differed between the regions. Euthanasia accounted for the least cases, but increased the most, while physician-assisted suicide accounted for most cases, but decreased the most in Region 3. Euthanasia and physician-assisted suicide were reported the least by general practitioners, but the most by other physicians, were carried out the least in patients' homes, but the most in hospitals, and were performed the least with cancer as the underlying disorder, but the most with a cardiovascular or pulmonary disorder in Region 3.

Figure 2 explores whether the differences in the averages (panels 2A and 2B) and the trends (panels 2C and 2D) of the numbers of euthanasia and physician-assisted suicide between the five regions could be explained by adjustments for demographic, socioeconomic, and health-related differences between these regions. The observed averages and trends (in blue) were compared with those estimated by eight models (in orange). The models adjusted for differences between the regions in, respectively, the distributions of ages and sexes, the household compositions, the numbers of non-Western immigrants, the levels of education and employment (panels 2A and 2C), the distances to service facilities, the distributions of religions, the distributions of political preferences, and health care use (panels 2B and 2D). Except for the model adjusting for differences in the levels of education and employment, which reduced the differences in the averages, none of the models could explain the differences in the numbers of euthanasia and physician-assisted suicide between the regions.

We explored whether the differences in the numbers of euthanasia and physician-assisted suicide between the five regions could be explained by differences in self-reported

Table 3. *Characteristics of euthanasia and physician-assisted suicide from 2002 through 2014 in the different regions in the Netherlands*

	Averages					Trends				
	Region 1	Region 2	Region 3	Region 4	Region 5	Region 1	Region 2	Region 3	Region 4	Region 5
Euthanasia or assisted suicide										
Euthanasia	90.1	93.7	87.8	93.1	96.0	+0.1	+0.3	+1.0	+0.4	+0.1
Assisted suicide	8.2	4.9	10.2	5.7	3.2	-0.7	-4.4	-6.8	-5.8	-4.0
Reporting physician										
General practitioner	91.8	89.6	86.2	89.1	87.4	0.0	+0.2	+0.3	+0.4	+0.4
Hospital specialist	4.8	6.0	9.0	7.0	8.0	-2.1	-12.4	-9.2	-8.6	-11.4
Nursing home physician	2.9	3.4	3.5	3.3	3.5	-1.5	+5.7	+4.5	+0.7	+7.0
Location										
Home	82.9	82.9	76.5	80.2	81.3	-0.4	-0.4	0.0	-0.1	-0.2
Hospital	4.4	5.7	9.0	6.4	7.6	-5.4	-10.2	-8.1	-9.2	-10.4
Nursing home	3.1	3.0	3.6	3.6	2.8	-1.2	+3.3	+1.2	+1.5	+2.3
Retirement home	4.6	3.6	4.6	3.6	3.0	+6.6	+9.5	+6.5	+1.9	+11.3
Hospice	3.8	5.7	5.9	5.8	6.5	NA	NA	NA	NA	NA
Underlying disorder										
Cancer	82.1	82.3	80.4	83.2	82.8	-1.7	-1.5	-1.9	-1.5	-1.8
Cardiovascular disorder	2.6	2.4	2.9	1.9	2.1	+16.0	+12.5	+10.7	+11.4	+16.8
Neurological disorder	5.1	5.0	4.0	5.2	5.4	+6.7	+1.8	+9.7	+3.5	+5.1
Pulmonary disorder	2.0	2.6	2.9	2.0	2.9	+5.9	+5.3	+3.7	+7.3	+10.7
Psychiatric disorder	0.3	0.9	0.6	0.5	0.7	NA	NA	NA	NA	NA
Dementia	1.2	1.5	1.4	1.5	1.6	NA	NA	NA	NA	NA
Combination of disorders	5.3	3.3	5.1	4.8	3.2	-4.9	+4.5	+8.9	+1.9	+4.8

Numbers of cases are given by characteristics as percentages relative to the numbers of all cases of euthanasia and physician-assisted suicide from 2002 through 2014. Trends are given as percentages by which these numbers have annually increased (+) or decreased (-) from 2002 through 2014. Because data on euthanasia and physician-assisted suicide located in hospices are only available for 2009 and from 2012 onward, estimates of trends are not available (NA) for this location. Because data on euthanasia and physician-assisted suicide with an underlying psychiatric disorder or underlying dementia are only available from 2012 onward, estimates of trends are not available (NA) for these disorders.

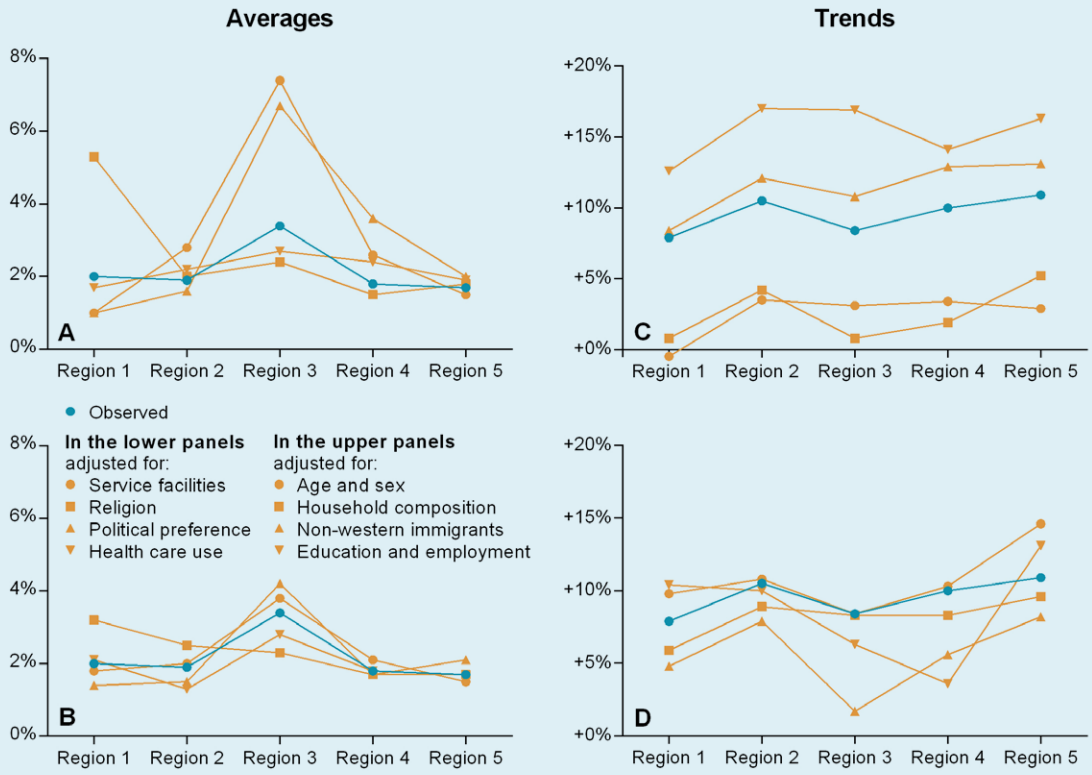
health between these regions. The numbers of euthanasia and physician-assisted suicide were not associated with any of the variables (data not shown).

DISCUSSION

This study aimed to compare the frequencies, characteristics, and trends of euthanasia and physician-assisted suicide between five regions in the Netherlands since their legalisation. It demonstrated that they differed, whereas the averages and trends of non-assisted suicide were similar. It tried to explain these regional differences by demographic, socioeconomic, and health-related differences between the regions, but failed to do so.

In the comparison of the regions, Region 3 stood out. This region corresponds to the province of North Holland and includes the national capital Amsterdam. Here, the

Figure 2. *Frequencies of euthanasia and physician-assisted suicide from 2002 through 2014 in the different regions in the Netherlands adjusted for demographic, socioeconomic, and health-related differences between the regions*



Average numbers of the totals of euthanasia and physician-assisted suicide are given as percentages relative to the numbers of all deaths from 2002 through 2014 (A and B). Trends are given as percentages by which these numbers have annually increased (+) or decreased (-) from 2002 through 2014 (C and D). The observed averages and trends, identical to those in *table 1*, are shown in blue. The averages and trends adjusted for demographic, socioeconomic, and health-related differences between the regions are given in orange.

average number of cases of euthanasia and physician-assisted suicide was highest, also when stratified per underlying disorder. Moreover, when compared with the other regions, cases most often concerned euthanasia and least often physician-assisted suicide, were reported least often by general practitioners but most often by other physicians, were carried out least often at patients' homes but most often in hospitals, and were least often with cancer but most often with a cardiovascular or pulmonary disorder as the underlying disorder. The trends in these frequencies and characteristics occasionally revealed the highest increase when the average was lowest in Region 3 and vice versa.

The regional differences in the averages and trends of euthanasia and physician-assisted suicide could not be explained by adjustment for demographic, socioeconomic, and health-related differences between the regions. Region 3 continued to stand out in all models, except for two models, which adjusted for household composition and religion, but which did not reduce the regional differences either. Only the model adjusting for levels of education and employment slightly reduced the regional differences in the averages. Furthermore, region-specific self-reported health was not associated with the numbers of euthanasia and physician-assisted suicide. Meanwhile, regional differences in the averages and trends of non-assisted suicide were almost absent.

Regional differences in the practice of euthanasia and physician-assisted suicide have never been studied within the Netherlands. Neither were regional differences reported in the recent elaborate evaluation of their legislation and practice, commissioned by the Dutch government.[7] However, regional differences in their practice have been studied in Belgium, where they were legalised a year after the Dutch legislation under similar conditions.[8] The large majority of cases reported to the Belgian Federal Review Committee originate from the Dutch-speaking regions. Physicians in these regions more often receive, grant, and report requests for euthanasia or physician-assisted suicide when compared with the French-speaking regions. The support of the legalisation is greater, the readiness to participate in its practice is more

common, and the knowledge about the legal conditions is more accurate among physicians, while the support of the legalisation is slightly greater among the general population in these regions when compared with the French-speaking regions.[9,10] Whether the characteristics and trends of euthanasia and physician-assisted suicide also differ between these regions has not been studied.

The practice of euthanasia and physician-assisted suicide has been compared between countries, mainly in Europe. Regardless of legalisation, frequencies of euthanasia and physician-assisted suicide vary between less than 1% to more than 3% of all deaths, while characteristics of the patients with whom such choices are made do not differ substantially.[3,5] The support for euthanasia and physician-assisted suicide by the general population varies widely between countries. Support is mostly dependent on life stance and religion and, additionally, on a younger age, a higher socioeconomic status, and a higher level of education – but these variables do not fully explain the differences in support.[11,12] The numbers of physicians supporting or opposing euthanasia and physician-assisted suicide vary widely too,[3,4,13,14] with 36% to 84% never willing to participate.[4] Those willing to participate are more often young, male, working in a hospital, experienced in palliative care, and influenced by a life stance or religion – but again these variables do not fully explain the differences in their willingness.[4,13,14] Likewise within the Netherlands, considerable variation exists in the perceptions and arguments based on which physicians determine whether a patient meets the legal conditions for euthanasia or assisted suicide, including their assessment of the voluntariness of the request and the unbearableness of the suffering. This variation may be due to differences in their knowledge and interpretation of these legal conditions and of the practice of euthanasia and assisted suicide.[15]

The results of this study suggest that the variation in the practice of euthanasia and physician-assisted suicide between regions in the Netherlands have other than demographic, socioeconomic, or health-related explanations. The previous comparisons between other regions suggest that this variation may be a result of regional differences in the attitudes and knowledge of physicians and patients with regard to euthanasia and physician-assisted suicide, which leads to regional differences in support by the general population, demand by patients, and willingness of physicians. As a consequence, euthanasia and physician-assisted suicide may be more or less readily available for patients and more or less expected of physicians across the country. This result becomes problematic insofar a patient's request for euthanasia or assisted suicide would be granted in some regions, but rejected in other regions, insofar a physician's refusal of a request would be accepted in some regions, but assailed in other regions, or insofar a patient's request and a physician's cooperation would be encouraged by others in some regions, but not in other regions. In other words, this result becomes problematic insofar it would foster inequality, arbitrariness, and legal uncertainty.

As another possible explanation of the regional differences, the reporting rates of cases of euthanasia and physician-assisted suicide may differ between the regions. This is known to be true in Belgium,[9,10] but has never been studied in the Netherlands. Here the national reporting rates have been constant and quite high since the legalisation, being 80% in 2005 and 77% in 2010. The most common reason not to report a case is the physician's perception that it does not concern euthanasia or assisted suicide.[16]

As a limitation, this study uses data from the Regional Review Committees that are aggregated per region and per year to compare the frequencies, characteristics, and trends of euthanasia and physician-assisted suicide. To understand in more detail and with more certainty why their frequencies, characteristics, and trends differ between regions in the Netherlands, smaller regions in the country should be compared. The five regions in this study consist of predominantly progressive urban agglomerations as well as more traditional rural communities. The variation within each region may be even greater than between the regions. Ideally, individual data on the characteristics of those requesting or receiving euthanasia or physician-assisted suicide would be used to compare regions of the country. Future studies that use data from other sources to compare smaller regions than the five regions of the Regional Review Committees are required to allow for more refined conclusions.

Regional differences in health care practice have received much public attention in the Netherlands. The surgery rates for carpal tunnel syndrome, cataract, cholecystitis, cholelithiasis, hip arthritis, inguinal hernia, and spinal disc hernia are under scrutiny since they have been revealed to vary widely between regions.[17] The same holds for cancer treatments[18] and perinatal and maternal mortality rates.[19,20] Demographic, socioeconomic, and health-related differences between the regions cannot fully explain these differences in health care practice. Rather, they are a consequence of regional differences in the organisation and availability of health care. Health care professionals, insurers, and policymakers regard the regional differences as infringements on the quality of care and strive to minimise them.

If we deem it important to understand the regional differences in health care practice and to minimise these differences insofar they cannot be justified by demographic, socioeconomic, or health-related differences

between the regions, then should we not likewise treat the regional differences in the practice of euthanasia and physician-assisted suicide? After the first exploration in this study, further research may specify in more detail how and why the practice of euthanasia and physician-assisted suicide differs between regions in the Netherlands and to what extent the regional differences reflect a deficiency in the quality of end-of-life care.

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DISCLOSURES

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ORIGINAL ARTICLE

Introduction of day care thyroid surgery in a Dutch non-academic hospital

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ABSTRACT

Objective: Hemithyroidectomy is the most common endocrine surgical procedure and is performed with low complication rates. Multiple international reports indicate that thyroid surgery in the day care setting is feasible and safe. Despite these results, day care thyroid surgery has not yet been implemented in the Netherlands. The objective of this study is to assess the safety of thyroid surgery in our institution and, when deemed safe, implement day care thyroid surgery.

Methods: All patients who underwent hemithyroidectomy in our institution between January 2010 and December 2014 were included in the retrospective analysis. Hypothetical candidates for day care surgery were identified. All patients undergoing thyroid surgery in 2015 were included in a prospective cohort. Data regarding baseline characteristics, surgical procedures, complications and adherence to the day care schedule are presented.

Results: A total of 210 patients were included in the retrospective cohort; 149 patients complied with the day care criteria. No complications occurred that would prevent day care surgery, or make it unsafe. Day care thyroid surgery was implemented from January 2015. In one year 43 patients underwent hemithyroidectomy. Thirty-one patients were eligible for day care surgery of which 18 patients were treated in day care. Failure of the day care regimen was due to the patient's own choice (n = 5), large retrosternal goitre (n = 2) or failure of logistics (n = 6). Besides transient hoarseness, no complications occurred in this group.

Conclusion: Based on a retrospective safety analysis we successfully introduced day care thyroid surgery in our clinic. Hemithyroidectomy can safely be conducted in day care setting. However, patient selection is of vital importance to minimise the risk of complications.

KEYWORDS

Day care surgery, hemithyroidectomy, patient safety, surgical outcomes

INTRODUCTION

Hemithyroidectomy is the most common endocrine surgical procedure performed in daily practice and indicated mainly due to mechanical and/or cosmetic complaints of a multinodular goitre or a solitary thyroid nodule. Furthermore, it is performed for diagnostic purposes in case of indeterminate cytology. Despite the increased rate of day care surgical procedures, thyroid surgery in the Netherlands is currently solely performed with overnight stays. It is assumed that the potential risk of life-threatening respiratory problems caused by postoperative bleeding, laryngeal nerve injuries or hypocalcaemia warranting (intravenous) supplementation are reasons for which thyroid surgery is not performed in the day care setting. Recently, Segel et al.[1] published their results regarding over 1000 thyroidectomies in the outpatient setting. The most feared complication, acute postoperative haemorrhage with a potentially life-threatening airway obstruction, did not occur. In general, the incidence of postoperative bleeding varies between 0.1-1.1%, and seldom causes acute airway problems or need for reinterventions.[2] In addition, laryngeal nerve injury after hemithyroidectomy is uncommon and the literature reports incidence rates of up to 3.7% of patients, with 0.4% permanent injuries to the laryngeal nerve.[3-7] Temporary hypocalcaemia occurred in about 3% of the outpatient patients treated in Segel's study.[1] Wound infection occurs in less than 1% of the patients, but

is a late complication and poses no threat in the day care setting.[4,6]

Worldwide, the number of outpatient thyroidectomies has increased by 39% over the last ten years.[8] Technological advancements in anaesthesia care and the widespread introduction of minimally invasive surgical techniques have fuelled this trend. The first report regarding thyroid surgery in the day care setting by Steckler dates back to 1986.[9] Since then, multiple studies have shown that day care thyroid surgery is safe and feasible with regard to hemithyroidectomy and even total or completion thyroidectomy.[1,2,4-7,10-13] The American Thyroid Association published a statement regarding outpatient thyroid surgery describing important safety criteria for selecting eligible patients.[14]

Given all the encouraging reports it is peculiar why day care thyroid surgery is not yet implemented in the Netherlands. One can only assume that the risk, albeit utterly small, of losing a patient due to respiratory distress caused by massive bleeding after discharge is the main reason. Therefore our first aim was to assess the safety of thyroid surgery in our institution by means of a retrospective risk analysis of all patients who underwent hemithyroidectomy in a five-year period from 2010 to 2014. Then we present the initial results of implementing day care thyroid surgery in our daily practice, strictly adhering to the international guidelines.[14]

METHODS

All patients were operated in the 'Reinier de Graaf Gasthuis' in Delft, a non-academic teaching hospital in the Netherlands, by one of two dedicated endocrine surgeons (P.C.S and F.M.G.). The retrospective cohort (part A) consists of all consecutive patients who underwent primary hemithyroidectomy between January 2010 and December 2014. These patients were identified by means of surgical codes from the hospital software system. All electronic patient charts were reviewed and baseline characteristics, medical history, indication for surgery, postoperative complications and hypothetical eligibility for day care surgery were noted. Complications were retrieved by manually checking the charts in conjunction with checking our prospective database where all operations and complications are prospectively recorded. The data were analysed and an overall judgement was made regarding the safety of day care thyroid surgery in our hospital. All patients in the retrospective cohort who were eligible for day care surgery[14] but received necessary in-hospital interventions from six hours to 24 hours postoperatively are considered 'day care safety failures'. As no 'day care safety failures' occurred, we proceeded to part B of the study: implementation of day care surgery.

All patients scheduled for their first hemithyroidectomy in 2015 were included in the prospective cohort (part B). Baseline characteristics, medical history, indication for surgery and postoperative complications were prospectively collected. All patients were assessed for eligibility for day care surgery according to the criteria published by the American Thyroid Association,[14] as listed in *table 1*. Patients eligible for day care surgery and willing to participate were discharged the same day at least six hours after skin closure with the permission of the surgeon and consent from the patient. All patients received information about the surgical procedure, a letter addressed to the general practitioner and standardised discharge instructions when discharged. These instructions provided information regarding pain and pain medication, wound dressings and signs of infection. Patients were instructed to contact the hospital in case of, but not limited to, voice changes, stridor, swelling of the wound and/or problems swallowing. All patients were contacted by telephone one day after discharge. Two weeks after surgery all patients were seen at the outpatient clinic for their first postoperative check-up. Hereafter, patients were referred back to their treating endocrinologist.

Statistical analysis was done using IBM SPSS software (version 21). Descriptive analysis is performed, where categorical data are expressed as frequency with percentage, and nominal data are expressed as mean with standard deviation. Group differences were analysed with the Chi-square test for categorical data, and the unpaired t-test for nominal data. Significant differences are defined as $p < 0.05$.

RESULTS

Retrospective cohort

A total of 210 patients were included in our retrospective risk analysis cohort, of which 149 patients (71.0%) were eligible for day care surgery. Baseline characteristics and complication rates are summarised in *table 2*. Patients eligible for day care surgery were significantly younger

Table 1a. *Eligibility criteria for outpatient thyroidectomy*[14]

No major comorbidities or ASA class 4
Provision and understanding of preoperative education
Team approach to education and clinical care
Primary caregiver willing and available
Social setting conductive to safe postoperative management
Proximity to skilled facility

Table 1b. *Relative contraindications to outpatient thyroidectomy*[14]

Clinical	Social	Procedure
Uncompensated cardiac or respiratory disease	Excessive distance from skilled facility	Massive goitre
Dialysis for renal failure	Living alone with no person to accompany	Extensive substernal goitre
Anticoagulant or antiplatelet therapy	Lack of transportation	Locally advanced cancer
Seizure disorder	Patient preference	Challenging haemostasis
Anxiety disorder	Communication barriers	Difficult thyroidectomy with Hashimoto's thyroiditis or Graves' disease
Obstructive sleep apnoea		
Hearing loss		
Visual impairment		
Mental impairment		
Pregnancy		

Table 2. *Baseline characteristics of retrospective cohort*

	Total	Meet day care criteria	Do not meet criteria	P
N	210	149 (71.0%)	61 (29.0%)	
Age in years (mean + SD)	51 (13.77)	49 (12.72)	55 (15.06)	0.001
Female sex (percentage)	179 (85%)	128 (86%)	51 (84%)	0.335
ASA score	ASA 1-89 (42%) ASA 2-107 (51%) ASA 3-12 (6%) Unavailable – 2 (1%)	ASA 1-73 (49%) ASA 2-74 (50%) ASA 3-1 (1%) Unavailable – 1 (1%)	ASA 1-16 (26%) ASA 2-33 (54%) ASA 3-11 (18%) Unavailable – 1 (2%)	0.000
Indication for surgery	Mechanical complaints: 151 (71.9%) Suspected malignancy: 36 (17.1%) Other reasons: 23 (11.0%)	Mechanical complaints: 104 (70%) Suspected malignancy: 28 (19%) Other reasons: 17 (11%)	Mechanical complaints: 47 (77%) Suspected malignancy: 8 (13%) Other reasons: 6 (10%)	0.186
Type of operation	LHT-105 (50%) RHT-105 (50%)	LHT-70 (47%) RHT-79 (53%)	LHT-35 (57%) RHT-26 (43%)	0.086
Total complications	9 (4.4%)	3 (2.0%)	6 (9.8%)	0.008
Transient hoarseness or vocal changes	5	1 (0.7%)	4 (6.6%)	
Anaphylaxis	1 (0.5%)	1 (0.7%)	0 (0%)	
Spontaneous tachycardia	1 (0.5%)	1 (0.7%)	0 (0%)	
Rebleeding	1 (0.5%)	0 (0%)	1 (1.6%)	
Wound infection	1 (0.5%)	0 (0%)	1 (1.6%)	

Values displayed as N + percentage unless stated otherwise. LHT = left hemithyroidectomy; RHT = right hemithyroidectomy.

Table 3. *Baseline characteristics of day care cohort*

	Day care setting	Clinical setting	P
N	18	25	
Age in years (median + range)	50 (14,86)	61 (16,37)	0.036
Female sex (percentage)	14 (78%)	21 (84%)	0.303
ASA score	ASA 1-6 (33%) ASA 2-10 (56%) ASA 3-2 (11%)	ASA 1-10 (40%) ASA 2-13 (52%) ASA 3-2 (18%)	0.440
Indication for surgery	Mechanical complaints: 16 (89%) Suspected malignancy: 2 (11%) Other reasons: 0	Mechanical complaints: 14 (56%) Suspected malignancy: 8 (32%) Other reasons: 3 (12%)	0.029
Type of operation	LHT-7 (38%) RHT-11 (61%)	LHT-10 (40) RHT-15 (60%)	0.471
Total complication	1 (5.6%)	2 (8.0%)	0.378
Transient hoarseness or vocal changes	1 (5.6%)	2 (8.0%)	
Rebleed	0 (0.0%)	0 (0.0%)	
Wound infection	0 (0.0%)	0 (0.0%)	
Meet day care criteria	n.a.	13 (52%)	

Values displayed as N + percentage unless stated otherwise. LHT = left hemithyroidectomy; RHT = right hemithyroidectomy.

(48 vs 55 years, p = 0.001) and had lower American Society of Anesthesiologists (ASA) classifications. The overall complication rate is 4.4% and in the hypothetical day care group this was 2.0%.

Five patients experienced transient hoarseness or vocal changes, one developed an anaphylactic reaction of unknown aetiology, and one patient experienced recurrence of a spontaneous tachycardia for which she required medical treatment. In the group not eligible for day care surgery, one patient required a re-operation due to a wound infection (0.5%) and one postoperative haematoma occurred (0.5%), which was managed conservatively. There were no complications in the 'eligible day care group' comprising patients safety in the hypothetical outpatient setting.

Since this retrospective analysis showed low complication rates, we concluded that hemithyroidectomy can be performed safely in a day care setting in our institution, and proceeded to implement this new strategy (part B).

Prospective cohort

In 2015 a total of 43 patients underwent primary hemithyroidectomy and were included in the prospective cohort. A total of 31 (72%) patients met the international guidelines for day care thyroid surgery published by the American Thyroid Association, of which 58% (n = 18) were eventually treated by means of day care surgery. Twenty-five (58%) patients stayed overnight after surgery. A flowchart of patients undergoing hemithyroidectomy is illustrated in *figure 1*. Baseline characteristics and complication rates for the prospective cohort are summarised in *table 3*. The day care group was younger than the clinical group (median 50 and 61 years, respectively). Indication for surgery in the day care group was mechanical complaints in 89% and suspected malignancy in 11%; in the clinical group the indication was mechanical complaints in 56% and suspected malignancy in 32%.

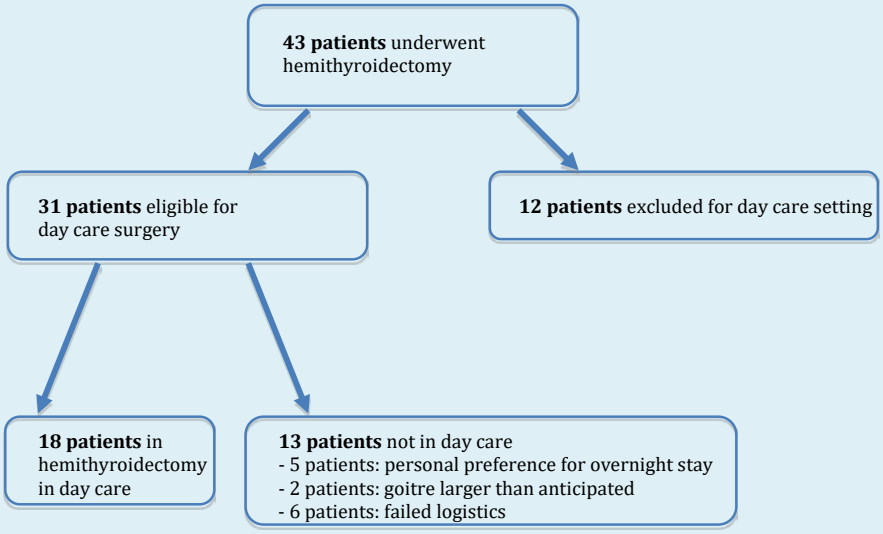
Two minor complications (transient vocal changes, n = 2) occurred in the clinical group and there was one minor complication (transient vocal change) in the day care group. There were no emergency department visits or readmissions following surgery. No wound infections, haematomas or laryngeal nerve damage occurred.

Thirteen patients (30%) were eligible for day care surgery, but were not treated as such. Five patients (12%) chose to stay overnight, two patients had a retrosternal goitre which was larger than anticipated, and in the remaining six (14%) patients our logistics failed for example as these patients were scheduled for surgery late in the afternoon.

DISCUSSION

The retrospective analysis shows that day care surgery could be safely implemented in our institution. Thereafter, day care thyroid surgery was implemented and 58% of the eligible patients were treated as such. This is the

Figure 1. *Flowchart*



first cohort in the Netherlands where thyroid surgery is performed in the day care setting. Patient safety is of paramount importance when installing a new regimen. Only one patient in the day care group experienced a complication, namely temporary hoarseness. No postoperative haematomas necessitating urgent interventions occurred. However, even though day care thyroid surgery was already reported in 1986,[9] it remains a delicate topic as airway compromise due to haematoma formation is a feared complication. This complication did not occur in either our retrospective or our prospective cohort. We do have to acknowledge the fact that our low number of patients is prone to be biased with respect to complication rates. In the literature, Snyder et al.[7] published the largest series of outpatient thyroidectomies, with over 1000 procedures in their cohort. Postoperative haematoma requiring reoperation was present in only one patient undergoing hemithyroidectomy.

A total of 31 patients met the international guidelines for day care thyroid surgery; however, only 18 were treated in day care surgery. In six patients our own logistics failed, so this is a major item to improve with this new strategy. Furthermore, it is important to interview patients to determine factors for which they chose to stay overnight, after which preoperative information can be adapted to address these factors.

Patients expressed their satisfaction when contacted by telephone the next day; however, no objective measurement of patient satisfaction was performed. Measurement and documentation of patient satisfaction is important to improve patient selection and improve preoperative information.

Despite the logistical hurdles and the low number of patients in this study, we advocate the introduction of day care thyroid surgery in the Netherlands.

However, although complications rates are supposedly very low, it is important to stay vigilant and carefully select patients suitable for day care surgery adhering to international guidelines.

CONCLUSION

Hemithyroidectomy performed in day care is feasible and safe with low complication rates provided that adequate patient selection is performed.

DISCLOSURES

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

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ORIGINAL ARTICLE

Oriental cholangiohepatitis (recurrent pyogenic cholangitis): a case series from the Netherlands and brief review of the literature

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ABSTRACT

Oriental cholangiohepatitis is a condition occurring in the Asian population, characterised by recurrent bacterial cholangitis and presence of calculi within the intrahepatic bile ducts, biliary strictures and an increased risk for cholangiocarcinoma. It is an uncommon disease in the West that may not always be considered. The therapeutic approach is multidisciplinary and highly individual, and includes antibiotic therapy, endoscopic and percutaneous biliary drainage with stone removal and dilation of strictures, and in selected cases surgical resection of affected liver segments.

We report our experience with five relatively young adult patients largely originating from China, who presented with pyogenic cholangitis and were considered to suffer from oriental cholangiohepatitis.

To our knowledge this is the first report of this condition in the Netherlands. Physicians treating patients with pyogenic cholangitis should be aware of this disease and consider the diagnosis in all Asian immigrants with biliary tract disease.

KEYWORDS

Oriental cholangiohepatitis, Hong Kong disease, pyogenic cholangitis

What was known about this topic?

Oriental cholangiohepatitis or recurrent pyogenic cholangitis, first described in 1930, is a clinical syndrome characterised by recurrent bacterial cholangitis with primary intrahepatic hepatolithiasis, biliary strictures and an increased risk for cholangiocarcinoma. The disease is endemic in East Asia, however uncommon in the West where this diagnosis may not always be considered. The therapeutic approach is multidisciplinary and highly individual, and includes antibiotic therapy, endoscopic and percutaneous biliary drainage with stone removal and dilation of strictures, and in selected cases surgical resection of affected liver segments.

What does this report add?

This case series should raise awareness about oriental cholangiohepatitis (or recurrent pyogenic cholangitis) as a possible cause of cholangitis and intrahepatic stone disease also in the West. Oriental cholangiohepatitis should be considered in all Asian immigrants presenting with pyogenic cholangitis associated with hepatolithiasis and biliary stricturing.

INTRODUCTION

Oriental cholangiohepatitis is a condition first described by Digby in 1930, who observed eight Chinese patients with recurrent bacterial cholangitis associated with hepatolithiasis.[1] Since then various other names have been used such as 'Hong Kong disease', 'primary hepatolithiasis', 'biliary obstruction syndrome of the Chinese' and 'recurrent pyogenic cholangitis'.[2,3] The condition is characterised by repeated episodes of cholangitis occurring in Asian populations associated with the formation of intrahepatic bile duct stones in the presence of biliary strictures. Oriental cholangiohepatitis is prevalent in East Asia and is more common in rural areas.[4] However, it is an uncommon condition in the Western world that may not always be considered in appropriate cases.[4] We here report our experience with five patients from a single Dutch centre.

CASE DESCRIPTIONS

Case 1

A 31-year-old male was referred for evaluation of recurrent episodes of cholangitis. Born in Bangladesh, he had moved to the Netherlands six years previously as a political refugee. Reportedly at the age of 10, analysis for abdominal pain revealed no abnormalities. His further medical history was unremarkable. The first episode of cholangitis occurred at age 30. Magnetic resonance cholangiopancreatography (MRCP) showed multifocal segmental strictures and biliary dilatation with multiple concrements in both intrahepatic and extrahepatic bile ducts. Subsequently endoscopic retrograde cholangiopancreatography (ERCP) was performed with biliary sphincterotomy and removal of multiple stones (*figure 1*). Since this first episode multiple hospital admissions occurred because of recurrence of bacterial cholangitis associated with hepatolithiasis. Colonoscopy showed no abnormalities. Given these epidemiological, clinical, and imaging findings a diagnosis of oriental cholangiohepatitis was made. We started ursodeoxycholic acid together with extensive endoscopic and percutaneous treatment of the biliary strictures and removal of the bile duct stones. In the follow-up period of 13 years the patient still has recurrences of bacterial cholangitis and hepatolithiasis about once a year.

Case 2

A 40-year-old female was admitted to our hospital with bacterial cholangitis. She was born in China and moved to the Netherlands at age 30. During two previous episodes of cholangitis she was treated with antibiotics and underwent endoscopic extraction of biliary stones. MRCP showed large impacted intrahepatic concrements together with biliary mural irregularities. A dark stone was removed endoscopically using mechanical lithotripsy. The patient did not attend further follow-up appointments.

Case 3

A 28-year-old male was referred for treatment of large intrahepatic stones. He was from Chinese origin and migrated to the Netherlands at age 17. He presented in another hospital with acute onset of abdominal pain. MRCP showed three large stones in a grossly dilated left hepatic duct with multifocal strictures and peripheral narrowing ('pruned tree'). The right hepatic duct showed an irregular aspect with subtle strictures. An initial attempt at endoscopic stone removal failed and

Figure 1. *Cholangiogram during ERCP showing multiple intrahepatic concrements of the right hepatic duct and dilatation of the left and right hepatic duct*

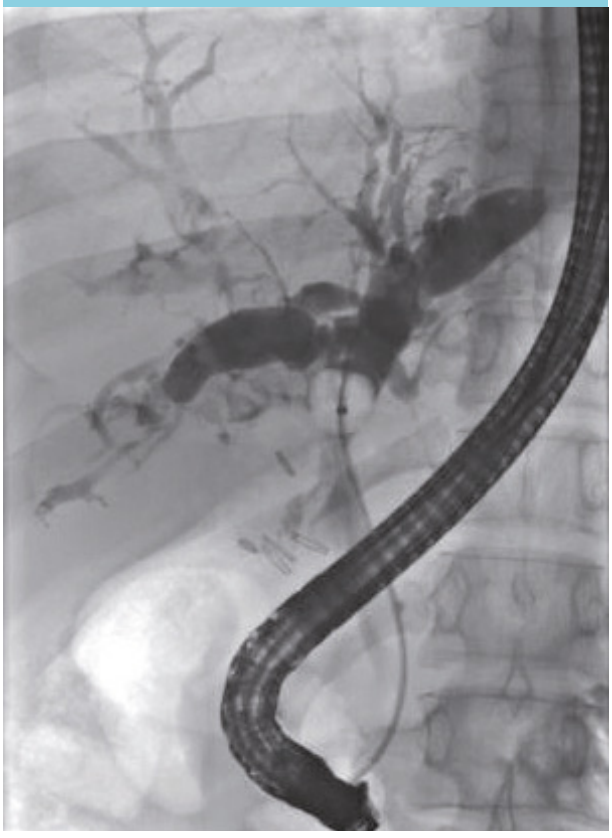
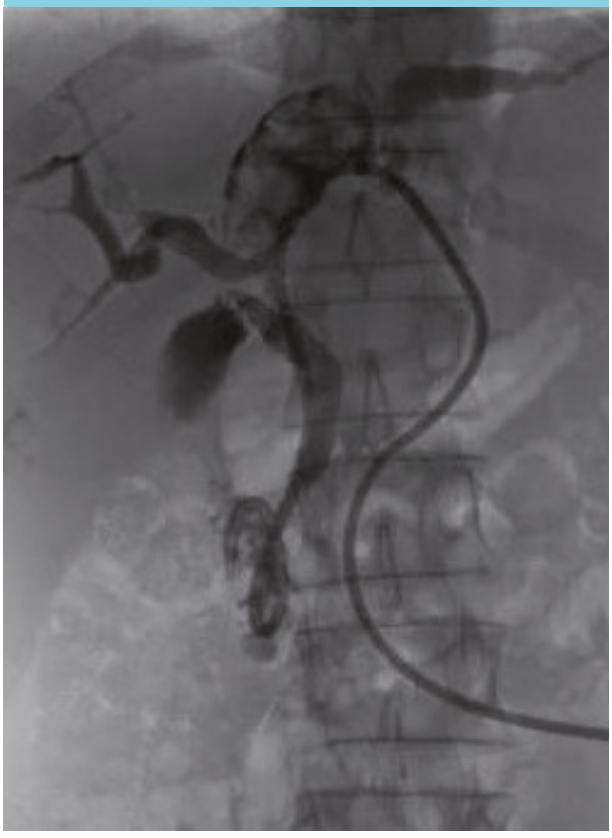


Figure 2. *Percutaneous transhepatic cholangiography showing large stones with dilatation of left bile duct. The right hepatic duct shows an irregular and angulated aspect*



a percutaneous transhepatic biliary drain was inserted in the left system (*figure 2*). Extracorporeal shock wave lithotripsy (ESWL) caused the stones to fragment. During subsequent ERCPs multiple dark stones and fragments could be removed. No further follow-up information is available.

Case 4

A 30-year-old female presented with recurrent episodes of severe upper abdominal pain without fever or cholangitis. The patient migrated from China to the Netherlands at age 20. MRCP demonstrated atrophy of the left liver lobe in combination with bile duct dilation and multiple intraductal calculi in segments II and III. The biliary tree showed no other obvious abnormalities (*figure 3*). After ERCP to remove the stones was unsuccessful, left hemihepatectomy with cholecystectomy was performed. Pathological examination showed cystic dilation of the bile ducts with stone formation and chronic inflammation. Over a one-year follow-up period the patient remained asymptomatic.

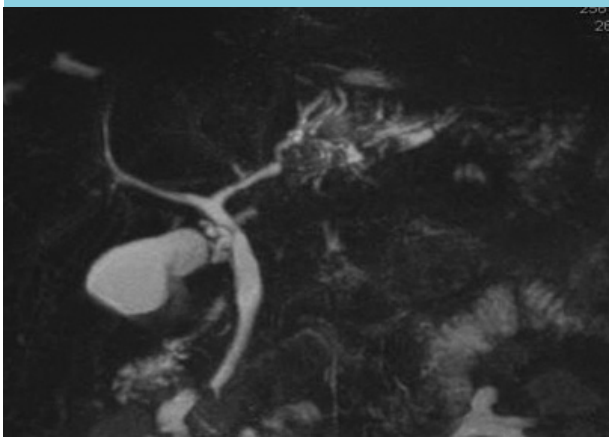
Case 5

A 31-year-old Chinese female was admitted with mild abdominal pain and fever. Her past medical history was unremarkable. MRCP showed segmental dilation of the intrahepatic bile ducts in segment V and VI with mural irregularity. Furthermore multiple small intrahepatic calculi were visualised. She was successfully treated with antibiotics. Because of this first mild presentation with a favourable response to antibiotic treatment a conservative approach was chosen. During a four-year follow-up period, the problems did not reoccur.

DISCUSSION

We report five relatively young adult patients largely originating from China, who presented with pyogenic cholangitis and were considered to suffer from oriental cholangiohepatitis. This is the first report of this disease in the Netherlands. The diagnosis was based on the combination of clinical and radiological findings. Primary sclerosing cholangitis was another important diagnostic consideration; however, the radiological findings were regarded to be atypical for that condition but fully compatible with oriental cholangiohepatitis. In addition, no clinical or endoscopic evidence was found for inflammatory disease, a condition seen in the large majority of patients with primary sclerosing cholangitis. Also, no clinical or radiological evidence was found for other disorders characterised by cholangitis, biliary structures and stone formation (*table 1*).

Figure 3. *MRCP showing bile duct dilatation of segments II and III with multiple intraductal calculi*



Oriental cholangiohepatitis is characterised by recurrent bacterial cholangitis and the presence of calculi within the intrahepatic bile ducts, biliary strictures and an increased risk for cholangiocarcinoma.[5] The incidence of the disease among men and women is comparable. The stones form within the intrahepatic biliary system and are mainly composed of calcium bilirubinate or brown pigment, in contrast to the cholesterol stones more commonly seen in patients with other gallstone-related diseases, which is the vast majority of patients in the West.

Oriental cholangiohepatitis is endemic in East Asia. In the West the disease is occasionally encountered, virtually restricted to Asian immigrants. Sporadic case reports describe the disease in Caucasian patients.[6,7] There is a possibility, however, that in these non-Asian patients the diagnosis was inaccurate and was mistaken for another disorder with intrahepatic stone formation and/or strictures. Intrahepatic stone formation in Caucasian patients is mostly due to primary sclerosing cholangitis, Caroli disease, low phospholipid-associated cholelithiasis, choledochal cyst and portal biliopathy. Possible causes of biliary tract obstruction and hepatolithiasis are shown in *table 1*.

There is evidence that the incidence of the disease is declining.[8] The improved economic situation and living standards associated with westernisation of diet are thought to be involved in the changing epidemiology in Asian countries.[8] The aetiology remains unknown. One hypothesis is a biliary tract infection with the parasites *Clonorchis sinensis* or *Ascaris lumbricoides* as an initiating factor. Infection with these parasites is endemic in the same region where oriental cholangiohepatitis is most prevalent and has been linked to dietary intake of pickled vegetables and uncooked and contaminated fish. *Clonorchis* infestation can cause bile stagnation and inflammatory changes of small bile ducts, resulting in duct obstruction.

Table 1. *Differential diagnosis of biliary tract obstruction and intrahepatic stone disease*

Stone-related disease	Pigmented stone-associated disease: Chronic haemolysis (malaria, sickle cell and other haemoglobinopathies) Oriental cholangiohepatitis/recurrent pyogenic cholangitis
	Non-pigmented stone-associated disease: Gallbladder related/common-bile duct stones Low phospholipid-associated cholelithiasis
	Salmonella-associated disease
Ductal disease	Primary sclerosing cholangitis
	Caroli disease
	Choledochal cyst
	Bile duct ischaemia
	Strictures post-surgery
	Cystic fibrosis
	IgG 4-related cholangitis
	Biliary papillomatosis
	AIDS associated cholangitis
	Cholangiocarcinoma
	Granulomatous disease (tuberculosis)
External compression	Portal biliopathy
	Hepatocellular carcinoma

However, the prevalence of *Clonorchis* infection is not increased in affected individuals compared with the general population.[9] Evidence against a causative role includes a high incidence of oriental cholangiohepatitis in Taiwan and Japan despite a low incidence of *Clonorchis* infestation. Smouldering bacterial infection, possibly associated with portal bacteraemia eventually leading to intraductal inflammation and hepatic stone formation, has also been suggested as a potential cause. This hypothesis, however, does not explain the specific epidemiological characteristics of the disease.[10]

Patients often present with recurrent pyogenic cholangitis. Physical examination may reveal hepatomegaly or a palpable gallbladder in a minority of cases. Laboratory findings are non-specific and may show increased inflammatory markers such as CRP and liver biochemistry abnormalities indicating biliary obstruction. The clinical course is usually characterised by recurrent episodes of bacterial cholangitis and abdominal pain. Pancreatitis can occur, possibly due to transpapillary stone passage. Potential complications are segmental liver atrophy, secondary biliary cirrhosis and cholangiocarcinoma. An incidence of cholangiocarcinoma of 3-9% has been reported.[11] The actual risk of this tumour, however, has not been firmly defined.

Diagnosis is established by characteristic radiological findings in patients with a clinically compatible socio-epidemiological background. Nearly all patients have intrahepatic stones of varying sizes, with predominant involvement of the left hepatic duct.[5] Biliary dilatation is present in all cases, especially of the central and left hepatic ducts. Abrupt tapering of the peripheral bile ducts with mural irregularity is frequently encountered (arrowhead sign). There may be paucity of (small) intrahepatic bile ducts resulting in a 'pruned tree' appearance. Up to 70% of the patients also have gallbladder stones.[5]

Computed tomography and MRCP are the main imaging procedures to provide accurate information on site, extent and severity of the disease but also to exclude other causes of intrahepatic stone disease and biliary tract obstruction. When cholangiographic findings are atypical or when there is any evidence of inflammatory bowel disease, colonoscopy should be considered.

In patients with suspected or established disease it is doubtful whether screening for parasitic infections is indicated considering the low likelihood of a causal relationship and absence of controlled trials to demonstrate efficacy of antiparasitic treatment on clinical outcome.

Oriental cholangiohepatitis seems to be associated with an increased risk of cholangiocarcinoma; however, at present established diagnostic markers or imaging modalities for early detection of cholangiocarcinoma are lacking. As there is no evidence-based guideline, the surveillance policy should be left to the discretion of individual centres.

Initial management should be directed at treatment of cholangitis with antibiotics and biliary drainage. A multidisciplinary approach is mandatory for the correct diagnosis and choice of proper management. In patients with dilated intrahepatic and extrahepatic bile ducts with intrahepatic stones, ERCP is usually the preferred interventional procedure. Percutaneous transhepatic cholangiography and drainage is an important alternative or additional therapeutic procedure. In specific cases, particularly with localised or uni-lateral involvement, segmental resection or hemi-hepatectomy with or without hepaticojejunostomy may be indicated and even be the therapy of choice. Symptoms recurred in 62% of patients without treatment aimed at biliary drainage compared with approximately 30% after presumably complete endoscopic or surgical stone removal with therapeutic ERCP or surgery.[12] Furthermore, a 30% risk of residual or recurrent stones after intentionally complete stone removal has been reported.[13] In a large retrospective cohort study the rate of cholangitis was higher among patients who underwent

biliary-enteric anastomosis (31%) than in those who did not (3.4%).[13]

Ursodeoxycholic acid treatment is not effective in dissolving existing stones in most patients since they are composed of calcium bilirubinate instead of cholesterol. Although occasional case reports have suggested a possible benefit[14] the value of this treatment remains to be determined.

The same applies to intermittent or long-term antibiotic therapy. With these uncertainties in mind, the widely used clinical resource UptoDate® advises to use ursodeoxycholic acid at a dosage of 20 mg/kg/day.[15]

In summary, oriental cholangiohepatitis is an incompletely understood disease, characterised by recurrent bacterial cholangitis associated with hepatolithiasis and biliary stricturing. In the West the diagnosis should be considered in all Asian immigrants with biliary tract disease. The therapeutic approach is multidisciplinary and highly individual, and includes antibiotic therapy, endoscopic and percutaneous biliary drainage with stone removal and dilation of strictures, and in selected cases surgical resection of affected liver segments.

DISCLOSURES

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

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CASE REPORT

A case of extreme hypokalaemia

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ABSTRACT

Hypokalaemia is a common clinical problem. It can lead to severe disturbances in cardiac, neurological and muscle function. We present the case of a 45-year-old woman who was transported to our hospital with cardiac arrest following ventricular fibrillation. Blood sampling revealed severe acidosis (pH 7.02) and extreme hypokalaemia (0.9 mmol/l). The low serum potassium level was most likely caused by the combination of a very deficient diet and use of a thiazide diuretic. She never reported any symptoms. An acute intracellular shift of potassium due to epinephrine and perhaps also the cathecholamines in Red Bull may have further decreased the serum potassium concentration. To our knowledge, this is the lowest potassium level reported in literature.

Longer-lasting hypokalaemia might be asymptomatic but when combined with even minor triggers of acute hypokalaemia, serious morbidity or mortality can suddenly occur. Patients on diuretic treatment with suspected malnutrition or chronic gastrointestinal losses require regular monitoring of electrolytes.

KEYWORDS

Arrhythmia, hypokalaemia, intake, potassium, redistribution, diuretics

What was known on this topic?

Hypokalaemia is usually caused by renal or gastrointestinal loss of potassium. Symptoms include muscle weakness or cramps, rhabdomyolysis, a variety of cardiac arrhythmias and ECG abnormalities. The severity of manifestations tends to be proportionate to the degree and duration of hypokalaemia.

What does this case add?

Severe hypokalaemia can be present in otherwise healthy patients and might be asymptomatic, but can cause severe morbidity or mortality. Patients on diuretic treatment, patients with suspected malnutrition or chronic gastrointestinal losses require regular monitoring of electrolytes.

INTRODUCTION

Hypokalaemia is a common clinical problem. It is defined as a serum potassium concentration lower than 3.5 mmol/l. Low serum potassium will increase the transmembrane gradient and therefore hyperpolarise the cell, which impairs the ability of the muscle to depolarise and contract. This can lead to severe disturbances in cardiac, neurological and muscle function.[1]

We report a case of extreme hypokalaemia leading to ventricular fibrillation. The profound hypokalaemia was likely aggravated by a very deficient diet and use of a thiazide diuretic; our patient never reported any symptoms. An acute intracellular shift of potassium aggravated the pre-existing hypokalaemia. To our knowledge, this is the lowest potassium level reported in literature.

CASE REPORT

A 45-year-old Caucasian woman was found unconscious at home. Upon arrival of the paramedics, the patient was unresponsive to stimuli but otherwise stable. There were no indications of a suicide attempt. In hospital she developed ventricular fibrillation; countershock therapy was followed by a pulseless rhythm. After 26 minutes of cardiopulmonary resuscitation and 6 mg of epinephrine, spontaneous circulation returned.

The electrocardiogram showed diffuse myocardial ischaemia with normal waveform and interval durations. CT scans of the cerebrum and thorax showed no abnormalities. Mild hypovolaemia was suspected following the presence of hypotension (90/60 mmHg)

and sinus tachycardia, for which fluid replacement and norepinephrine were started. Blood sampling (*table 1*) revealed severe acidosis (pH 7.02) with lactic acid > 20.0 mmol/l and extreme hypokalaemia (0.9 mmol/l). A random urine sample showed low potassium and normal sodium concentrations; however, interpretation was difficult due to the very low creatinine level. Toxicology screening and screening for laxatives were negative.

Her history included hypertension, anxiety disorder and heroin abuse. She never reported any muscle weakness, vomiting or diarrhoea. Her dietary pattern was very deficient, with a high consumption of Red Bull energy drinks. She used metoprolol, valsartan, hydrochlorothiazide, clomipramine and methadone. The last routine laboratory test, including potassium, was performed one year earlier and showed no abnormalities.

She was admitted to the ICU and we started intravenous potassium supplementation at a constant rate of 20 mmol/hour. In the following hours, the serum potassium level increased very slowly; a total amount of 300 mmol potassium was administered to achieve a nearly normal value of 3.2 mmol/l. Because of hypophosphataemia, phosphate supplementation was given. Lactic acid levels decreased quickly and no cardiac events reoccurred. However, her neurological status was poor due to postanoxic injury and the somatosensory evoked potential test showed absent cortical responses. After withdrawal of ventilatory support, death was pronounced. Autopsy was performed; other than chronic thyroiditis there were no relevant findings. Extreme hypokalaemia was listed as the cause of death.

Table 1. *Most important causes of hypokalaemia*[2]

Renal losses
Adrenal steroid excess
Ingestion of glycyrrhizin (liquorice)
Bartter syndrome
Gitelman syndrome
Liddle syndrome
Gastrointestinal tract losses
Diarrhoea
Clay ingestion
Vomiting
Protracted gastric suction
Villous adenoma of the colon
Intracellular shift
Glycogenesis during TPV or enteral hyperalimentation
Administration of insulin
Stimulation of sympathetic nervous system, particularly with β2-agonists
Thyrotoxicosis
Familial periodic paralysis
Renal tubular diseases
Hypomagnesaemia
Drugs
Diuretics
Laxatives
Amphotericin B
Antipseudomonal penicillins
Penicillin in high doses
Theophylline

DISCUSSION

The aetiology of hypokalaemia is often apparent from the history or physical examination. Most cases result from unreplenished urinary or gastrointestinal losses, sometimes induced or aggravated by medication. Decreased intake alone rarely causes significant hypokalaemia. Serum potassium levels can be transiently decreased by the entry of potassium into cells (*table 2*).

In humans, the total body potassium is about 3500 mmol. On average, a 0.3 mmol/l decrease in serum potassium corresponds to a 100 mmol deficit in total body potassium.[3] With this formula we estimated the total body potassium deficit in our patient to be at least 800 mmol. However, our patient only needed 300 mmol of potassium to achieve a nearly normal serum potassium concentration. This indicates that, alongside an absolute potassium deficit, a significant part of the decrease in serum potassium was caused by a shift to the intracellular space.

The cause of hypokalaemia is often apparent from the history or physical examination. Our patient's history was remarkable for medication, a deficient diet and excessive consumption of energy drinks. There were no signs of intoxication or gastrointestinal losses. Chronic thyroiditis was found during autopsy. Thyroiditis may cause periodic paralysis when accompanied by thyrotoxicosis.[4] In our patient this is an unlikely cause given the measurement of TSH and fT4 (*table 1*).

Diuretics are an important cause of renal potassium loss; they stimulate the renin-angiotensin-aldosterone pathway, increase distal tubule flow, increase the release of vasopressin and generate alkalosis, all of which enhance potassium secretion.[5] Valsartan, on the other hand, elevates potassium levels by decreasing aldosterone. When

Table 2. *Laboratory results*

Parameter	Unit	Reference	Result									
			00:00h	00:30h	02:30h	04:00h	05:00h	06:00h	08:00h	10:00h	12:00h	14:00h
Haemoglobin	mmol/l	7.4-9.9	8.7									
Haematocrit	mmol/l	0.36-0.46	0.46									
Sodium	mmol/l	135-145	145	146	148	149	151	152	153	154	154	156
Potassium	mmol/l	3.5-4.7	0.9	1.1	1.2	1.7	1.8	2.0	2.2	2.5	2.6	3.2
Chloride	mmol/l	97-107	96		105				113	114		
Calcium (ionised)	mmol/l	1.10-1.30	0.91		0.96			0.93	1.02	1.03		
Magnesium	mmol/l	0.7-1.10						1.16				
Phosphate	mmol/l	0.8-1.4						0.4				
Creatinine	µmol/l	45-90	94					90				
eGFR	ml/min/ 1.73 m²	> 90	56					59				
Hs troponin T	ng/l	< 14	153					162				
Glucose	mmol/l	5.0-12.2	17.2		6.4	6.8	7.2	7.0	7.4			
TSH	mU/l	0.27-4.20	37.34									
fT4	pmol/l	12-22	9									
pH arterial		7.35-7.45	7.02	7.19	7.45	7.42	7.42	7.43	7.40			
pCO2 arterial	kPa	4.7-6.4	10.2	7.1	6.6	7.4	7.3	7.0	7.7			
pO2 arterial	kPa	11.0-14.4	67.0	52.6	11.0	14.7	12.7	13.4	13.6			
HCO3 arterial	mmol/l	21-28	19.6	20.2	34.1	36.1	35.7	34.5	35.9			
BE arterial	mmol/l	-2.0-3.0	-12.1	-8.2	8.7	9.1	9.0	8.3	8.7			
Lactate	mmol/l	0.5-1.8	>20.0	16.5	4.0	1.6	1.4	7.5	1.2			
Anion gap	mmol/l	8±3	30.3		10.1			6.3				
Urine												
Sodium	mmol/l	28-150			38							
Potassium	mmol/l	17.0-80.0			6.0							
Creatinine	mmol/l	4.0-16.0			0.5							

hydrochlorothiazide and valsartan are combined, the different effects on serum potassium balance each other in many patients.[6] Interpretation of the urine sample was difficult. The urine was very dilute, as demonstrated by the low creatinine concentration. Some authors have argued that a urinary potassium-to-creatinine ratio of 2.5 is the cut-off between renal potassium loss and an adequate renal response.[7] In this case the urinary potassium-to-creatinine ratio was 12, indicating renal potassium loss. However, a low potassium concentration with a normal sodium concentration is more suggestive of renal potassium sparing. There was no time for a 24-hour urine collection. We could not calculate the transtubular potassium gradient in retrospect since serum and urine osmolarity were not determined. Hence, we could neither prove nor disprove renal potassium wasting.

Metoprolol, clomipramine and methadone do not affect the potassium concentration. However, methadone might

be interesting in this case since it is a potent blocker of IKr potassium channels found in myocytes. In susceptible individuals this leads to QT-complex prolongation, a condition that predisposes to fatal arrhythmias.[8] The electrocardiogram of our patient showed normal interval durations. Clenbuterol adulteration of heroin should also be considered a cause of hypokalaemia in drug users;[9] our patient had not used heroin for several years and toxicology screening was negative.

By the time we took the first blood sample from our patient, she had received several doses of epinephrine. Catecholamines promote a transient shift of potassium into cells by stimulating membrane Na-K-ATPase activity.[10] A proposed physiological role for this effect of increased beta-2 adrenergic activity is to moderate the acute hyperkalaemia of exercise.[11]

Energy drinks such as Red Bull contain high amounts of caffeine. Caffeine and its breakdown product theophylline will not contribute to sustained hypokalaemia, but can induce an inward cellular shift of potassium by antagonism of the adenosine A2 receptor, resulting in the release of catecholamines.[12] Earlier it was believed that increased Na-K-ATPase activity through inhibition of phosphodiesterase was the main mechanism of action, but this requires much more caffeine than consumed through food and drinks.[13]

Potassium is commonly found in a variety of unrefined foods such as meat, fish, vegetables and fruits. The World Health Organization suggests a potassium intake of 90 mEq/day. Food processing reduces the amount of potassium in food products, and a diet high in processed foods and low in fresh fruits and vegetables is often lacking in potassium.[14]

A striking fact in this case is the co-existence of extreme hypokalaemia and severe metabolic acidosis, a peculiar situation because acidosis will elevate the serum potassium concentration. When acidosis is present, cells absorb hydrogen ions to raise the serum pH and release potassium in exchange.[15] This implies that with a normal serum pH, as probably was the situation before cardiac arrest, serum potassium concentrations might have been even lower than 0.9 mmol/l. On the other hand, it is likely that elevated catecholamine levels during resuscitation worsened the pre-existing hypokalaemia. This makes it difficult to reason about the situation before cardiac arrest. No sodium bicarbonate was given to correct the lactic acidosis.

We did not further investigate the hypophosphataemia in our patient. We suggest that an inward cellular shift played an important role. Total body stores might have been deplete as well; possible contributors are a deficient diet or urinary losses caused by diuretic use and metabolic acidosis.

To our knowledge, this is the lowest potassium level ever reported in the literature. The combination of reduced dietary potassium intake and use of a thiazide diuretic most likely caused the profound hypokalaemia. An acute intracellular shift of potassium due to epinephrine and perhaps also the cathecholamines in Red Bull further decreased the serum potassium concentration. Longer-lasting hypokalaemia might be asymptomatic but when combined with even minor triggers of acute hypokalaemia, fatal arrhythmias can suddenly occur. Patients on diuretic treatment, patients with suspected malnutrition or chronic gastrointestinal losses require regular monitoring of electrolytes.

DISCLOSURES

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CASE REPORT

An impressive response to pazopanib in a patient with metastatic endometrial carcinoma

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ABSTRACT

The incidence of endometrial carcinoma is rising and the patients with distant metastases have a poor prognosis, especially when progression of disease occurs after systemic treatment with hormonal therapy or chemotherapy. Pazopanib, a multi-targeted inhibitor of several oncogenic receptor tyrosine kinases, has been investigated in patients with chemotherapy-resistant endometrial carcinoma or patients for whom chemotherapy is contraindicated. In this report we will describe a spectacular response to pazopanib in a patient with recurrent metastatic endometrial carcinoma.

KEYWORDS

Endometrial carcinoma, endometrial cancer, pazopanib, tyrosine kinase inhibitor, complete remission

What was known on this topic?
Pazopanib is a selective multi-targeted receptor tyrosine kinase inhibitor of VEGFR-1/2/3, PDGFR-α/β, FGFR1/2/3 and c-kit. Its mechanism of action is dual, via direct inhibition of oncogenic signalling in target-positive cancer cells and via angiogenesis inhibition. Pazopanib is registered for treatment of renal cell carcinoma and soft tissue sarcoma and has shown activity in ovarian cancer. Pazopanib is currently being investigated in endometrial carcinoma in the PAZEC study (EudraCT Number: 2011-000287-99).

What does this add?
This case report describes an impressive response to pazopanib in a 57-year-old patient with FGFR2-positive endometrial cancer who developed resistance to one line of hormonal therapy and two lines of palliative chemotherapy. No data of pazopanib and endometrial carcinoma have been published until now.

INTRODUCTION

Endometrial carcinoma is the most common gynaecological malignancy in developed countries. Worldwide incidence is estimated at 290,000 patients per year and the incidence is rising. In the Netherlands it is diagnosed in approximately 1900 women each year. Usually the disease is diagnosed early with symptoms such as postmenopausal vaginal bleeding or an atypical bleeding pattern[1-3] and therefore the prognosis in general is good.

Approximately 20% of the patients with endometrial carcinoma present with regionally extended disease and 8% of them have distant metastases. In patients with early stage disease effective treatment consisting of surgery with or without radiotherapy can be given. In patients with high risk or advanced endometrial carcinoma, the prognosis is much worse, resulting in more extensive treatment with frequent addition of chemotherapy. Once disease recurs outside the pelvis, cure is impossible and palliative treatment remains. Systemic palliative treatment consists of either hormonal therapy or chemotherapy.[3] Despite good initial response rates, the disease will finally progress and prognosis after recurrence is poor. Moreover, patients with endometrial cancer frequently have comorbidities prohibiting multi-agent chemotherapy. New approaches are therefore needed.

The PAZEC study is a multicentre, open-label, non-randomised phase II study which investigates the use of pazopanib in patients with chemotherapy-resistant endometrial carcinoma or patients for whom chemotherapy is contraindicated. The study is subdivided into two stages. If after stage I (n = 15) > 6 patients are free of progression the study will continue and proceed to stage two (n = 46). If at the end of the study > 18 patients are free of progression the study will be positive. Currently the inclusion is closed and results are expected at the end of this year. We think this trial might be positive and present a patient with a metastatic endometrial carcinoma who was treated with pazopanib.

CLINICAL CASE

A 57-year-old patient presented in 2009 with a FIGO stage IIb grade II endometrioid adenocarcinoma of the endometrium for which she underwent a bilateral salpingo-ophorectomy and a total abdominal hysterectomy. Postoperatively she received adjuvant radio-chemotherapy according to the PORTEC-3 protocol, which contained a total of two cycles cisplatin 50 mg/m^2 on day 1 and 22 during radiotherapy and four cycles of carboplatin AUC 5 and paclitaxel 175 mg/m^2 every three weeks. The cisplatin was combined with 27 fractions of 1.8 GY radiotherapy. After completion of this regimen she remained in remission for two years.

In 2011, the disease recurred with an abdominal wall metastasis and para-aortic lymph node metastases. Since the tumour expressed oestrogen and progesterone receptors, the patient was treated with 200 mg medroxyprogesterone acetate. After two months, progressive disease was diagnosed. She restarted with six cycles of carboplatin and paclitaxel resulting in a partial response. When, in February of 2012, two months after discontinuation of chemotherapy, the disease progressed, the chemotherapy schedule was intensified to a weekly scheme of carboplatin and paclitaxel, with initial response after three months but progression after six months. At that point she had a reddish-purple abdominal wall metastasis of 7 x 6 cm. Surgery was technically not feasible according to the surgeons and gynaecologists, so she was informed about the PAZEC study. After signed informed consent was given, she started on pazopanib 800 mg once daily.

Two days after starting pazopanib the patient noticed a change in the abdominal wall metastasis. It looked as if it had broken through the skin and there was leakage of bloody exudate from the wound.

Two weeks after starting pazopanib there was a defect in the abdominal skin of 4 x 2.5 centimetres, in which a necrotic tumour mass was visible (*figure 1 and 2*).

Based on the apparent potent antitumor activity of pazopanib, the treatment was continued. During the next two weeks the dosage needed to be adjusted to 600 mg daily because of grade 2 erythro-palmar toxicity, grade 2 hypertension and grade 1 diarrhoea and anorexia according to the NCI Common Terminology Criteria for Adverse Events. After two months an impressive reduction in tumour size of both the para-aortic lymph nodes and abdominal wall metastases was diagnosed on a CT scan. After taking pazopanib for four months, the patient noticed leakage of defecation through the abdominal wound. An entero-cutaneous fistula was confirmed radiologically. The abdominal wall defect was resected including the fistula, as was a part of the small

Figure 1. *Abdomen of the patient showing a large defect in the abdominal wall two weeks after starting pazopanib. Tumour mass and necrosis is visible in the defect*

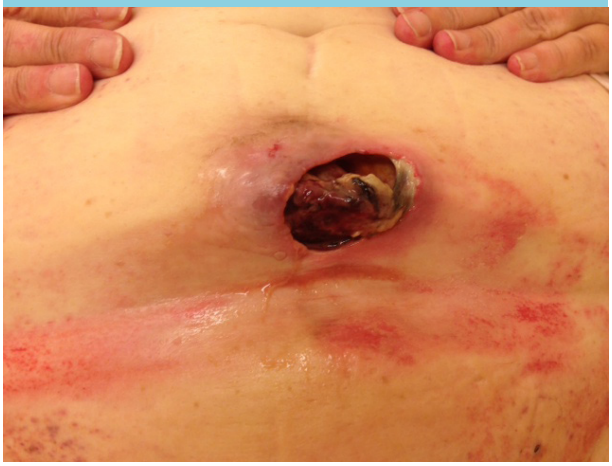


Figure 2. *The defect in the abdominal wall was 4 x 2.5 cm in size*

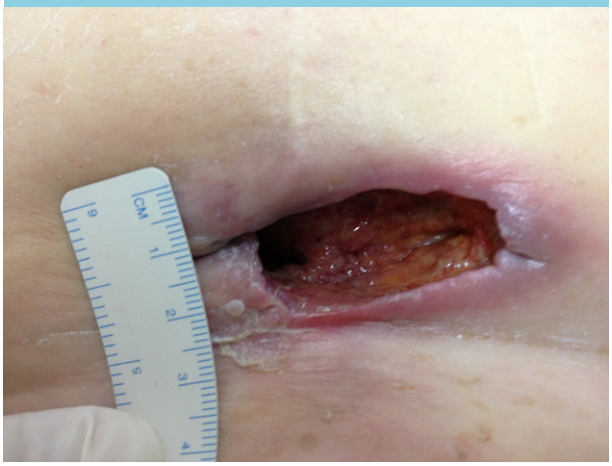
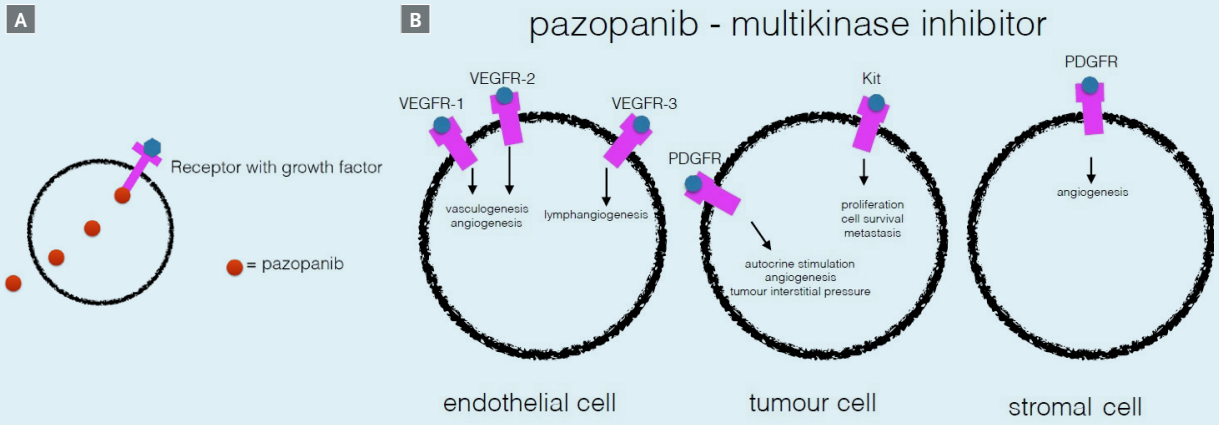


Figure 3. *Working mechanism of pazopanib. a: pazopanib migrating through the cell wall blocking a receptor; b: Examples of pazopanib inhibiting cell proliferation and angiogenesis by inhibition of different receptors. Not all receptors are mentioned; interleukin-2 receptor inducible T-cell kinase, leukocyte specific tyrosine kinase, and transmembrane glycoprotein receptor kinase are missing in the figure*



bowel and the enlarged para-aortic lymph nodes. Histological examination confirmed the entero-cutaneous fistula with extensive necrosis and infiltration of lymphocytes, and location of a few tumour nests of endometrial carcinoma in the fistula wall. The abdominal wall and intestines were free from tumour cells, as were the para-aortic lymph nodes. Because there were no visible metastases left, pazopanib was not restarted after surgery.

The patient is currently, 30 months after discontinuation of pazopanib, still in complete clinical remission.

Pazopanib and current adjuvant therapy in high-risk endometrial cancer

Pazopanib is an orally available multi-targeted inhibitor of several oncogenic receptor tyrosine kinases, i.e. platelet-derived growth factor receptor alpha (PDGFRα), fibroblast growth factor receptor (FGFR1-3), cytokine receptor (KIT), interleukin-2 receptor inducible T-cell kinase, leukocyte-specific protein tyrosine kinase (Lck) and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). It also potently inhibits endothelial cell tyrosine kinases which are critically involved in angiogenesis i.e. vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3) and PDGFR-beta (PDGFRβ) (*figure 3*).

Receptor tyrosine kinase inhibition is a novel cancer treatment strategy that has proven efficacy in a variety of tumours, such as colorectal cancer, renal cell carcinoma, breast cancer and lung cancer.[7] This receptor tyrosine kinase plays an important role in tumour growth, invasion and angiogenesis, also leading to progression of endometrial cancer. It is therefore an important target for cancer drug development.

The most common known adverse events of pazopanib are fatigue, diarrhoea, nausea, anorexia, vomiting, hypertension, headache, abdominal pain, skin rash, cough, muscular pain, elevated transaminases and bilirubin, and hair discoloration.[8]

The anti-angiogenic agent thalidomide has shown only limited activity in endometrial cancer. The VEGF inhibitor bevacizumab showed promising results with a response rate of 13.5% in recurrent and resistant endometrial cancer, and over one third of patients are progression-free at 6 months.[9]

A study of the effects of pazopanib monotherapy on various tumour types showed only one hit for complete response in a patient with soft tissue sarcoma metastases in the lung.[10] Furthermore, one report mentions a complete radiological response to the combination pazopanib with everolimus in a patient with a metastatic urothelial cell carcinoma.

TUMOUR ANALYSIS

We analysed the metastases before pazopanib treatment (2009) and the tissue retrieved from surgery after the intestinal perforation to the abdominal wall after pazopanib treatment (2013). Immunohistochemistry for MET, VEGFR,2 FGFR2,3, PDGFRα, KIT, RET and ALK revealed high tumour expression of FGFR2, whereas expression of KIT, RET and ALK were low. FGFR2 expression has also been reported in pazopanib-sensitive lung squamous cell cancer and gastric cancer.[12-14] This suggests that high FGFR2 expression could be a predictive biomarker for response to pazopanib.

CONCLUSION

We found a spectacular response to pazopanib monotherapy in a patient with recurrent metastatic endometrial carcinoma. The tissue samples before and after pazopanib treatment were investigated and intact FGFR2 was found to be a possible biomarker for response.

DISCLOSURES

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

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PHOTO QUIZ

Limb weakness and pain in a patient with primary Sjögren syndrome

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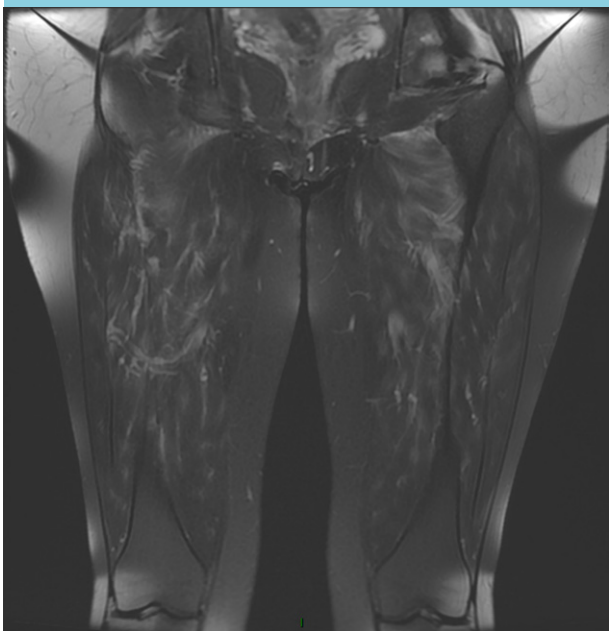
CASE REPORT

A 44-year-old woman presented with pain in her arms and legs and walking difficulties lasting for one month, partially relieved by ketoprofen. She had a medical history of primary Sjögren syndrome (PSS) (5/6 criteria of the American-European Consensus Group were fulfilled: ocular and oral symptoms, ocular signs, lymphocytic sialoadenitis with a focus score ≥ 1 on minor labial accessory gland, and positive anti-SSA antibodies) and autoimmune thyroiditis, and was treated with hydroxychloroquine and levothyroxine. On physical examination, she appeared healthy, her temperature was 37.8°C. She could move her arms but was unable to walk because of thigh pain and weakness. The remainder of the physical examination was normal. Her young son had had a febrile rash six weeks before. The blood cell count, serum creatinine, creatinine phosphokinase, lactate dehydrogenase, thyroid-stimulating hormone, and urinalysis were unremarkable, the alanine aminotransferase level was 110 U/l (N < 32), aspartate aminotransferase 57 U/l (N < 32), C-reactive protein 79 mg/l (N < 5), serum electrophoresis showed an increased level of alpha-2 globulin and polyclonal hypergammaglobulinaemia. Antinuclear and anti-ECT antibodies titres were unchanged; a search for myositis-specific and anti-neutrophil cytoplasmic antibodies was negative. No cryoglobulinaemia was found, complement proteins C3 and C4 levels were increased. High levels of Parvovirus B19 (PvB19) immunoglobulin G (IgG) and immunoglobulin M (IgM) were found in her serum and the PCR was positive at 21,816 IU/ml. Electromyogram, thoraco-abdomino-pelvic scan and 18-fluorodeoxyglucose PET/computed tomography detected no abnormalities. MRI of the thighs showed diffuse muscular oedema without amyotrophia of the anterior and posterior muscles of the thighs (*figure 1*).

Figure 1. *Coronal STIR sequence MRI showing oedema of the anterior and posterior muscles of the thighs*



WHAT IS YOUR DIAGNOSIS?

See page 415 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 414)

LIMB WEAKNESS AND PAIN IN A PATIENT WITH PRIMARY SJÖGREN SYNDROME

DIAGNOSIS

Muscle biopsy of the thigh revealed skeletal muscle non-necrotising vasculitis in the endomysium and perimysium tissue but no fibre necrosis or focal myophagocytosis (*figure 2*). Diagnosis of skeletal muscle vasculitis secondary to an acute PvB19 infection (that probably also presented in her son) was established. Of note, a viral infection was suggested because of the febrile eruption in her son, temperature and hepatitis. The patient declined treatment with intravenous immunoglobulins or glucocorticoids. Progressive resolution of pain and weakness was observed within two months under ketoprofen and the PvB19 PCR was negative four months later.

In patients with PSS, development of inflammatory myopathic conditions (polymyositis and dermatomyositis) is well known as well as vasculitis (mainly cutaneous vasculitis and mononeuritis multiplex), and in this latter case mainly associated with systemic disease activity of PSS and cryoglobulimaemia.[1] Skeletal muscle vasculitis without any associated inflammatory myopathic conditions is rare. In a retrospective series including 40 patients with skeletal muscle vasculitis, clinical features consisted mainly of muscle pain, numbness in the extremities, fever, skin lesions and paresthesias, joint stiffness and pain.[2] It has been described in association with rheumatoid arthritis, scleroderma, malignancies, and viral infections.[2] Of note, two patients in this series had PSS.[2] Histology revealed skeletal muscle necrosis, rarely non-necrotising vasculitis and neurogenic changes. Concomitant sural nerve biopsy showed nerve vasculitis and axonal loss. This nerve biopsy was not performed in our patient since the neurological examination and electromyogram were normal. Usually treatment relies on steroid therapy alone or associated with immunosuppressors.[2]

Acute PvB19 infections can develop in healthy adult patients but also in patients with hereditary haemolytic anaemia and underlying immunodeficiency. Besides cytopenia, clinical manifestations have been described including arthralgias, acute -rarely prolonged- symmetric arthritis, tenosynovitis, myocarditis, glomerulonephritis, encephalitis, exanthema, gloves-and-socks syndrome, hepatitis, rarely myositis and dermatomyositis,[3] and cutaneous and skeletal muscle vasculitis including periarteritis nodosa.[4] Administration of intravenous immunoglobulins is the first-line therapy, possibly in association with glucocorticoids.

Limb weakness and pain in a patient with PSS can indicate inflammatory myopathic conditions but also skeletal muscle vasculitis possibly related to acute PvB19 infection, as in our patient.

Figure 2. *Quadriceps muscle biopsy showing non-necrotising vasculitis with mixed infiltrates composed of lymphocytes and neutrophils surrounding and disrupting the vessel wall (haematoxylin eosin, magnification x 570)*

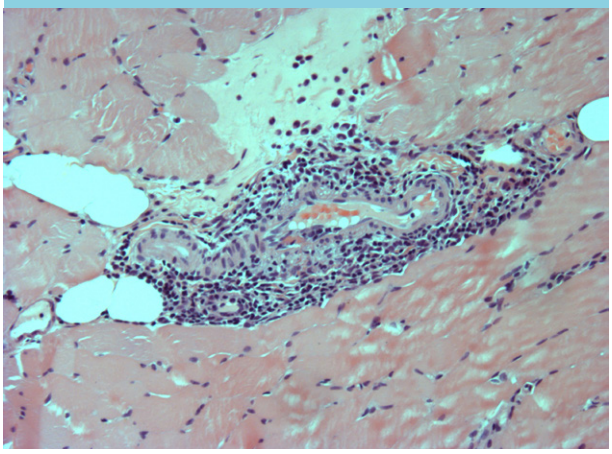


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PHOTO QUIZ

Recurrent lesions after taking an oral drug

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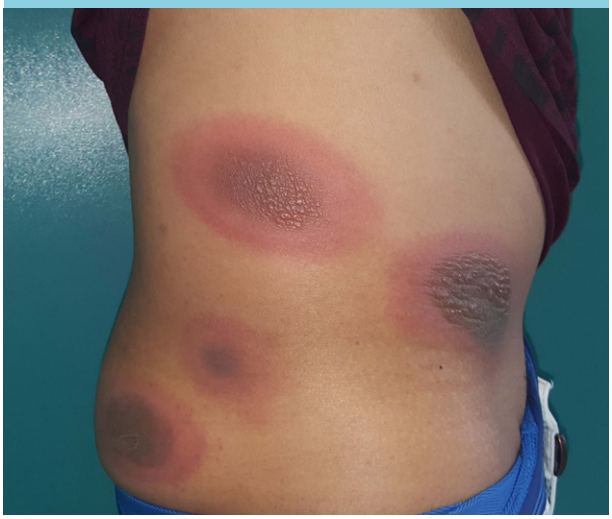
CASE REPORT

A man in his 20s presented with a one-day history of lesions on his right side, starting two hours after taking a metamizole tablet for a headache. He related a history of similar lesions, at exactly the same locations, a year before, after taking the same drug. On examination he presented well-demarcated erythematous patches, with violaceous bullous centres (*figure 1*). He had no fever or other systemic symptoms. No significant findings were present in the rest of the examination.

WHAT IS YOUR DIAGNOSIS?

See page 417 for the answer to this photo quiz.

Figure 1. *Details of the lesions*



ANSWER TO PHOTO QUIZ (PAGE 416)
RECURRENT LESIONS AFTER TAKING AN ORAL DRUG

DIAGNOSIS

Given his clinical and medical history, we arrived at the diagnosis of bullous fixed drug eruption (FDE). The medication was discontinued with evolution towards hyperpigmentation and subsequent resolution of lesions in a week.

FDE is a cutaneous adverse drug eruption characterised by skin lesions which recur at the same sites upon re-exposure to the drug.[1] The most common drugs causing FDE are analgesics, antibiotics, muscle relaxants and anticonvulsants.[2] FDE typically resolves after discontinuation of the causative drug, leaving a circumscribed hyperpigmented area at the site of resolved lesions. Treatment recommendations include identifying and cessation of the causative drug. If the patient takes the same drug again, the lesions will reappear in the same places. Therefore, if he needs an analgesic, he should choose one from a different drug group (in this case, other than the pyrazolone group).

Bullous variants often produce very striking pictures, which can pose a differential diagnosis with herpes zoster infection (if lesions are linear or localised) or bullous dermatosis (pemphigus, pemphigoid). Therefore, it is essential to recognise the so typical presentation of fixed drug eruption, with the appearance of lesions all at once, and the possibility of recurrence at the same site. Physicians should be aware of this disease because of its association with commonly used medications, to reach an early diagnosis and avoid performing unnecessary additional tests.

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