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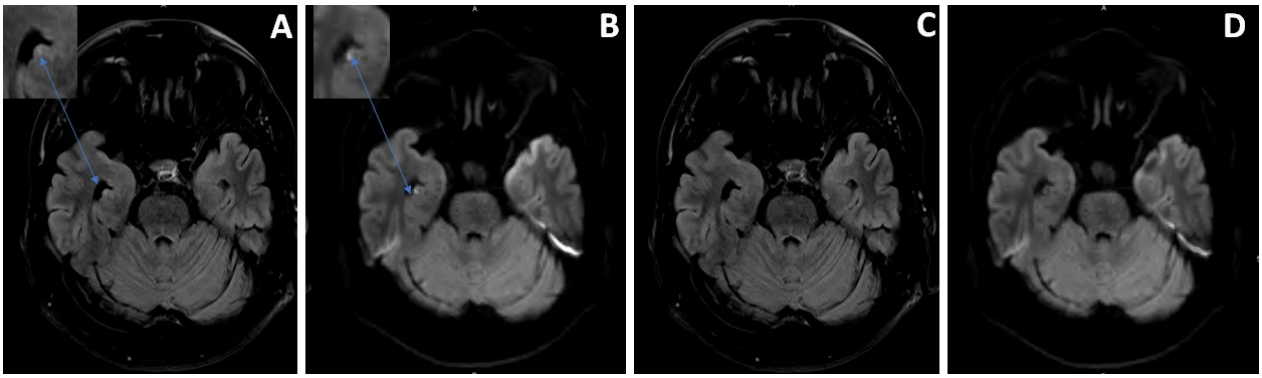

A memory gap; what is your diagnosis?

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EDITORIAL

Vitamin D, many associations but few that seem to matter

P.L.A. van Daele

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In the current issue of the journal, Keshavarz et al. describe the association between vitamin D levels and metabolic disturbances in patients with polycystic ovary syndrome (PCOS).[1] Only about 3% of patients in this study had normal vitamin D levels, which they define as a vitamin D level above 30 ng/ml. On top of this, they find an association with various clinical and metabolic parameters.

Vitamin D, a nutrient in name, but much more a hormone in function, has been extensively studied in many diseases, not only in endocrine disorders, but also for instance in cardiovascular disease, cancer, psychiatric disease and autoimmunity.[2-5] It appears that almost invariably, an association is found making vitamin D a very rewarding topic for researchers and an important issue for decision makers. Searching the Cochrane Library for vitamin D already yielded almost 10,000 hits.

But studies looking for associations do not provide evidence of causality. For causality to be plausible either experiments examining or demonstrating a pathogenetic mechanism involving vitamin D or clinical trials showing benefit of supplementation are necessary.
Metabolic bone disease fulfills both. Vitamin D, or rather its metabolites, are important in bone metabolism and deficiency is associated with bone disease. Furthermore, already in the 1930s, vitamin D supplementation was shown to be beneficial in rickets.[6]

Yet, for most other conditions for which an association with vitamin D levels has been demonstrated neither is true; no well-established pathogenic mechanism and, not surprisingly, many clinical trials on vitamin D supplementation come out negative or at best show conflicting results. This suggests that in several diseases in which an association is found, this indicates consequence rather than causality.

Keshavarz concludes that there is a need to perform intervention trials to examine the causal relationship, hoping that intervention may also lead to improvement. In fact, this has already been done. A recent meta-analysis once more showed a lack of effect of vitamin D supplementation, this time in PCOS.[7]

Should we stop doing association studies on vitamin D? In my opinion yes, given the abundance of negative trials after supplementation, unless there is a sound pathogenetic concept.

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REVIEW

The truth on current peritoneal dialysis: state of the art

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ABSTRACT

The share of peritoneal dialysis (PD) in the spectrum of chronic dialysis has decreased markedly in the Netherlands in the last 15 years. Consequently, the knowledge of nephrologists and nursing staff on PD has declined leading to a negative spiral in which loss of experience resulted in loss of enthusiasm to offer PD to patients and also in less interest in the new PD developments. All these changes took place while the results of PD improved and patient survival was at least similar to that on haemodialysis.

The aim of this review is first to give a summary of the principles and practice of patient and staff education and to describe the role of the medical contribution in decision-making. On this basis, the second aim is to update internist-nephrologists on a number of issues that have been underexposed in the past.

Recent patient and technique survival data of PD patients is reviewed, and also the new insights into dialysis adequacy. The presence of residual renal function is the main determinant of patient survival together with prevention of overhydration. Urea and creatinine removal are not important at all when patients are still passing urine. Many early problems with PD are due to the peritoneal catheter and suggestions are made for improvement of its function. The prevention and management of infections is reviewed, and also the regular assessment of peritoneal function. Free water transport is a predictor of encapsulating peritoneal sclerosis (EPS), which should be assessed regularly. The pathogenesis of EPS, treatment and the decreasing incidence are discussed.

KEYWORDS

Assessment of peritoneal dialysis, education in peritoneal dialysis, encapsulating peritoneal sclerosis, infections in peritoneal dialysis, peritoneal dialysis

INTRODUCTION

Peritoneal dialysis (PD) is a modality for chronic renal replacement therapy which was introduced in the Netherlands in 1979. This form of home dialysis developed well and 31% of all dialysis patients were treated with PD in 2002, while the number of home haemodialysis patients was very small (< 5%) and the remaining 69% of patients received in-centre haemodialysis (ICHD).[1] The 'Planningsbesluit Dialyse' was abolished by the Dutch government in 2002, making it relatively easy to increase the number of ICHD facilities. This was associated with a progressive rise in the number of ICHD patients since 2003 and a concomitant decrease in the contribution of PD to 15% in 2015, but with a wide variation among centres.[2] The contribution of ICHD in 2015 was 82%, while home haemodialysis accounted for only 3%. This increase in ICHD was initially tolerated by health insurance companies, who considered dialysis costs a minor fraction of their total budget and had no objection to the most expensive treatment. The current emphasis of these companies on home dialysis mainly concerns haemodialysis, but health managers often lack the necessary insight into the type of patients that can be treated with either home haemodialysis or PD.

The declining share of PD in the spectrum of renal replacement therapy in the Netherlands, despite similar or even better patient survival[3] and other advantages such as longer preservation of residual renal function,[4,5] caused a negative spiral. In this spiral, loss or absence of knowledge on PD leads to an unwarranted pessimistic view of this form of renal replacement therapy and thus has an impact on predialysis patient education. On the other hand, use of PD is increasing worldwide, especially in South East Asia and South America. The aim of the current review is to update nephrologists on the state of the art of PD, thereby also improving the knowledge of the nursing staff, and to ensure access to this mode of renal replacement therapy for all well-informed patients.

Patient education

The impact of dialysis on all aspects of quality of life for patients and their families makes patient-centred and shared decision-making of utmost importance.[6] In the absence of medical contraindications, the choice of dialysis modality should be based on the preference of a well-informed and well-prepared patient. Balanced and unbiased information about haemodialysis and PD, including their relative benefits and drawbacks, should be given early in the disease process. Being confronted with end-stage renal failure, many patients do not feel the urge to choose between renal replacement modalities. This can be due to fear, non-acceptance or being overwhelmed by information. Patient engagement by a dedicated multidisciplinary team may identify possible barriers and overcome these by providing timely patient-tailored care, education and support. Such multidisciplinary teams should consist of a physician, nurse, dietician, social worker and include family members or support persons. The team should address health literacy, and psychosocial and cultural values related to the choice. Indeed, several studies indicate that patients who are educated about their treatment options will choose PD in 50 to 60% of the cases.[7-9] This is not surprising, since important themes from a patient's perspective such as keeping as much independence as possible, quality and quantity of life, flexibility of the daily treatment schedule[6] are all met by PD. Have patient preferences changed over time, explaining the generally observed decrease in PD utilisation? In the past, a randomised controlled trial (RCT) comparing PD with haemodialysis, which was included in the observational Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), had to be stopped early due to poor patient recruitment; ~50% of patients exhibited a strong preference for PD and refused to be randomly assigned to either haemodialysis or PD.[8] A more recent Dutch study on a structured multidisciplinary predialysis education program with a home-focused approach, showed that with this program the uptake of home dialysis increased.[10] The use of dialysis decision tools in patient education appears to be effective and also influences the choice and uptake of PD.[6-8,10-12] All studies show that predialysis patient education and training is a key target for more widespread utilisation of PD.[13] It can therefore be concluded that the decrease in the number of PD patients is not the result of changed patient preferences.

The wide range in penetration of PD among dialysis centres in the Netherlands raises a number of questions.[1] Have nephrologists and nurses in the Netherlands developed a somewhat biased view of PD over time by judging several factors as being relative contraindications for PD,[14] not confident with the fact that some of these can be overcome by more intense and individualised training?[2] Is it seen as a treatment in the short run because of previous overemphasis on the required dialysis dose and/or fear of encapsulating peritoneal sclerosis?[3] Did the low penetration of PD in the past decade already decrease experience with and thereby confidence in this modality? Clinician preference plays a major role in the multidisciplinary team.[15] To offset the concerns about nephrologists not being comfortable with PD, training programs must provide young doctors adequate exposure to PD, for instance by offering elective rotation in centres with larger PD populations.[13] Other team members may also have similar views on contraindications. Decision-making tools may help the team think differently about the treatment they recommend for individual patients. A continuing nursing education initiative was able to modify the opinions of in-centre haemodialysis nurses towards home modalities.[16] Most of the perceived barriers to PD in the elderly, such as dexterity, and visual and cognitive impairments, can be overcome with appropriate care, education and support, including social help, psychological counselling and assisted PD.[17,18] Also, limited health literacy is common in patients on chronic peritoneal dialysis, but is not associated with key adverse infectious complications or hospitalisations.[19] The importance of a dedicated team and the need for individualised support and training is even more true for elderly patients. Training that encompasses self-efficacy can enhance self-management skills.[20]

Modality education programs mainly direct their efforts to patients with advanced chronic kidney disease prior to initiation of dialysis therapy, but ~50% of patients will start dialysis urgently in the hospital.[21] This subset of patients typically start renal replacement therapy with haemodialysis by a catheter, although some centres offer acute PD. In these cases targeted modality education specifically addressing modality choice appears to be effective, since high-performing centres convert a significant number of such patients to PD in the first six months of therapy.[7-9] Alternatively, an acute start with PD only requires a dedicated surgeon, nephrologist or

radiologist for catheter placement. It can be regarded as a safe and feasible alternative to acute haemodialysis through a central-venous catheter, also in older patients and with ~10% incidence of minor peri-catheter leaks without a detrimental effect on patient outcome or PD technique survival (i.e. survival on PD after censoring for death and transplantation).[22,23]

Beyond patients preferences and nephrologists choices, other clinical, social, macro-economic and macro-organisational factors might explain why PD is underused. To turn the tide, a number of issues need to be addressed. These include patient-tailored education and training, investigation of perceived barriers, and the creation of a collaborating network to share experience, confidence and expertise with centres that are more supportive of PD use. Hopefully the recent initiative to follow patients prospectively by patient-reported outcome measures (PROMs, results of healthcare reported from patients points of view), will shine light on some of these issues. The same holds true for the recent initiative by the DOMESTICO group (Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes), which aims to assess whether home dialysis is associated with better quality of life, at least comparable clinical outcomes and reduced costs compared with in-centre haemodialysis. In addition, implementation of 'Best Practices' for home dialysis may lead to a change in treatment modality choices for end-stage renal disease patients and their doctors.

Patient and technique survival

Despite the initial poor results of PD, already in 1997 the Canadian Organ Replacement Register reported a better 2-year survival in almost 12,000 patients who started PD between 1990 and 1994, compared with haemodialysis.[24] These results were later confirmed in other parts of the world, including the Netherlands.[25] Recently a study from the European Renal Association Registry showed slightly higher adjusted five-year survival with haemodialysis and PD for patients who started dialysis between 2003 and 2007, with a hazard ratio for mortality on PD of 0.91 (confidence interval: 0.88-0.95) compared with haemodialysis.[3] Technique survival with PD has always been lower than with haemodialysis. This is partly related to the experience of the attendant, as was shown by Huisman et al.[26] A more detailed analysis of reasons for drop-out in the NECOSAD cohort, including about 2000 patients on haemodialysis and PD, showed that catheter-related and abdominal complications were the most important reasons for early PD discontinuation. Analysis of the 709 patients who started PD between 1997 and 2007 showed that after four years, 22% had been transplanted, 19% died and 24% were transferred to haemodialysis.[27] Ignorance on the part of the nephrology community in the Netherlands regarding survival data may be an important reason for the decreased penetration of PD.

Adequacy of dialysis

A high plasma concentration of urea is generally considered a representation of uraemic toxicity in non-dialysed patients with chronic renal failure, despite the fact that it is not toxic. Urea and creatinine are made up of small molecules and are therefore easily removed from the body by dialysis techniques, where diffusion is the main transport mechanism. The removal of unmeasured larger molecules and protein-bound toxins by dialysis is almost absent or much lower. This contrasts to native kidneys that remove solutes by glomerular filtration and tubular secretion, neither of which are influenced by their molecular weight. It follows from this reasoning that plasma urea is a poor marker of uraemic toxicity in patients treated with chronic dialysis. Yet, adequacy of dialysis is usually defined by the clearance of urea (Kt/V_{urea}), while in PD the clearance of creatinine is also used (weekly creatinine clearance/1.73 m^2 body surface area).

Targets for solute removal in PD were first formulated by the Dialysis Outcomes Quality Initiative (DOQI) in 1997 and were intended for use in the USA.[28] These consisted of the following targets: Kt/V_{urea} 2.0/week and weekly creatinine clearance 60 l/1.73 m^2. In comparison, an average continuous ambulatory peritoneal dialysis (CAPD) patient has a peritoneal Kt/V_{urea} of 1.5-1.7 and a peritoneal creatinine clearance of 40-45 litres/ week.

The above recommendations, based on results from the CANUSA study,[29] have been extremely harmful for the further development of PD. This study included 680 new PD patients from Canada and the USA and showed that higher solute clearances were associated with better survival. However, the mean follow-up was only 15 months, which makes confounding by residual renal function a likely explanation for the superior survival. This was confirmed in many other studies that found no effect of peritoneal solute clearances on mortality. A re-analysis of the CANUSA study indeed showed that mortality was not associated with peritoneal clearances, but only with urine production.[30] The importance of residual renal function was confirmed in the NECOSAD cohort, not only concerning patient survival, but also for patients' perceived quality of life.[31] Therefore a $Kt/V_{urea} < 1.7$ in the absence of uraemic symptoms is not a reason to transfer a PD patient to haemodialysis. The absence of evidence for the DOQI recommendations has been established firmly in two RCTs: from Mexico[32] and from Hong-Kong.[33] Both were unable to detect any effect of increasing peritoneal solute clearances to reach the DOQI targets on patient survival, not even in anuric patients. So, it is clear that pushing-up peritoneal Kt/V_{urea} from 1.6 to 2.0 per week in patients without signs of underdialysis has no effect on their survival: the effect of peritoneal solute clearance is overpowered by that of residual renal function. A number of studies have shown that the latter is better preserved in PD than in haemodialysis.[4,5]

Evidently a minimum dialysis dose is required in anuric patients. For ethical reasons this cannot be investigated in an RCT. A NECOSAD analysis showed that only Kt/V_{urea} < 1.5 and creatinine clearance <40 litres/week were associated with increased mortality.[34] Both targets are easily achieved with CAPD. Also a minimum target for ultrafiltration was investigated, but was impossible to establish. This is not really surprising, because the development of overhydration is not only dependent on fluid removal, but also on patients' fluid intake.

Only a few patients with a slow solute transport state who are treated with an automated peritoneal dialysis (APD) scheme consisting of many short (e.g. 30 min) exchanges, can have a discrepancy between a normal Kt/V and a creatinine clearance < 40 litres/week. These patients often have clinical signs of underdialysis. All discussed data reveal that the emphasis on peritoneal solute clearances is a misconception, based on guidelines that were not evidence-based and that considered residual renal function to be equal to a dialysis clearance, thereby neglecting the fact that kidney function consists of more than just glomerular filtration.

Catheter complications

It is frustrating for patients and dialysis staff when a carefully planned start of PD training is disturbed by catheter problems. These include leakage and catheter dysfunction, the latter usually presenting as outflow obstruction. Leakage generally responds well to temporary interruption of PD, but catheter dysfunction is a more serious problem that usually needs surgical intervention.[35] Attempts to salvage the catheter are often postponed, which regularly leads to the urgent start of haemodialysis using a central venous catheter. All in all, catheter problems are still amongst the leading causes of early PD technique failure.[25,36-38]

Fortunately, this situation can be improved, but nephrologists will have to adopt an important role by investing in a local, multidisciplinary peritoneal access team. According to the International Society for Peritoneal Dialysis (ISPD) guideline for Peritoneal Access, this team should consist of surgeons, nurses and nephrologists.[39] However, as fluoroscopic wire catheter manipulation may also be used to rescue a non-functioning PD catheter (see below), it may be advisable to include an interventional radiologist. The goals of such a team would be to reduce the incidence of primary PD catheter failures, and to develop and maintain the skills and infrastructure needed to rescue a non-functioning PD catheter.

One study suggested that larger centre size is associated with less catheter dysfunction.[40] Unfortunately, the almost 45% reduction in the number of patients on PD in the Netherlands since 2002[1] has been accompanied by an increasing number of dialysis centres to 112 at present, many of these being small. The resulting reduction in the number of catheter insertions per centre must have reduced the surgical experience in catheter placement and salvage techniques, inducing a vicious circle of poor catheter outcomes, a defeatist attitude towards PD and low PD prescription. In the current situation, therefore, providing additional training in PD catheter insertion and salvage techniques seems mandatory. This need has been recognised in North America by the institution of a Peritoneal Dialysis University for Surgeons,[41] an initiative that was recently also introduced in Europe by the International Society for Peritoneal Dialysis (ISPD). Interestingly, a post-course analysis of this theoretical program revealed that it resulted in a considerable increase in the use of techniques that may improve catheter outcomes.[41] In the Netherlands, a PD catheter workshop for surgeons has been held in Maastricht for many years, and continuation of such a program would obviously be very helpful in the current situation. However, providing training in surgical PD catheter management will need time to become effective. For the short term, therefore, it may also be necessary to cluster PD catheter surgery in dedicated regional centres that have maintained relatively large PD patient populations. Such institutions could also serve as practical training centres for surgeons wishing to improve their PD catheter management skills.

The present ISPD guideline, which dates from 2010, recommends that '... local expertise at individual centres should govern the choice of method of PD catheter insertion' and does not recommend a specific catheter insertion method.[39] A more recent guideline approved by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) in 2014 contains a similar statement.[42] Nevertheless, a balanced and comprehensive literature review included in the latter guideline shows that dedicated surgical teams applying advanced forms of laparoscopy, including adhesiolysis, catheter tip suture fixation, preperitoneal tunnelling or omentopexy during insertion or combinations of the above, can obtain very low catheter dysfunction rates being in the region of only 0-10%. In accordance with this, a recent meta-analysis showed that laparoscopic PD catheter insertion is associated with a clinically relevant reduction in migration rate and a higher one-year catheter survival.[43] Interestingly, it has recently been suggested that, despite higher initial costs, laparoscopic PD catheter insertion may reduce the total costs due to fewer postoperative complications.[44] All in all, the literature clearly supports the view that advanced laparoscopic PD catheter insertion by dedicated surgical teams can help PD units struggling with high PD catheter dysfunction and failure rates. The guidelines mentioned earlier do not express a preference for a particular type of

PD catheter.[39,42] However, a recent meta-analysis showed that PD catheters with a straight intraperitoneal segment had a significantly better survival than those with a coiled tip, suggesting preferential use of straight catheters.[45]
Another promising method is the use of the self-locating catheter, featuring a tip with a 12-gram tungsten weight. A large non-randomised multicentre trial reported a marked reduction in the percentage of dislocations when comparing the self-locating catheter with Tenckhoff catheters, and superior two-year survival of the self-locating catheter.[46] A subsequent RCT comparing insertion of the straight Tenckhoff catheters with the self-locating catheter in 61 patients showed that reoperations for obstruction had to be performed in 22% of the Tenckhoff catheter insertions, but in none of the procedures involving the self-locating catheter.[47] In a larger RCT in 78 patients, the self-locating catheter had a significantly longer malposition-free survival rate than the straight Tenckhoff catheter.[48] The Tenckhoff catheter had a 4.5-fold increased probability of malfunction.[48] In these two studies, a surgical technique under local anaesthesia and sedation was used, but laparoscopic insertion with its additional advantages is also feasible.[49]
Finally a robust program has to be available to salvage malfunctioning PD catheters. An often neglected procedure that can be performed timely without general anaesthesia is wire manipulation under fluoroscopic control, which is quite often successful without major complications.[50-52] If this approach fails, the usefulness of laparoscopy, which allows repositioning of the catheter under direct vision and performing interventions, including adhesiolysis, relief of omental wrapping, catheter tip fixation, omentopexy or partial omentectomy, has been documented extensively.[53-55] In a recent study from the Netherlands, malfunction of PD catheters could be corrected by laparoscopy in almost 80% of cases.[56]
Improving catheter outcomes in PD patients in the Netherlands is possible, but this requires close cooperation between enthusiastic and optimistic nephrologists and surgeons who are willing to apply advanced laparoscopy for PD catheter insertion and salvage. Other methods to prevent catheter dysfunction may include the preferential use of catheters with a straight intraperitoneal segment or application of the self-locating catheter.

Infections

Dialysis procedure-related infections occur more often in PD patients than systemic infections.[57] These include exit-site infections, tunnel infections and peritonitis, and are an important reason for dropout from PD.[25] To reduce the incidence of PD-related infections, a number of prophylactic measures should be employed.
First, a single dose of an intravenous antibiotic should be administered prior to or at the time of PD catheter insertion or repositioning to reduce the risk of subsequent peritonitis.[58] A randomised controlled trial found that 1000 mg vancomycin intravenously before catheter insertion was superior to 1000 mg intravenous cefazolin.[59] However, this study was performed before 2000 and in the USA, where there is a different spectrum of antibiotic resistance. In addition, vancomycin has to be administered slowly to avoid the 'red man syndrome'. Furthermore, there is a risk of development of vancomycin-resistant microorganisms. In daily clinical practice a first-generation cephalosporin is most frequently used as prophylactic agent and is probably a good choice.
Second, patients must be trained to perform good hand hygiene while carrying out an exchange, to prevent touch contamination. Indeed, a multidisciplinary education program including retraining was associated with a lower peritonitis rate.[60] Home visits may be useful for detecting problems. Furthermore, each centre should have an appropriate protocol to deal with contamination to prevent the development of peritonitis.[61] Cultures of the PD effluent should be taken and prophylactic antibiotics should be prescribed if a PD solution is infused after contamination or if the catheter administration set is open and exposed to bacteria. Although there is no standard regimen for this situation, a single dose of intraperitoneal antibiotic could be given, for instance vancomycin with or without Gram-negative coverage. Positive culture results are helpful in the determination of subsequent therapy.
Third, all PD patients should use a topical antibiotic either at the exit site, intranasally, or both.[61] A systematic review showed that application of mupirocin at the exit site or intranasally reduced the risk of exit-site infections by 57% and of peritonitis due to all microorganisms by 41%. The risk reduction was even 70% for infections with *S. aureus*.[62] Topical application of mupirocin cream (2%) and gentamicin cream (0.1%) at the exit site were compared in an RCT in 133 patients.[63] The use of gentamicin was associated with lower rates of catheter infection and peritonitis. Gentamicin was as effective as mupirocin in preventing *S. aureus* infections but more effective in preventing Gram-negative peritonitis and *P. aaeruginosa* catheter infections. Unfortunately, the availability of gentamicin is limited in the Netherlands. In patients with a history of *P. aeruginosa* exit-site infection or in carriers of mupirocin-resistant *S. aureus*, prophylaxis with gentamicin cream may be warranted. Studies of other solutes than antibiotics are attractive to prevent the development of resistance. Regrettably, a recent RCT concluded that there is no role for medihoney in the prevention of PD-related infections.[64]
Fourth, prophylaxis to prevent fungal peritonitis should be considered in PD patients who are treated with a course of antibiotics for longer than a week. This was investigated in two RCTs. In the first RCT[65] 199 PD patients received

oral nystatin (500,000 units 4 times a day) whenever a course of antibiotics was prescribed, regardless of the indication for the antibiotic therapy. In the control group, no nystatin was routinely co-prescribed. Patients in the nystatin-treated group had a significantly higher *Candida* peritonitis-free survival after two years. A more recent RCT in 420 patients with bacterial peritonitis showed that administration of oral fluconazole 200 mg every 48 hours throughout the time they received antibiotics significantly prevented fungal peritonitis.[66] Given the mild side effect profile, nystatin may be a good choice.

Fifth, intravenous antibiotic prophylaxis is recommended to prevent peritonitis in PD patients undergoing invasive gastrointestinal and gynaecological procedures, including colonoscopy.[67] The optimal antibiotic regimen is unknown. A single dose of 1000 mg cefazolin intravenously combined with 500 mg metronidazole intravenously prior to the procedure is possibly a good choice. In all cases, the abdomen should be emptied of PD fluid before the procedure. Furthermore, oral antibiotic prophylaxis two hours prior to extensive dental intervention, for example 2000 mg amoxicillin, is also suggested to prevent peritonitis.[67]

Catheter infections can lead to subsequent peritonitis.[68] Therefore, early detection and prompt treatment with appropriate antibiotics is recommended.[67] Empirical antibiotic therapy should be based on patient history and centre-specific sensitivity pattern. In most cases, an oral agent can be given. Intraperitoneal vancomycin could be necessary if a *Corynebacterium* species is cultured that is resistant to oral antibiotics. This treatment should also be considered in case of refractory culture-negative exit-site infections, because *Corynebacterium* is sometimes difficult to isolate and not always recognised as a pathogen. Treatment must be continued until the exit site appears normal, but for at least two weeks.[67]

The very high incidence of peritonitis in the past has been reduced to less than one episode/patient year.[69] A target of 0.5 has been included in the ISPD guideline.[67] Abdominal pain and/or cloudy effluent are the presenting symptoms of peritonitis, but it should always be considered in PD patients with gastrointestinal symptoms. The diagnosis is confirmed by a PD effluent white blood cell count > 0.1 x 10^9/l or 100/µl after a dwell time of at least two hours with > 50% polymorphonuclear cells and/or a positive PD effluent culture.[67] In case of a short dwell time, a proportion of > 50% polymorphonuclear cells is highly suggestive for peritonitis, even if the white blood cell count is < 0.1 x 10^9/l. Although Gram's staining of the PD effluent is often negative, presence of yeast cells or pseudohyphae allows prompt initiation of antifungal therapy.

Empirical antibiotic therapy should start immediately and cover both Gram-positive and Gram-negative microorganisms. Intraperitoneal administration is generally preferred.[67] No antibiotic regimen has been proved to be superior to others as empirical therapy.[70] Gram-positive microorganisms can be treated with vancomycin or a first-generation cephalosporin and Gram-negative microorganisms by a third-generation cephalosporin or an aminoglycoside.

Culture reveals a Gram-positive, non-enterococcal microorganism in more than 50% of peritonitis episodes, with coagulase-negative staphylococci being the most common species.[69,71,72] Such episodes are mostly due to touch contamination. While most coagulase-negative staphylococci peritonitis episodes respond well to intraperitoneal antibiotic treatment and catheter removal is required in only 4% of cases,[69] relapsing peritonitis can occur suggesting biofilm formation. Intracatheter urokinase in combination with oral rifampicin could be considered in those cases to prevent catheter removal.[73] *S. aureus* peritonitis is frequently due to catheter infection, resulting in catheter removal.[74-76] This underscores the need for topical prophylaxis. *Corynebacterium* species should be treated with effective intraperitoneal antibiotics for three weeks to prevent a relapse.[77]

Gram-negative microorganisms are cultured in 20-30% of all PD-related infections. *Pseudomonas* species and *Enterobacteriaceae* are the most relevant pathogens.[69,71,72] While *Pseudomonas* species are considered to be 'water' bacteria, especially known for causing pulmonary infections, *Enterobacteriaceae* are labelled as enteric microorganisms with *E. coli*, *Klebsiella*, *Serratia*, and *Enterobacter* species as typical representatives. Peritonitis caused by these Gram-negative microorganisms is associated with a high catheter removal rate, approaching 40%[69] and therefore a high technique failure rate. Therefore, the ISPD advises to treat *Pseudomonas* peritonitis with two antibiotics with different modes of action for which the microorganism is sensitive, for instance intraperitoneal gentamicin or oral ciprofloxacin combined with intraperitoneal ceftazidime.[67] Recently, a study from the Netherlands showed that the poor outcome of peritonitis caused by enteric microorganisms in PD patients aged > 50 years could be improved by applying a treatment protocol involving temporary discontinuation of PD without catheter removal (peritoneal rest) and intravenous and intracatheter meropenem.[72] This Mero-PerRest protocol resulted in a cure rate of 90%, a lower catheter removal rate of 4%, and a better technique survival of 90%. These figures are far superior to the results of a more traditional intraperitoneal gentamicin-rifampicin based regimen. The Mero-PerRest protocol was most effective in patients with polymicrobial enteric peritonitis and also in peritonitis episodes caused by non-enteric microorganisms.

In case of fungal peritonitis the ISPD recommends immediate catheter removal, resulting in a high technique failure rate.[67] Therefore, antifungal prophylaxis is recommended. In case of *Candida albicans*, catheter removal can sometimes be prevented by treatment with intraperitoneal administration of amphotericin B and 5-flucytosine.[78] Similar results have been reported more recently with intracatheter instillation of amphotericin B as a catheter lock after each CAPD exchange combined with intraperitoneal fluconazole and oral flucytosine.[79]

In summary, PD-related infections are still encountered, but are usually a manageable problem. Unconventional treatment strategies such as peritoneal rest and antibiotic catheter locks could contribute to improving technique survival.

Functional assessment of the peritoneum as dialysis membrane

Overhydration is probably the most important risk factor for death in peritoneal dialysis patients.[80] Yet, assessment of the transport function of the peritoneum used as a dialysis membrane, has mainly focused on small solute clearances. A standardised test for functional peritoneal assessment, the peritoneal equilibration test (PET), was published in 1987 and has been widely promoted ever since.[81] The PET consists of a four-hour dialysis exchange with a 2.27% glucose-based dialysis solution and a blood sample. Calculated parameters after drainage include the dialysate/plasma concentration ratio (D/P) of creatinine, the ratio of the dialysate glucose concentration before inflow (D0) and after drainage (Dt/D0), and net ultrafiltration being the difference between the drained and the instilled volume. D/P creatinine is dependent on the number of perfused peritoneal microvessels. Therefore it represents the effective peritoneal surface area. Ultrafiltration failure is an important, but not the only factor that can lead to overhydration. Mismatches between fluid intake, urine production and peritoneal fluid removal are common causes of overhydration. The 2.27% glucose may not be ideal for assessment of ultrafiltration capacity, because it only induces a limited quantity of ultrafiltrate. Consequently the arousal (incomplete drainage) may overwhelm the signal (ultrafiltered volume). The 3 x 4 rule is considered the best parameter for the presence of ultrafiltration failure.[82] According to this rule, ultrafiltration failure is present when net ultrafiltration is less than 400 ml after a four-hour dwell with a 3.86%/4.25% glucose dialysis solution. Longitudinal data from the Netherlands showed that ultrafiltration failure, as defined by the 3 x 4 definition, developed in <4% of patients within two years after starting PD, but in 21% at some time after more than two years.[83]

Investigations on net ultrafiltration assume that fluid transport occurs through a system of pores of uniform size within the vascular wall. Already in 1969 it became evident that the dialysate Na^+ concentration decreased in the initial phase of exchanges with very hypertonic dialysis solutions, i.e. 3.86% glucose or higher.[84] It took more than 30 years to demonstrate that this dilutional phenomenon was caused by the peritoneal water channel aquaporin-1 (AQP-1).[85] Glucose-induced crystalloid osmosis is required for free water transport (FWT) without transfer of solutes. Ultrafiltration during the first hour of a dwell usually consists of 40% FWT and 60% fluid transport through the so-called interendothelial small pores, which also allow transport of small solutes, such as urea, creatinine and glucose.[86] FWT is decreased in some long-term patients and extremely low in those with encapsulating peritoneal sclerosis (EPS).[83,87] The determination of FWT in long-term patients might identify those with extensive peritoneal fibrosis.[88] A simple calculation of FWT in patients is possible with the use of a one hour of 3.86% glucose exchange. Fluid transport together with Na+ transport is calculated as Na+ clearance. Subtraction of this from net ultrafiltration gives FWT.[89,90] However D/P and Dt/D0 ratios cannot be interpreted. This problem is solved with the modified (3.86% glucose instead of 2.27%) PET with temporary drainage after one hour for weighing and sampling, followed by reinfusion and final drainage after four hours (MoPET 1/4).[91] It follows from the abovementioned data that modern peritoneal dialysis should include regular measurement of peritoneal function, especially parameters of fluid transport. The MoPET 1/4 provides the best information that can be achieved in clinical practice.

Encapsulating peritoneal sclerosis

EPS is a clinical entity defined by signs and symptoms of (intermittent) bowel obstruction caused by excessive fibrosis of the visceral peritoneal membrane constricting the intestines. Although rare, it is a feared complication of PD as morbidity is high and mortality within the first year after diagnosis is on average 40%.[92] The number of patients who developed EPS has varied in time and between countries from 0.7-3.3%.[92] Duration of PD is by far the major determinant of the risk for the development of EPS.[93] For instance, in most case series and registries the occurrence of EPS in patients treated with PD for three years was almost absent. However, the incidence has been reported to rise with increasing time on PD to values of more than 10% in patients treated with PD for > 8 years.[94] Relatively recently, EPS was also documented as a complication in former PD patients relatively shortly after kidney transplantation. This has been coined

post-transplantation EPS and is in general less severe and associated with a substantially better patient survival.[95,96]
The current view on the pathogenesis of EPS distinguishes this entity from simple sclerosis of the peritoneal membrane, which is a limited fibrotic response to the exposure to conventional peritoneal dialysis fluids that contain not only extremely high glucose concentrations, but also glucose degradation products, and are acidic. Instead, EPS is a condition with much more extensive and dense collagenous peritoneal interstitial tissue, sometimes characterised by infiltration with helper T lymphocytes and type 2 macrophages, merging into a severe and advanced fibrotic response.[97,98] The growth factors CCN2, TGFβ and VEGF are key players.[99] The presence of an inflammatory reaction is also evidenced by activation of T cells[100] and the description in some studies of elevated concentrations of several markers of inflammation in the blood, such as C-reactive protein and soluble CD25. Also an increased dialysate interleukin-6 has been reported before the clinical diagnosis of EPS.[101-103] At present, it is not known why the peritoneal membrane of some PD patients responds with increased chronic inflammation and excessive fibrosis to long-term exposure to PD fluids.
Ultrafiltration failure is present in all EPS patients, but only 20% of patients with late ultrafiltration failure develop EPS.[104] Therefore, the presence of late ultrafiltration failure is not a predictor of EPS. The most striking abnormality in and before the condition, is a marked reduction of FWT,[83,87] which is an early sign of imminent EPS, as judged from its high discriminative power of 0.82.[104] A cut-off value of FWT < 75 ml in the first 60 minutes of a 3.86% glucose dwell is the best predictor of EPS.[104] In contrast, signs of EPS on abdominal imaging are usually only found late in the disease process.[105,106]
An important notion of the last decade is that EPS is no longer a condition without potentially therapeutic options. Especially tamoxifen and steroids are now considered an important first step in medical treatment.[107] When patients remain dependent on parenteral feeding or have a bowel perforation, surgeons specialised in EPS may perform peritonectomy and enterolysis (PEEL) with impressively good results.[108] In particular, patients with localised EPS are amenable to surgery.[109]
The risk for EPS was seen by many nephrologists in the Netherlands as an important factor to take into account when deciding to offer PD instead of haemodialysis.[110] In fact, this may have been fuelled by an unexpected rise in EPS cases documented between 1998 and 2005.[111] For this reason, the Dutch EPS Registry was started in 2009 with the goal to register all EPS cases in the Netherlands.[110] A recent analysis showed a significant decline by at least six-fold in the yearly incidence of EPS from 0.85% in 2009 to 0.14% in 2014. A clear explanation for this observation was not identified. However, this trend is strikingly similar to the decline in EPS prevalence recently reported from Japan and Germany.[112,113] The prevalence of EPS after eight years of PD treatment in Japan has fallen to 2.3%.[112] This may have been the result of the increased use of biocompatible solutions and glucose-sparing dialysis schedules.[112,114] Indeed, a recent study from Spain showed that the use of biocompatible PD solutions was associated with better preservation of the mesothelial layer, less thickening of the submesothelial compact zone, and less hyalinising vasculopathy.[115] Also, the incidence of post-transplantation EPS seems currently low. In a recent Dutch prospective study, no cases of post-transplantation EPS were found in PD patients undergoing kidney transplantation between 2009 and 2013.[116] This is probably for the greatest part explained by the average PD duration of 31 months in this cohort, reflecting the current kidney transplantation policy in the Netherlands.
At present, EPS should be considered a rare complication of PD in the Netherlands for which therapeutic interventions exist, specifically tamoxifen and PEEL by experienced surgeons. Given the severity of the condition, a high awareness for EPS remains needed, for instance by the measurement of FWT in long-term patients, but the risk for EPS should not be a reason to refrain from starting PD or to avoid transplantation of PD patients.

CONCLUSIONS

The decline of PD in the Netherlands cannot be explained by medical reasons. Whatever the causes, it has resulted in a downward spiral where loss of experience and insufficient knowledge on important pathophysiological and other related pertinent issues of this home dialysis modality have resulted in an almost exclusive attention to haemodialysis. This happened while it is now evident that patient survival on PD is at least similar or even better than that on haemodialysis, also in the long-term. To change the tide, the quality of education of patients, nurses and doctors needs updating. The above review is an effort by a group of professionals involved in peritoneal dialysis to revitalise the interest of the Nephrology and Internal Medicine communities in up-to-date PD. Important conclusions are that patient education can be improved, that PD leads to better preservation of residual kidney function, that the value of small uraemic toxin removal is less important than good management of the hydration state of patients, that peritonitis is a manageable problem, that EPS is a lesser problem than it used to be, and that imminent EPS can be identified before the clinical signs and symptoms appear. Therefore it can be concluded that PD is an excellent chronic dialysis modality that deserves a larger penetration than is currently present.

DISCLOSURES

None of the authors has anything to disclose.

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ORIGINAL ARTICLE

Association between serum 25(OH) vitamin D and metabolic disturbances in polycystic ovary syndrome

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ABSTRACT

Background: To assess the relationship between serum 25(OH) vitamin D levels and metabolic parameters together with androgenic hormone levels in women with polycystic ovary syndrome (PCOS).

Methods: This is a single-centre study from the Endocrinology Institute at Firouzgar Hospital in Iran. Seventy-three women aged 15-45 years were recruited from May 2013 to December 2013. Serum 25(OH) vitamin D level, other laboratory biomarkers and anthropometric indexes were measured. Data were analysed with statistical software SPSS version 16.0 for windows and we used specific analytical tests to assess data.

Results: Serum 25(OH) vitamin D levels were < 20 ng/ml in 64 patients (79%). Nine patients (12.3%) were diagnosed with metabolic syndrome. A significant difference was found between the women with and without severe vitamin D deficiency with regard to waist circumference, fasting insulin level and HOMA-IR, and abnormal systolic and diastolic blood pressures. The serum 25(OH) vitamin D levels had a reverse but weak correlation with systolic and diastolic blood pressures.

Conclusion: This study showed an association between serum 25(OH) vitamin D levels and some metabolic parameters; however, there was no significant linear correlation between serum 25(OH) vitamin D levels and metabolic variables, except for systolic and diastolic blood pressure.

KEYWORDS

Vitamin D, polycystic ovary syndrome, metabolic syndrome, body mass index

INTRODUCTION

Polycystic ovary syndrome (PCOS) has been recognised as the most common endocrine disorder among women in reproductive age with an overall prevalence of 5-10%.[1,2] This syndrome is characterised according to the Rotterdam criteria with the presence of at least two of three diagnostic criteria including a) lack of or reduced ovulation (with amenorrhoea or oligomenorrhoea), b) clinical symptoms and/or biochemical hyperandrogenism and c) the presence of polycystic ovaries on ultrasound examination. In recent years, it was found that the syndrome is frequently associated with the increased risk of cardiovascular disease, impaired glucose tolerance and risk of type 2 diabetes and lipid abnormalities.[3-5]

Vitamin D, a fat-soluble vitamin, can be produced in two ways: by intestinal absorption and endogenous synthesis from a precursor of 17-hydroxyl cholesterol on the skin with sufficient exposure to ultraviolet sunlight. Most references consider a serum 25(OH) vitamin D of < 20 ng/ml as vitamin D deficiency.[6,7] Some studies have suggested that there is an association between serum levels of vitamin D and obesity and also other metabolic parameters in women with PCOS, including fasting glucose levels, fasting insulin, insulin resistance, high blood pressure, lipid disorders, fertility and other clinical and laboratory-related parameters associated with PCOS.[6-13]

Given the high prevalence of vitamin D deficiency in the population, especially in the population of women with PCOS, as well as evidence from recent studies indicating a link between vitamin D levels with some markers and laboratory parameters related to PCOS and also due to heterogeneous and controversial results from the studies,[14-16] we aimed to assess the relationship between the serum level of 25(OH) vitamin D and metabolic parameters

and levels of androgenic hormones in women with PCOS in a different demographic and geographical context.

MATERIALS AND METHODS

Ethical approval

The study was approved by the ethics committee of Iran University of Medical Sciences. Written informed consent was obtained for all patients. The study was carried out according to the principles of the Declaration of Helsinki.

Study participants

This cross-sectional study was performed at the Endocrinology Institute of Firouzgar Hospital in Iran from May 2013 to December 2013. Included were 73 women aged 15 to 45 years with the diagnostic criteria of PCOS (Rotterdam Criteria 2003) who were selected from 120 patients referred to the PCOS clinic at the institute. The exclusion criteria were pregnancy, history of chronic disorders such as liver or kidney diseases, diabetes mellitus, hypothyroidism, congenital adrenal hypoplasia, Cushing's syndrome, hyperprolactinaemia, androgen-secreting tumours, history of using vitamin D supplements within three months ago, or use of any medication influencing endocrine parameters.

Data collection

A blood sample was taken from peripheral blood (after 8-12 hours of fasting) to measure serum levels of 25(OH) vitamin D, total testosterone, dehydroepiandrosterone sulphate (DHEAS), sex hormone-binding globulin (SHBG), fasting glucose, and lipid profile at a single laboratory. The serum levels of 25(OH) vitamin D (IDS kit, Germany), fasting insulin, total testosterone, DHEAS, and SHBG (DIAMETRA kit, Italy) were assessed by the ELISA technique. The levels of triglyceride and total cholesterol (Pars Azmoon kit, Iran), and fasting blood sugar (ZistShimi kit, Iran) were assessed by the enzymatic method. In addition, serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels (ZistShimi kit, Iran) were measured by the direct method. The body mass index (BMI) was measured by dividing the mass by the square of the body height. The insulin resistance index and free androgen index were calculated using the following formula:

$$\text{HOMA-IR} = [\text{Fasting Insulin } (\mu\text{IU/l}) \times \text{FBS(mg/dl)}] / 405$$

$$\text{FAI (free androgen Index)} = [\text{total testosterone (nmol/lit)}/\text{SHBG(nmol/lit)}] \times 100$$

Hirsutism score was classified based on the Freeman Galway Score. It represents the hair growth score in nine parts of the body. A score of more than 8 was defined as positive. Also, metabolic syndrome was diagnosed based on the Adult Treatment Panel III (ATP III) guidelines. All information obtained from history taking, physical examination, and also para-clinical measures was entered in a checklist. Written informed consent was obtained from all the patients in the study and they were assured that all information would remain confidential.

Data analysis

The results are presented as mean (± SD) for quantitative variables and were summarised by absolute frequencies and percentages for categorical variables. Normality of data was analysed using the Kolmogorov-Smirnoff test. Categorical variables were compared using the χ^2 test or Fisher's exact test when more than 20% of cells with an expected count < 5 were observed. Continuous variables were compared using the t test. Whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the group, the Mann-Whitney U test was used. Association between quantitative indices was determined using the Pearson's or Spearman's correlation tests. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. Statistical analysis was considered to be statistically significant at $p < 0.05$.

Results

Among the 73 participants in the present study, the serum level of 25(OH) vitamin D was < 20 ng/ml in 64 (78.7%), while 50 (68.5%) had the level of < 10 ng/ml. In the remaining subjects, 7 (9.6%) had insufficient 25(OH) vitamin D (20-29 ng/ml) and only 2 patients (2.7%) had a normal 25(OH) vitamin D ≥ 30 ng/ml. In this study, 25 patients (34.2%) were married, the others were single; the difference in 25(OH) vitamin D between married and single women was not significant (10.3 ± 6.3 ng/ml versus 10.8 ± 8.0 ng/ml, $p = 0.73$). Also, 52 patients (71.2%) had a college degree; the difference in 25(OH) vitamin D between those with and without a college degree was not significant either (10.9 ± 8.0 ng/ml versus 9.9 ± 5.9 ng/ml, $p = 0.74$). Among the women with and without vitamin D deficiency, waist circumference, systolic blood pressure, diastolic blood pressure, LDL-C and SHBG were significantly different between the two groups (*table 1*).

With regards to the high prevalence of severe vitamin D deficiency, the baseline characteristics were compared between women with and without severe deficiency, indicating a significant difference in waist circumference, fasting insulin levels, homeostatic model assessment-

Table 1. *Clinical, biochemical and endocrine characteristics among patients with and without vitamin D deficiency*

Variable	PCOS patients (total)	Vitamin D deficiency (≤ 20 ng/ml) Mean (± SD) (N = 64)	Without vitamin D deficiency (> 20 ng/ml) Mean (± SD) (N = 9)	P-value
Clinical variables				
BMI (kg/m²)	26.9±6	27.3±6.1	24.1±4.2	0.14
Waist circumference (cm)	88.3±12.9	89.3±13.4	81.3±6.3	0.01
Systolic BP (mmHg)	105±10.6	106.3±10.5	96.1±6.5	0.002
Diastolic BP (mmHg)	71.6±6.8	72.6±6.5	65±5	0.001
Hirsutism (FGS)	10.9±4.5	4.6±11.1	3.7±9.6	0.35
Metabolic biochemical variables				
FBS (mg/dl)	87.3±8.6	8.4±87.0	89.0±10.5	0.53
Fasting insulin (µU/ml)	11.8±7.2	7.4±12.0	10.0±5.0	0.42
HOMA-IR	2.7±2.3	2.4±2.8	2.2±1.2	0.53
Total cholesterol (mg/dl)	170.4±33.6	34.3±172.6	154.9±24.2	0.14
Triglyceride (mg/dl)	105.3±49.3	50.2±106.7	95.3±43.0	0.72
HDL (mg/dl)	37.7±10.0	9.5±37.4	39.0±13.6	0.67
LDL (mg/dl)	82.3±22.1	22.9±83.7	72.3±11.7	0.03
Endocrine biochemical variables				
Total testosterone (ng/l)	1.03±0.46	0.97±1.04	0.97±0.45	0.53
DHEAS (µg/dl)	306.8±142.0	127.1±296.3	381.7±216.9	0.57
SHBG (nmol/l)	41.1±23.0	20.5±38.9	56.6±33.4	0.03
FAI	11.9±9.5	9.9±12.4	8.5±5.9	0.17

BMI = body mass index; BP = blood pressure; FGS = Freeman Galway score; FBS = fasting blood sugar; HOMA-IR = homeostatic model assessment-insulin resistance; HDL = high-density lipoprotein, LDL = high-density lipoprotein; DHEAS = dehydroepiandrosterone sulphate; SHBG = sex hormone-binding globulin; FAI = free androgen index.

insulin resistance (HOMA-IR), and systolic and diastolic blood pressures. After adjusting for BMI and waist circumference, the difference only remained significant for systolic blood pressure and diastolic blood pressure (p = 0.04, p = 0.03 respectively).

Nine patients (12.3%) were diagnosed to have metabolic syndrome; despite the lower level of 25(OH) vitamin D in patients with metabolic syndrome than in those without this syndrome, this difference remained insignificant (8.6 ± 2.5 ng/ml versus 10.9 ± 7.9 ng/ml, p = 0.91). In the patient with metabolic syndrome, HDL-C < 50 mg/dl was the most frequent criteria (86.3%).

In our study, 41 women with PCOS (56.2%) were overweight (BMI ≥ 25 kg/m²) and 32 women were normal weight. The difference in clinical and biochemical markers between the PCOS women with and without overweight is summarised in *table 2*. In this context, the serum level of 25(OH) vitamin D in these women with PCOS had an adverse but weak correlation with systolic and diastolic blood pressures, but no significant correlation was revealed between 25(OH) vitamin D and other baseline parameters (*table 3*).

DISCUSSION

In recent years, several studies have been performed to examine the relationship between clinical features and laboratory findings (metabolic and endocrine) and serum levels of vitamin D status in patients with PCOS. Although there is no general agreement on the cut-off point for vitamin D to define deficiency or insufficiency, according to existing guidelines, serum 25(OH) vitamin D < 20 ng/ml is considered as vitamin D deficiency, 20-29 ng/ml as insufficiency, and also the values < 10 ng/ml as severe deficiency.[7-17] In this regard, in our study population,

Table 2. *Clinical, biochemical and endocrine characteristics in women with PCOS according to BMI*

Variable	BMI ≥ 25 (N = 41) Mean (±SD)	BMI ≤ 25 (N = 32) Mean (±SD)	P-value
Clinical variables			
Age (year)	26.2±6.4	24.1±5.5	0.15
Waist circumference (cm)	96.0±11.5	78.5±6.2	**0.00**
Systolic BP (mmHg)	108.4±11.7	100.6±6.9	**0.003**
Diastolic BP (mmHg)	73.8±7.3	68.9±4.9	**0.004**
Hirsutism (FGS)	10.8±4.7	10.9±4.3	0.89
Metabolic biochemical variables			
25(OH)D (ng/ml)	9.3±5.0	12.3±9.5	0.29
FBS (mg/dl)	87.5±8.4	87.0±9.1	0.82
Fasting insulin (µU/ml)	13.9±7.8	5.3±9.1	**0.004**
HOMA-IR	3.0±1.7	1.3±2.0	**0.006**
Triglycerides (mg/dl)	122.6±51.4	34.8±81.6	**0.00**
Total cholesterol (mg/dl)	177.6±33.9	31.3±161.3	**0.04**
HDL-C (mg/dl)	39.4±10.2	9.4±35.4	0.09
LDL-C (mg/dl)	84.5±20.4	24.1±79.6	0.36
Endocrine biochemical variables			
Total testosterone (ng/ml)	1.02±0.44	0.48±1.04	0.82
SHBG (nmol/l)	290.1±139.5	140.0±335.8	0.15
DHEAS (µg/dl)	32.2±19.2	23.6±51.3	**0.00**
FAI	14.3±10.8	6.4±9.1	**0.02**

BMI = body mass index; BP = blood pressure; FGS = Freeman Galway score; FBS = fasting blood sugar; HOMA-IR = homeostatic model assessment-insulin resistance; HDL = high-density lipoprotein, LDL = high-density lipoprotein; DHEAS = dehydroepiandrosterone sulphate; SHBG = sex hormone-binding globulin; FAI = free androgen index.

68.5% had severe 25(OH) vitamin D deficiency, 78.7% had 25(OH) vitamin D deficiency, 9.6% had 25(OH) vitamin D insufficiency, and only 2.7% had a normal level of 25(OH) vitamin D.

In a study by Wehr et al. on Austrian PCOS women, 2.9% had severe 25(OH) vitamin D deficiency and in total 38.8% had 25(OH) vitamin D deficiency.[12] In another study by Li et al. on English PCOS women, 25(OH) vitamin D deficiency was revealed in 72.0%.[17] The wide difference observed in the studies might be due to the difference in climate, food and cultural habits (such as differences in the type of coverage) as well as in the methods used to measure serum levels of vitamin D and quality of laboratory kits.

Our study showed that the values of some clinical and biochemical parameters, including waist circumference, systolic and diastolic blood pressures and serum levels of LDL-C, were significantly higher in women with vitamin D deficiency (compared with women without deficiency), while the former group had lower levels of SHBG. Moreover, after dividing the study population into two groups of PCOS women with and without severe vitamin D deficiency, it was shown that the levels of fasting insulin and HOMA-IR, and blood pressure were significantly higher in women with severe vitamin D deficiency than in the other group before adjustment for BMI and waist circumference, but after adjusting for these variables, the difference only remained for systolic and diastolic blood pressures.

In most similar studies, a significant relationship was identified between low vitamin D levels and increased levels of glucose and fasting insulin and HOMA-IR in patients with PCOS.[11-17] Although the exact mechanism underlying the association between low levels of vitamin D and insulin resistance is unknown, researchers in this field have proposed several possible mechanisms. First, vitamin D may have a stimulatory effect on the appearance

Table 3. *Correlation between serum level of 25(OH)D and clinical/biochemical parameters of women with PCOS*

Variables	r	P value
Age (year)	0.07	0.54
Weight (kg)	-0.003	0.98
Height (cm)	0.11	0.36
BMI (kg/m²)	-0.41	0.73
Waist circumference (cm)	-0.11	0.34
Systolic BP (mmHg)	-0.30	0.01
Diastolic BP (mmHg)	-0.26	0.03
Hirsutism (FGS)	-0.16	0.18
FBS (mg/dl)	0.03	0.77
Fasting insulin (µU/ml)	-0.18	0.13
HOMA-IR	-0.15	0.22
Triglyceride (mg/dl)	-0.04	0.75
Total cholesterol (mg/dl)	0.14	0.22
HDL-C (mg/dl)	0.11	0.36
LDL-C (mg/dl)	-0.18	0.12
Total testosterone (ng/ml)	-0.014	0.91
SHBG (nmol/l)	0.004	0.98
DHEAS (µg/dl)	-0.02	0.84
FAI	0.02	0.86

BMI = body mass index; BP = blood pressure; FGS = Freeman Galway score; FBS = fasting blood sugar; HOMA-IR = homeostatic model assessment-insulin resistance; HDL = high-density lipoprotein, LDL = high-density lipoprotein; DHEAS = dehydroepiandrosterone sulphate; SHBG = sex hormone-binding globulin; FAI = free androgen index.

of the insulin receptor and consecutively the increase in insulin response and glucose transport into cells. Second, vitamin D may regulate intracellular and extracellular calcium, which has a major role in intracellular processes related to insulin function in insulin responsive tissue such as skeletal muscle and adipose tissues. Also, vitamin D has a modulating effect on the immune system so hypovitaminosis D may increase the immune response that is associated with insulin resistance.[18,19] Also, the possibility of malfunction in the β cells in women with PCOS has been raised as another possible mechanism.[20-22]

In our study, 12.3% of the PCOS patients suffered from metabolic syndrome; according to the mean age of our population (25.3 ± 6.1 years), this frequency can be interpreted homogeneously and is in line with previous studies in the general population. So, in the study on the adult population in Iran, the overall prevalence of metabolic syndrome was 42% in women as 9.3% in the age group 20 to 29 years, 24.3% in the age group 30 to 39 years, and 48.3% in the age group 40 to 49 years.[23] Also, in the Wehr and Vural survey, the prevalence of metabolic syndrome in PCOS women aged 16 to 41 years and 18 to 22 years was 12.2% and 11.0%, respectively.[12,24]

In our study, similar to some previous studies, no significant association was found between serum levels of vitamin D and clinical and biochemical parameters of hyperandrogenism such as total testosterone, DHEAS, SHBG and the free androgen index.[11,12,17]

The study found that women with PCOS and BMI ≥ 25 kg/m² compared with women with a normal BMI had a higher mean waist circumference, triglycerides, total cholesterol, fasting insulin, HOMA-IR, blood pressure and also a lower mean SHBG, but contrary to some previous studies, no difference was found in mean serum vitamin D between the two subgroups of BMI, which might be due to the small sample size.[8-10]

Similar to some other studies on the general population and in women with PCOS, mean systolic and diastolic blood pressures in those with vitamin D deficiency was higher than those without deficiency with an adverse correlation between the level of vitamin D and blood pressures. Some laboratory investigations have shown that 1,25(OH)2 vitamin D can prevent the formation and increase of renin in the juxtaglomerular apparatus and subsequently cause adverse endocrine effects on the renin-angiotensin-aldosterone system. Also, this active metabolite can affect blood pressure by inhibiting the proliferation of smooth muscle cells of the vessel wall.[25-28]

In several studies, the effect of vitamin D supplementation in reducing blood pressure in the general population and also in specific groups has been examined leading controversial results.[29-31] For instance, in a study by Larsen et al. on 112 hypertensive patients receiving cholecalciferol (3000 IU/day), it was indicated that following administration of these supplements for 20 weeks, despite the lack of a significant reduction in 24-hour blood pressure in those receiving supplements (compared with placebo), the subgroup of patients with an insufficient level of vitamin D had a better response to supplementation of vitamin D and also experienced a 3.4 mmHg decrease in blood pressure compared with the baseline value.[29]

One limitation of this study is the small sample size, which may have provided inadequate statistical power to detect some meaningful associations as statistically significant. Hence, the genuine validity of our findings will need to be confirmed in larger replication studies.

This study does not include a control group. Thus, we are not able to correlate the effects of low 25(OH) vitamin D levels with the metabolic profile of PCOS women specifically or with that of obese women in general. However, we performed subgroup analyses of lean and

obese PCOS women with different 25(OH) vitamin D levels to address this limitation.

CONCLUSION

In our study, it was found that a high percentage of PCOS women were vitamin D deficient. The study also showed a significant difference in the values of some clinical and metabolic parameters such as waist circumference, systolic and diastolic blood pressure, LDL-C, fasting insulin, HOMA-IR and SHBG between PCOS women with and without vitamin D deficiency; however, no linear correlation was found between serum levels of vitamin D and baseline variables, except for systolic and diastolic blood pressures. Also, due to the need for assessing the causality relation and to determine the effect of vitamin D on these parameters, it is necessary to perform further randomised clinical trials in these patients.

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DISCLOSURES

We declare that the authors have no conflict of interest.

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ORIGINAL ARTICLE

Microbiological outcomes and antibiotic overuse in Emergency Department patients with suspected sepsis

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ABSTRACT

Objective: To study the presence of bacterial disease and antibiotic use in patients in the emergency department (ED) included in the local sepsis protocol.

Methods: An observational retrospective cohort study. Adults aged > 18 years, presenting to the ED of a large teaching hospital, from 1 January to 1 June 2011, with more than two SIRS criteria and a clinical suspicion of sepsis were included.

Results: Bacterial disease was suspected or confirmed in only 71% of all the patients with suspected sepsis (2008 definition) and consequently treated with antibiotics. Most of these patients (58%) suffered from systemic inflammatory response syndrome (SIRS) without signs of organ dysfunction, hypotension or hypoperfusion. Despite absence of bacterial disease in 29% of the patients after rigorous diagnostics, median antibiotic treatment in this group was still seven days (IQR 4-10).

Conclusions: Standard sepsis detection using SIRS criteria and clinical suspicion identified patients with suspected or confirmed bacterial disease in 71% of the cases. A significant proportion of patients were exposed to prolonged antibiotic use without proof of bacterial disease. This study illustrates the difficulties in correctly identifying bacterial disease and sepsis, and shows that overuse of antibiotics may be the consequence.

KEYWORDS

Sepsis, SIRS, anti-infective agents, antibiotics, inappropriate subscribing, stewardship

INTRODUCTION

Over the last decade, sepsis has been increasingly recognised as a major cause of death. After Rivers' publication and the start of the Surviving Sepsis Campaign, early detection and treatment has become a general endeavour with a special focus on the early administration of antibiotics.[1] It should be noted that current evidence regarding early treatment with antibiotics was founded on studies including only patients with severe sepsis (mostly needing ICU treatment) or septic shock.[1-4] However, in the effort to avoid delays in identifying sepsis many emergency departments (EDs) have started using the criteria of systemic inflammatory response syndrome (SIRS) and a clinical suspicion of infection as a way to screen their patients. The difficulty in identifying severe sepsis is that testing for organ damage (for example: renal function) takes time, whereas the recommendation is to treat severe sepsis within one hour (2012 Sepsis Guidelines[5]). Under the presumption that this waiting time may harm the patient, patients are increasingly treated with antibiotics without awaiting (all) the test results.

The Surviving Sepsis Guidelines of 2004 recommended administration of antibiotics in patients with severe sepsis or septic shock. The 2008 guideline did not give guidance as to how patients should be screened, but the 2012 guideline recommended screening of potentially infected seriously ill patients. The proposed instrument to screen for severe sepsis was an instrument based on SIRS criteria and clinical judgment, which was, however, only validated in ICU patients.[3]

From the very start, the SIRS criteria were criticised as defining condition for sepsis and recent publications refuelled the discussion.[6-8] In February 2016, sepsis was redefined, removing the SIRS criteria and adding that the

term sepsis had to be reserved for patients with severe organ dysfunction. The term 'severe' sepsis was dismissed and replaced by sepsis-3 and septic shock.[9] However, SIRS criteria are still in use in clinical practice.

This study was undertaken to evaluate current practice and study the likelihood of bacterial infection in patients treated for sepsis in the ED according to the SIRS criteria. To address issues regarding antimicrobial stewardship, duration of antibiotic therapy was also evaluated.

METHODS

Study design and setting

A retrospective analysis was conducted using a cohort of consecutive adult patients presenting to the ED of the Albert Schweitzer Hospital (a large teaching hospital in Dordrecht, the Netherlands) from 1 January to 30 June 2011.

Inclusion

Patients diagnosed with sepsis (2008 definition) according to two or more SIRS criteria and a clinical suspicion of an infection, as assessed by the resident or ED physician, who received antibiotics upon admission were eligible.

Data collection

Data regarding vital parameters were extracted from the standard protocol form if completely filled out. All additional and missing data were extracted by hospital chart review. If more than one measurement of parameters was done in the ED, the most aberrant measurement was used in the analysis (the lowest BP recorded in the ED, or the highest respiratory rate or pulse). The primary investigator, as well as authors Spruyt and Huisman, performed the data extraction. The primary investigator then checked the data and in case of doubt regarding the primary outcome measures the case was discussed between the primary investigator and Dr. Levin until consensus was reached. Consensus was reached in all 37 patients that were discussed.

Definitions

The definitions for SIRS, sepsis, severe sepsis, sepsis-induced hypotension and septic shock were derived from the guidelines of the Surviving Sepsis Campaign in 2008. For the sake of clarity, in this article sepsis conform the old criteria will be referred to as sepsis and if referring to the new definition, sepsis-3 will be used.

The criteria to define confirmed or suspected bacterial infection were derived from an article by Limper,[10] as displayed in *figure 1*. In addition to these criteria another criterion, as found in previous literature, was added for further clarification of suspected bacterial disease: 'Clinically documented infection: presence of gross purulence or an abscess (anatomical and/or by imaging and/or histological evidence), which may not be microbiologically documented if the culture remains sterile due to antibiotic therapy.'[11]

Outcome measures

Primary outcome measures were the number of patients with confirmed or suspected bacterial infection as assessed by the primary investigator using predefined criteria (stated above) and days of antibiotic use in these patients. Secondary outcome measures were severity of sepsis, rate of ICU admission, and mortality.

Data analysis

Results are expressed as mean ± standard deviation (SD), or median ± inter-quartile range (IQR) depending on normality of the data. Comparison between patients with and without bacterial infection was performed using the χ^2 test for categorical variables and the Students t-test (equal variances) or nonparametric Mann-Whitney U test for continuous data with non-normality. Statistical analyses were carried out using IBM SPSS 22.0.0 for OSX (SPSS, Chicago, IL). Missing data were excluded list-wise.

Ethics

The local institutional ethics review board approved the study design and a waiver for the retrieval of informed consent was obtained.

RESULTS

Patients and likelihood of bacterial infection

From 1 January 2011 to 30 June 2011, a total of 269 patients were diagnosed with sepsis (2008 definition) in the ED and received antibiotic treatment in the ED. *Table 1* shows the baseline characteristics and main outcome measures. Retrospective analysis of clinical signs, cultures and other investigations using predefined criteria[10] (*figure 1*) showed a confirmed bacterial infection in 98 (36%) patients, of whom 51 patients had bacteraemia. In addition, 93 patients (35%) were classified as suspected bacterial disease without microbiological proof. A total of 78 patients (29%) did not have objective evidence of bacterial disease. Amongst them 21 suffered from proven or suspected viral infection. *Figure 2* illustrates the proportions.

Severity of illness

In total 71% of patients, identified with sepsis in the ED, were likely to have bacterial infection. In the group with bacterial infection, the largest proportion (58%) fulfilled criteria for sepsis, 30% fulfilled criteria for severe sepsis, and only 9.5% showed sepsis-induced hypotension. A small

Table 1. *Baseline characteristics*

	Confirmed / suspected bacterial infection (n = 191)	Absent bacterial infection (n = 78)	P-value
Age, years (± SD)	67 (± 17,8)	61 (± 18,8)	,009ˆ
Males, %	89 (46,8%)	37 (46,8%)	,900*
Comorbid conditions			
Immune deficiency	43 (22,6%)	24 (30,4%)	,155*
Current malignancy	28 (14,7%)	11 (13,9%)	,906*
Liver cirrhosis	2 (1.1 %)	2 (2.5 %)	,351*
Renal insufficiency	30 (15,8%)	6 (7,6%)	,080*
Congestive heart failure	8 (4,2%)	5 (6,3%)	,446*
Respiratory disease (COPD)	28 (14,8%)	19 (24,1%)	,060*
Laboratory findings			
C-reactive protein (CRP) day 0	151 (± 132,0)	66 (± 66,97)	,000ˆ
CRP maximum (first 72 hrs)	212 (± 124,1)	99,7 (± 74,0)	,000ˆ
Bilirubin	16,0 (± 10,5)	17,7 (± 38,8)	,571ˆ
Creatinine	95 (± 54,7)	85,3 (± 39,1)	,143ˆ
Lactate	2,31 (± 2,89)	1,94 (± 1,19)	,292ˆ
Bacterial outcomes			
Positive blood cultures	51 (26,8%)	-	
Sepsis severity			
Sepsis	111 (58.1%)	55 (70,5%)	,058*
Severe sepsis	57 (30,0%)	20 (26,3%)	,511*
Sepsis-induced hypotension	18 (9,5%)	2 (2,6%)	,057*
Septic shock	5 (2,6%)	1 (1,3%)	,506*
Length of stay (days) (median (IQR)	8 (5-11,7)	6 (3-10)	,006§
ICU admission %	8 (10,1%)	17 (8,9 %)	
Duration of antibiotic treatment (median + IQR)	10 (7-14)	7 (4-10)	,000§
Mortality	4 (5%)	17(8,9%)	,295*

Continuous data are presented as mean ± standard deviation, unless otherwise mentioned. Categorical data as number (percentages); *chi square, ˆt-test, § Mann-Whitney U test.

percentage (3%) suffered from septic shock. This means that the largest proportion of the patients identified with bacterial infection (58%) would probably not fulfil the current sepsis-3 definition, although mental status was not documented reliably in all patients.

Factors associated with patients without bacterial infection

As shown in *table 2* no significant differences in sex or comorbidity between patients with and without bacterial disease were established. The patients with bacterial disease were significantly older compared with the group without bacterial disease (p = 0.014). C-reactive protein at day 0 and day 3 was significantly higher in patients with bacterial disease than those without (p < 0.001 in both cases).

The number of SIRS criteria was significantly associated with the presence of bacterial disease. The odds ratio of having a bacterial infection was 2.32 (CI 1.3-4.3) if all four SIRS criteria were met in comparison with ≤ 3 criteria. The mean arterial pressure was significantly lower in the group with proven infection (p = 0.012), even though this was not reflected in the systolic blood pressure, but rather in the diastolic blood pressure. Leucocyte count was significantly

Figure 1. *Definitions of groups of infection, derived from Limper*[10]

- Confirmed bacterial infection: positive culture result in concordance with clinical findings.
- Suspected bacterial infection: clinical findings strongly suggestive for bacterial infection, but without positive culture result; for instance, a patient with fever, purulent cough, crackles on auscultation and a lobar infiltrate on the thoracic X-ray.
- Confirmed viral infection: positive viral PCR in concordance with clinical findings.
- Suspected viral infection: clinical findings indicative of viral disease in the absence of positive bacterial cultures despite extensive culture taking and in the absence of underlying auto-immune or auto-inflammatory disease, malignancy, thromboembolic disease or medication use that could explain clinical finding.
- Non-bacterial/non-viral infection: positive fungal culture or proven parasite in concordance with clinical finding.
- Non-infectious disease: no evidence of infectious fever despite extensive supplementary diagnostics and a strong alternative diagnosis.

Absent bacterial infection

higher in the group with bacterial infection (p = 0.001). Unexpectedly, patients with bacterial disease had a lower pulse than patients without a bacterial disease (p < 0. 001). Taking into account the severity of sepsis, the patients with more severe forms of sepsis (severe sepsis, sepsis-induced hypotension or septic shock) were significantly (p = 0.046) more likely to have bacterial infection compared with the group with sepsis alone.

Alternative diagnosis in patients without bacterial infection

To further understand how patients become misdiagnosed as possible sepsis we carefully studied the alternative diagnoses in the residual group (*table 3*). The most frequent alternative diagnosis was exacerbation of chronic obstructive pulmonary disease (COPD) with or without viral respiratory infection (n = 26). Congestive heart failure (n = 7), neutropenic fever (n = 5), pulmonary embolism (n = 4) and viral pneumonia due to H1N1 influenza (n = 4) were the most prevalent alternative diagnoses, apart from quite a large group (n = 15), in which no clear diagnosis was made.

Antibiotic use

Data regarding duration of antibiotic treatment were available for 251 patients. In the remaining patients, data could not be retrieved, for example due to transfer to another hospital.

The median duration of antibiotics for all patients was 9 days (IQR 3-15), but median 11 days (IQR 7-14) in patients with bacterial infection and 7 days (IQR 4-10 days) in patients without bacterial infections as displayed in *table 4*.

The most frequent infection was respiratory infection, which was treated for a median of 10 days. This is remarkable as evidence has shown that shorter treatments are safe and effective.[12-14]

Antibiotics were stopped in the first 5 days in only 23 (32%) of the patients without bacterial infection, see *figure 3* for more information. In this group antibiotic duration was

Figure 2. *Presence of bacterial disease*

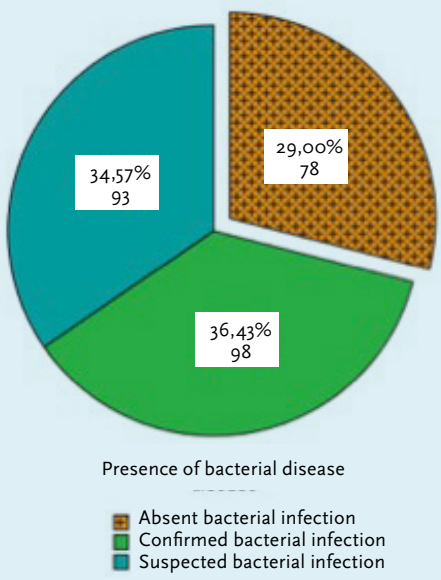

Table 2. *SIRS criteria and bacterial infection*

Mean (± SD)	Confirmed / suspected bacterial infection (n = 191)	Absent bacterial infection (n = 78)	P-value
Temperature (continuous)	38,99	38,89	,475ˆ
Normothermia (36-38 °C)	n =2 (2,5%)	n = 17 (8,9%)	,061*
Leucocytes count (mean ± SD)	13,6 (± 7,2)	10,5 (± 5,4)	,001ˆ
Blood pressure (MAP)	91,9 (± 17,3)	97,7 (± 15,3)	,013ˆ
Systolic BP	129,3 (± 25,3)	133,5 (± 19,7)	,205ˆ
Diastolic BP	73,3 (± 17,8)	79,7 (± 16,1)	,007ˆ
Respiratory rate	24,6 (± 6,7)	23,6 (± 6,6)	,279ˆ
Pulse	107,8 (± 18,7)	115,6 (± 22,9)	,004ˆ
SIRS criteria			
≤3	n = 132	n = 62	,018*
4	n = 74	n = 17	

ˆ Students t-test, * Pearson c2

significantly longer (p = 0.037) in patients with COPD in relation to patients with other comorbidities (current malignancy, congestive heart failure, liver cirrhosis, chronic renal insufficiency). Median duration was shortest in patients with confirmed or suspected viral disease (median 3 and 4 days, IQR 1-10.5 and 1.5-7.5).

DISCUSSION

This study demonstrates that in almost 30% of the patients with suspected sepsis in the ED no objective evidence of bacterial disease could be found. This puts patients at risk of overtreatment with antibiotics. This finding is in concordance with an earlier report of patients admitted to the ICU with a diagnosis of sepsis,[15] in whom no evidence of bacterial infection could be found in 13% and only a possible infection could be established in 30%. In spite of the improved outcome of patients treated early with antibiotics for severe sepsis or septic shock, this antibiotic overtreatment in patients with sepsis is a very important finding and often underreported. It is of paramount importance to establish that patients included in sepsis research (on clinical suspicion) are in fact suffering from an infectious disease. Future research will have to report infectious outcomes in detail, to enable correct interpretation and extrapolation of the results.

Antibiotic treatment within the hour

The most important intervention in severe sepsis treatment in the last decades, next to fluid treatment, has been the emphasis on early antibiotic treatment. The problem in every ED, however, is that signs and symptoms of severe sepsis can be deceiving or occult. Postponing antibiotic treatment whilst awaiting basic test results (i.e. kidney function, chest X-ray) does not fit well within the one-hour target which has been outlined by the sepsis guidelines. The

Figure 3. *Distribution of antibiotic duration among subgroups*

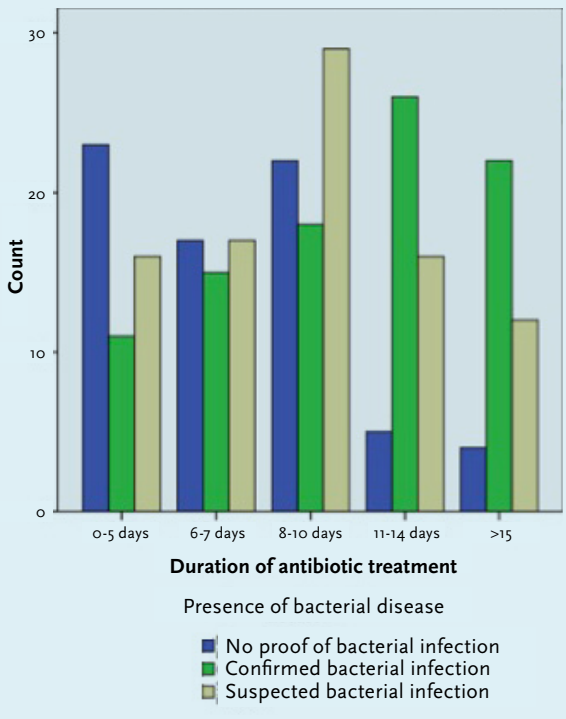

Table 3. *Final diagnosis in patients without bacterial infection*

Characteristics of patients in sepsis protocol without bacterial infection			
Clinical severity of sepsis	**N = 78**	**Final diagnosis**	**N**
Sepsis	55	Arrhythmia / congestive heart failure	5
		Exacerbation of COPD or upper respiratory infection (viral)	21
		Neutropenic fever	3
		Pulmonary embolism	3
		Malignancy (tumour-related fever)	2
		Epstein-Barr virus infection	1
		Meningitis (viral)	1
		Pericarditis (viral)	1
		Unclear diagnosis / insufficient information	12
Severe sepsis	20	Neutropenic fever	2
		Fever in immunocompromised host (not neutropenic)	3
		H1N1 infection / pneumonia	3
		Viral hepatitis (Epstein-Barr virus)	1
		Exacerbation of COPD / upper respiratory infection	5
		Pulmonary embolism	1
		Congestive heart failure	2
		Unclear diagnosis / insufficient information	3
Sepsis-induced hypotension	2	H1N1 pneumonia	1
		Multi organ failure in a patient with new diagnosis of aggressive lymphoma (DLBCL) and history of mRCC	1
Septic shock	1	Diabetic keto-acidosis	1

COPD = chronic obstructive pulmonary disease; H1N1 = influenza of subtype H1N1; DLBCL = diffuse large B-cell lymphoma; mRCC = metastatic renal cell carcinoma

benefit of early antibiotic treatment has been established in suspected sepsis patients admitted to the ICU.[1-4,16-18] Two other studies showed benefit of early antibiotic treatment in ED patients but selected only patients with sepsis and organ dysfunction or patients with hypotension/ hyperlactataemia (lactate > 4 mmol/l).[19-21] However the largest group identified by our screening did not have organ dysfunction, and only about 10% needed ICU care. This means that more than half of our patients could have awaited basic test results (which might have raised suspicion of alternative diagnoses), thus allowing more time to consider if antibiotic treatment is really indicated. In pneumonia, studies have shown that treatment within four hours is safe.[22] This leaves more than enough time for at least a chest X-ray and lab results to come in.

Antibiotic treatment in the ED within the hour should generally be reserved for critically ill patients, patients deteriorating quickly, or specific patient groups such as neutropenic patients. Future research will hopefully guide us further as to which risk-stratification score (Modified Early Warning Score (MEWS), National Early Warning Score (NEWS) or Quick Sequential Organ Failure Assessment (qSOFA) is most helpful with identifying patients at risk of deterioration or death.

Duration of antibiotic therapy

Overall the duration of antibiotic therapy was long in our cohort. This may reflect local standards or may be because our patients were selected in 2011.

Of concern, patients in our cohort without evidence for bacterial disease were treated with antibiotics for a median duration of 7 days, pointing to overuse. Antibiotic treatment was stopped in the first 5 days in only 32% of the patients with negative culture results. Several reasons for the prolonged use of antibiotics can be suggested.

1. The ED presumptive diagnosis of sepsis makes it hard to stop antibiotics despite negative cultures. This could be due to cognitive errors such as the tendency to stick to first impressions (anchoring error) and the tendency

to stick to prior diagnoses (confirmation bias) despite conflicting evidence.
2. The large number of patients suffering from COPD in this subgroup, in whom antibiotic treatment is often given despite negative cultures. Even so, evidence is mounting that shorter regimens are safe for bronchitis and pneumonia.[12-14]
3. Clinical improvement of patients after admission and starting antibiotics.
4. Fear of undiagnosed bacterial disease by physician or patient.
5. Fear of inducing antimicrobial resistance if antibiotics are stopped prematurely. This is a theoretical problem which is hard to prove or refute in practice. Though widespread, it has been challenged over recent years. New research in the area of pneumonia shows that shorter treatment regimens are safe without signs of inducing microbial resistance.[12-14] A review in 2016, looking at de-escalation of antimicrobials, concluded that de-escalation appears safe and effective for certain conditions, but calls for further, high-quality, research.[23] All in all, de-escalation seems safe, and if antibiotics are used for too long for fear if inducing resistance, this might actually constitute antibiotic overuse.

Limitations

Limitations of the study are its retrospective character and the single-cohort design in a single hospital. Another point of concern is the allocation of patients to groups suffering from proven/ suspected or no bacterial disease. It has been pointed out before that many patients suffering from a bacterial infection (i.e. pneumonia) may not have positive culture results. A patient suffering from urosepsis may have negative cultures due to prior treatment initiated by the primary care physician. In these patients, it is hard to determine in retrospect if they were truly suffering from bacterial disease. We have put a lot of effort into accurately determining the correct group for each patient, but in some cases it is inevitable that discussion will always remain. However, as this reflects daily practice it does not reduce our concerns of overtreatment and the protracted duration of antibiotic use.

Future investigations evaluating the sepsis campaign or regarding screening in the ED should report microbiological outcomes and include overuse and possible harm of antibiotics as endpoint to avoid a singular focus on benefits of early sepsis treatment.

Relevance and recommendations

With the new sepsis-3 definition, treatment within one hour based only on SIRS criteria cannot be substantiated. However, it is still difficult to know which patients in the ED have to be treated within the hour. qSofa was introduced as an instrument to identify patients with sepsis who are likely to fare poorly and should thus be treated early with broad-spectrum antibiotics.[9] This is

Table 4. *Antibiotic duration in subgroups*

n = 251	Duration of antibiotic treatment (median, days)	IQR
Absent bacterial infection (n = 72)	7	4-10
Suspected / confirmed bacterial infection (n = 179)		
Pulmonary (n =88)	10	7-11
Abdominal (n = 25)	7	5-12
Urinary tract (n = 39)	10	7-15
Soft tissue / skin infection (n = 15)	13	8-14
Endocarditis (n = 4)	35	N/A
Joints / bone infection (n = 3)	9	N/A
CNS (epidural abscess) (n = 1)	84	N/A
PM line associated infection (n = 1)	42	N/A
Ear-nose-throat (n = 1)	8	N/A
Bacteraemia with unknown focus (n = 2)	16 (mean)	N/A
Total n = 251		

IQR = interquartile range; CNS = central nervous system; PM = pacemaker; N/A not applicable

an important step forward. However, it was noted that early treatment should not be limited to patients with a positive qSofa. Several reports have been made since, but acceptance of qSOFA is not universal. One investigation showed poor sensitivity of 63% for qSOFA in the ED population.[24] The same report found that the NEWS was the most accurate tool in predicting in-hospital and ICU mortality. In the UK, use of NEWS is mandatory and qSOFA has not been implemented. Since the best way to identify a septic patient in the ED is still under discussion, this study offers valuable information regarding the use of SIRS criteria.

With respect to antibiotic duration and de-escalation, the current guidelines recommend daily reconsideration of antibiotic therapy. Unfortunately, only a few studies have been performed regarding the safety of early de-escalation in patients outside the ICU. More research is needed in the area of de-escalation in suspected sepsis patients.

CONCLUSION

Sepsis detection in the ED is a continuous challenge. This study shows that early recognition of sepsis using SIRS criteria leads to over identification of sepsis. More than half of the patients suspected of sepsis would probably not fulfil the current sepsis-3 definition, and almost 30% did not have objective evidence of a bacterial infection. In some of the patients without bacterial infection, awaiting basic tests might have confirmed an alternative diagnosis and antibiotic treatment could have been avoided.

In a significant proportion of patients, empiric therapy was justified but with a median duration of therapy of seven days de-escalation should have been much more rigorous.

DISCLOSURES

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

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CASE REPORT

Transient thyrotoxicosis during nivolumab treatment

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ABSTRACT

Two patients presented with transient thyrotoxicosis within 2-4 weeks after starting treatment with nivolumab. This thyrotoxicosis turned into hypothyroidism within 6-8 weeks. Temporary treatment with a beta blocker may be sufficient.

KEYWORDS

Checkpoint inhibition, thyrotoxicosis, thyroiditis, lung cancer, immune related adverse reactions

What was known on this topic?
It is known that treatment with immune checkpoint-inhibitor nivolumab can induce thyroid dysfunction such as hypothyroidism and hyperthyroidism. This thyroid dysfunction occurs mainly around 12 weeks after starting nivolumab treatment. Little is known about the aetiology and management of this thyroid dysfunction.

What does this add?
Until now it was not known that a transient destructive thyroiditis is probably the underlying mechanism behind this nivolumab-induced thyroid dysfunction. Therefore, in case of thyrotoxicosis, hyperthyroidism would not be the correct definition. We have observed that this thyrotoxicosis can occur as early as 2-4 weeks after initiation with nivolumab. In case of a transient destructive thyroiditis, prescription of beta blockers to reduce symptoms is the most obvious treatment.

INTRODUCTION

The immune checkpoint-blocking antibody nivolumab is a promising new drug to treat different malignancies. It promotes immune responses by blocking programmed death-1 (PD-1) receptor immune cells. Patients with lung cancer treated with nivolumab have a better overall survival, response rate, and progression-free survival than those treated with chemotherapy.[1,2] One out of five patients show a durable tumour response, but a good biomarker is still lacking.[3] Besides its benefits, nivolumab may cause immune-related adverse reactions such as skin toxicity (31%), gastrointestinal toxicity (11%), pneumonitis (3%), thyroid dysfunction (3%), and hypophysitis (< 1%).[4] Thyroid dysfunction is expressed as hypothyroidism (7%), hyperthyroidism (1%), and thyroiditis (< 1%), mostly described around week 12 after the start of therapy with nivolumab.[5-7] Thyroid dysfunction occurred more often in patients treated with anti-PD-1 than in patients treated with CTLA-4 immune checkpoint inhibitors such as ipilimumab (1.8-9%).[8-10] Another PD-1 blocker, pembrolizumab, has also been related to thyroid dysfunction, such as hypothyroidism and hyperthyroidism, 10.1% and 6.5% respectively.[11,12] Cytology in these patients on pembrolizumab shows lymphocytic thyroiditis with multinucleated giant cells.[13] The optimal treatment and the underlying pathophysiological mechanism causing thyrotoxicosis as an immune-related adverse reaction during treatment with anti-PD-1 have not yet been established.[14] We speculate that a transient destructive thyroiditis is the most likely underlying pathophysiology and, therefore, prescription of beta blockers to reduce symptoms is the most logical approach.

CASE REPORTS

We report two cases with temporary thyrotoxicosis turning into hypothyroidism during nivolumab treatment. Both patients had a clinical benefit from nivolumab treatment with a partial tumour response and are still on nivolumab treatment.

Case report 1

A 63-year-old female, diagnosed with squamous-cell non-small-cell lung carcinoma (NSCLC) stage cT3N3M1b developed symptomatic thyrotoxicosis: progressive fatigue, excessive sweating, weight loss, tachycardia, and a non-tender, enlarged, diffuse goitre, four weeks after initiation of treatment with nivolumab. Laboratory findings revealed FT4 47.5 pmol/l (11.0-19.5), FT3 10 pmol/l (4.4-6.7), thyroid-stimulating hormone (TSH) 0.020 mU/l (0.5-4.0), and negative thyroid antibodies (thyrotropin binding inhibiting immunoglobulins (TBII), anti-thyroid peroxidase (TPO)). Medical history was negative for thyroid disease. Second-degree relatives were known to have hyperthyroidism and goitre. In the assumption that a possible Graves' disease had been induced by immunotherapy, temporary treatment with atenolol (50 mg daily) and methimazole (30 mg daily) was started, resulting in immediate resolution of the symptoms. Two weeks later the FT4 normalised (*figure 1*), the clinical symptoms improved, and TBII was found to be negative, leading to discontinuation of the methimazole. ^{18}F-fluorodeoxyglucose positron emission tomography computed tomography (FDG-PET/CT) performed six weeks after starting nivolumab showed a partial tumour response, but also symmetrically increased uptake in the thyroid, which was not present at baseline FDG-PET/CT (*figure 2*). Levothyroxine was started eight weeks after starting nivolumab therapy when hypothyroidism occurred (FT4 7.2 pmol/l). Anti-TPO levels were < 33 IU/ml before therapy and 78 IU/ml four weeks after starting nivolumab (negative < 100 IU/ml). Moreover, Sjögren's syndrome was diagnosed based on typical symptoms and elevated Sjögren syndrome antigen antibodies 3-4 months after initiation of the nivolumab therapy.

Case report 2

A 71-year-old female, diagnosed with squamous-cell NSCLC stage T2aN2-3M1b presented with symptoms of thyrotoxicosis: excessive sweating, palpitations and a diffuse enlarged and tender thyroid, two weeks after initiation of treatment with nivolumab. Laboratory findings revealed FT4 53.1 pmol/l, FT3 14.3 pmol/l, TSH 0.010 mU/l, and negative thyroid antibodies (TBII, anti-TPO). Medical and family histories were negative for thyroid diseases. Atenolol (50 mg daily) and methimazole (30 mg daily) were started because of the suspicion of Graves' disease, especially based on subtle eye signs. Nivolumab was continued and treatment with methimazole was stopped after two weeks because of declining FT4 levels (*figure 1*) and the rising suspicion of a temporary phenomenon. Six weeks after starting nivolumab a FDG-PET/CT scan showed symmetrical, increased FDG uptake in the thyroid, which was not visible at the baseline FDG-PET/CT, without clear reduction in metabolic activity or size of the primary tumour in the lung, see *figure 2*. Eight weeks after the start of nivolumab therapy hypothyroidism developed (FT4 8.4 pmol/l) and levothyroxine was started. Anti-TPO levels were < 33 IU/ml after initiation of therapy and changed to 65 IU/ml over time.

Figure 1. *Course of FT4 levels showing transient thyrotoxicosis in two patients treated with nivolumab. Laboratory results on FT4 levels starting at initiation of treatment with nivolumab from case 1 (left) and case 2 (right), black bar represents temporary medication with methimazole, dotted bars indicate normal FT4 range.*

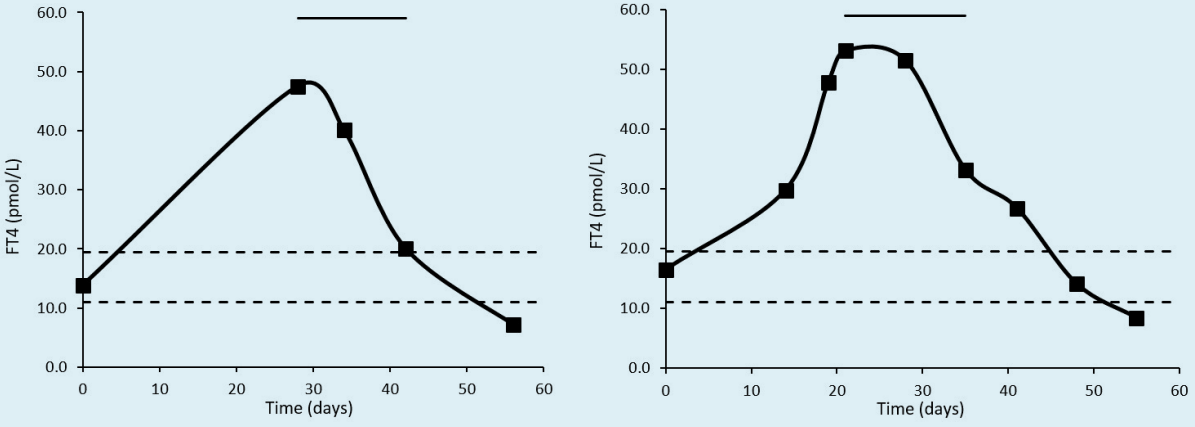
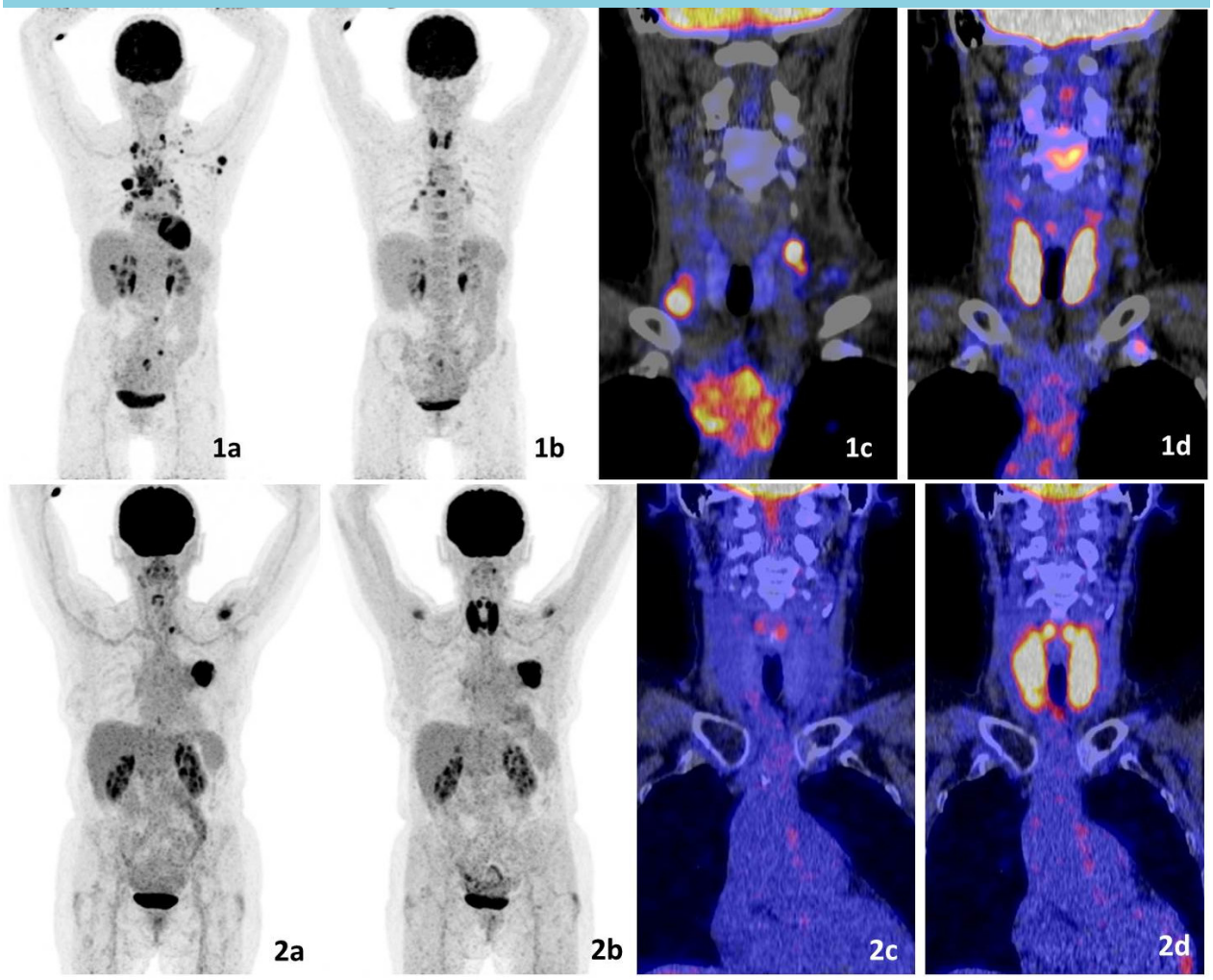


Figure 2. *Overview of the tumour response and change in metabolic activity in the thyroid.*
Case 1:
a) Coronal maximum intensity projection (MIP) FDG-PET at baseline: increased uptake in the primary lung tumour and in lymph nodes (hilar, mediastinal, supraclavicular regions, left axilla), bone and liver metastases.
b) Coronal MIP FDG-PET at six weeks: increased uptake in the thyroid gland and regression in lung tumour and lymph node metastases.
c) Fused coronal FDG-PET/CT image baseline: increased uptake in lymph node metastases in the neck region.
d) Fused coronal FDG-PET/CT image at six weeks: no uptake anymore in the lymph nodes, but increased uptake in the thyroid gland.

Case 2:
a) Coronal maximum intensity projection (MIP) FDG-PET at baseline: high uptake in the lung tumour and in a lymph node metastasis in the left supraclavicular region.
b) Coronal MIP FDG-PET at six weeks: markedly increased uptake in the thyroid gland and no change of uptake in the primary lung tumour or in the supraclavicular lymph node metastasis (obscured by the high uptake in the thyroid).
c) Fused coronal FDG-PET/CT image baseline: only physiological uptake in the vocal cords.
d) Fused coronal FDG-PET/CT image at six weeks: markedly increased uptake in the thyroid gland.



A tracer dose of radioiodine was deemed not to be informative regarding the recent repeated gifts with iodinated contrast in both patients. Neither cytology nor histology from the thyroid was obtained.

CONCLUSION

Both cases demonstrate a transient thyrotoxicosis already within 2-4 weeks after starting treatment with

nivolumab, with a rapid transition to hypothyroidism. Temporary treatment with a beta blocker may be sufficient. Afterwards thyroid hormone substitution may follow, whether or not in the long term. We speculate that the underlying pathophysiological mechanism is a transient destructive thyroiditis, a conclusion based on the relatively rapid resolution and temporarily increased FDG uptake.[12] Therefore thionamides should not be used during the initial period with thyrotoxicosis, unless there are clear signs of Graves' disease, or a more sustained thyrotoxicosis.

Since the number of patients treated with nivolumab is expected to increase, our cases should increase awareness of the evaluation and management of this form of thyrotoxicosis.

DISCLOSURES

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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CASE REPORT

Torsade de pointes in a patient with severe hypercalcaemia and multiple myeloma

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ABSTRACT

We report a case of a 48-year-old female patient with newly diagnosed multiple myeloma. She developed recurrent torsade de pointes and required cardiopulmonary resuscitation and defibrillation. Atrial arrhythmias in patients with multiple myeloma and hypercalcaemia have been described, but, to the best of our knowledge, this is the first report of torsade de pointes in this setting.

KEYWORDS

Arrhythmia, hypercalcaemia, multiple myeloma, torsade de pointes

What was known on this topic?
Ventricular arrhythmias, including ventricular fibrillation, have been described in patients with hypercalcaemia due to hyperparathyroidism.

What does this add?
Torsade de pointes can occur as a complication of hypercalcaemia in patients with multiple myeloma.

INTRODUCTION

Hypercalcaemia is a frequent complication of multiple myeloma.[1] Cardiac arrhythmias may occur, but are rare and have primarily been described in patients with primary hyperparathyroidism. There are no published reports of ventricular arrhythmias in patients with hypercalcaemia and multiple myeloma.[2]

CASE REPORT

We report a case of recurrent torsade de pointes arrhythmia in a 48-year-old female patient with hypercalcaemia and newly diagnosed multiple myeloma.
On admission, she complained of fatigue, weight loss, dry cough and bone pain. A complete blood count showed normocytic anaemia (haemoglobin 7.9 g/dl), elevated plasma protein (140.6 g/l), renal insufficiency (creatinine 1.6 mg/dl, GFR(aMRD) 36.4 ml/min/1.7), hypalbuminaemia (27.9 g/l, range 35-52 g/l) and severe hypercalcaemia (3.91 mmol/l [4.1 mmol/l corrected for hypalbuminaemia], range 2.15-2.55 mmol/l). Potassium levels were normal (4.13 mmol/l, range 3.5-5.3 mmol/l). She received intravenous fluids and zoledronic acid. The electrocardiogram on admission showed no abnormalities and a normal QT time (QTc 387ms) (*figure 1*).
Shortly afterwards, the patient went into cardiac arrest and was resuscitated. She was transferred to the intensive care unit (ICU) and placed on calcium-free dialysis. Over the course of 24 hours, she experienced seven episodes of torsade de pointes requiring defibrillation (*figure 2*). Echocardiography revealed no structural heart disease and normal left ventricular function.
Bone marrow biopsy confirmed multiple myeloma (IgG kappa, 80% infiltration in bone marrow aspirate smears, M-gradient 73.8 g/l).
The calcium levels returned to the normal range after two sessions of dialysis and treatment with bortezomib, thalidomide and dexamethasone was started.[3]
No remission could be achieved after two courses of this treatment. She had multiple lines of therapy over the course of her illness, including lenalidomide, dexamethasone and bortezomib, chemotherapy with cisplatin, etoposide, cyclophosphamide and dexamethasone[4] and autologous stem cell transplantation (Melphalan 200 mg/m^2). She achieved only short-lasting

Figure 1. *Initial ECG obtained on admission before the first episode*

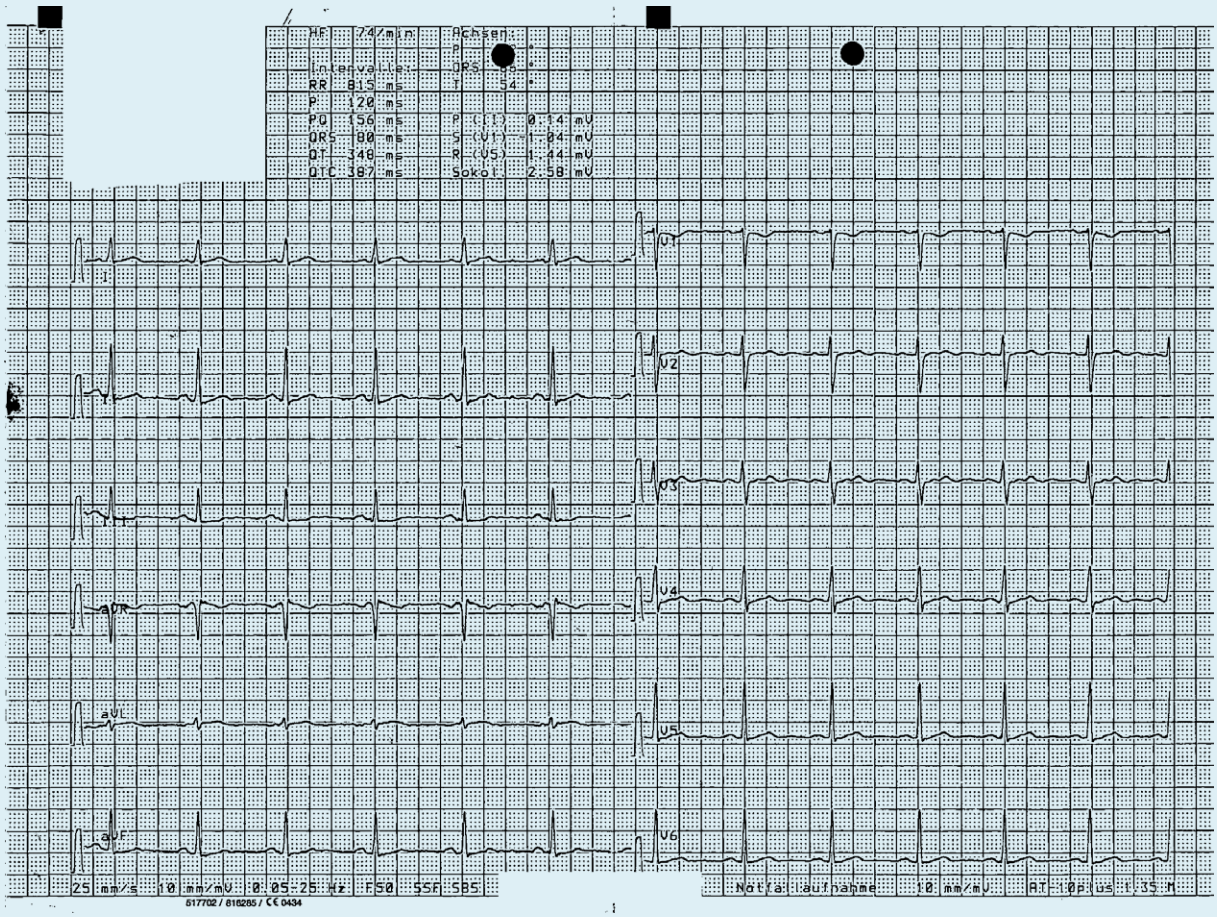
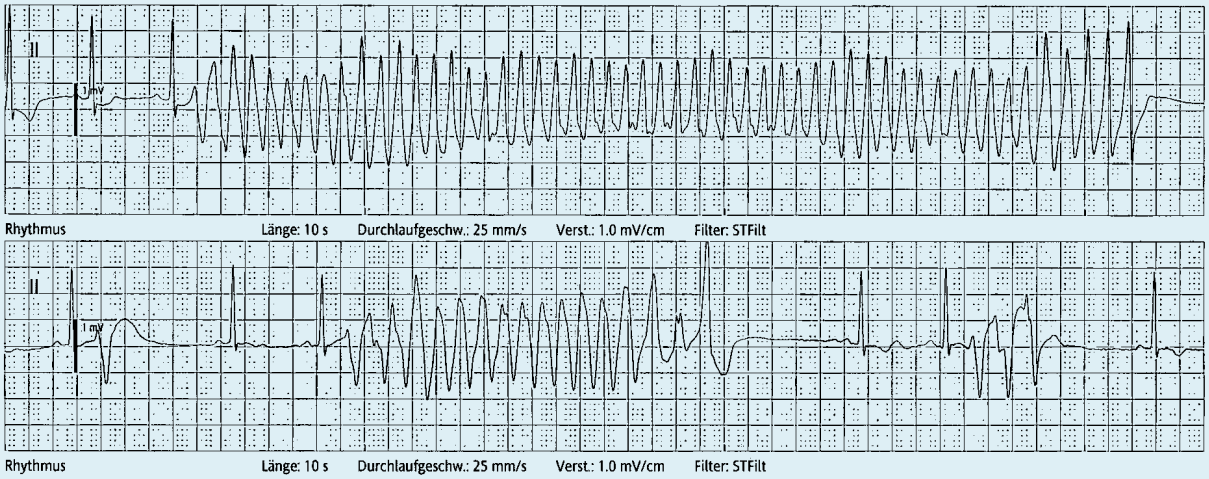


Figure 2. *Rhythm strips in intensive care after the initial episode. The initiation of the arrhythmia was caused by a short-coupled variant of torsade de pointes*



remissions on all lines of therapy and was ultimately started on pomalidomide and dexamethasone, but died 10.5 months after her initial diagnosis. Over the course of her illness, hypercalcaemia recurred only once after progression on lenalidomide, dexamethasone and bortezomib, but no further arrhythmia was recorded.

Autopsy revealed lymphocytic and haemorrhagic myocarditis as the leading cause of death and also showed a thrombotic formation in the right atrium, pulmonary oedema, jaundice and intrahepatic cholestasis. Findings about jaundice and intrahepatic cholestasis dominated the last phase of the patient's life and myocarditis was not suspected clinically while she was alive.

In severe electrolyte abnormalities, arrhythmia is a frequent finding. In hypercalcaemia, atrial arrhythmias have been described, but reports of ventricular arrhythmias in patients with hypercalcaemia are rare and have only been published in patients with hypercalcaemia due to primary hyperparathyroidism.[5-7]

In our patient, there were no other risk factors for torsades apart from hypercalcaemia (no hypokalaemia, bradycardia, heart failure, left ventricular hypertrophy, hypothermia or hypothyroidism), although magnesium levels were not checked until two weeks after the first episode, when they were normal. The only medications she received before her first episode were morphine, dalteparin and paracetamol – none of which are known risk factors for either torsade de pointes or QT abnormalities.

Calcium plays an important role in cardiac conduction velocity and hypercalcaemia is usually associated with shortening of the QT interval, while torsade de pointes are most commonly expected in patients with QT prolongation.[8] However, hypercalcaemia may cause torsade de pointes by enhancing early afterdepolarisation, which may have been a contributing factor in our case presented here.[9]

To the best of our knowledge, this is the first report of torsade de pointes as a complication of hypercalcaemia and multiple myeloma. It is important for haematologists and cardiologists to be aware of this rare, but serious, complication.

DISCLOSURES

The authors declare that they have no conflict of interest. This case report received no funding.

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CASE REPORT

A patient with a 'typical presentation' of Wernicke encephalopathy was found to have sporadic Creutzfeldt-Jakob disease

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ABSTRACT

Creutzfeldt-Jakob disease (CJD) has a significant degree of clinical heterogeneity that is especially found in the features at onset. Here we present a patient with the sporadic form of CJD mimicking Wernicke encephalopathy. We first treated him with a high dose of thiamine; however, the vitamin B1 levels proved to be normal, which ruled out Wernicke encephalopathy. Meanwhile, his clinical condition progressively worsened and he developed a rapidly progressive cognitive disorder, mutism and myoclonus of the muscles. At this point, the diagnosis of CJD was most likely. The patient died two months after the first symptoms. Autopsy showed prion-protein depositions in several regions. Genetic analysis was negative for familial CJD. Those findings confirmed the diagnosis of 'sporadic Creutzfeldt-Jakob disease'. CJD presents in a wide range of sequences and clinical symptoms. Therefore, recognition in the early stage can be difficult.

KEYWORDS

Creutzfeldt-Jakob disease, Sporadic, Wernicke encephalopathy

What is known on this topic?
Creutzfeldt-Jakob disease (CJD) has a significant degree of clinical heterogeneity that is especially found in the features at onset. Recognition of the disease is exceedingly difficult.

What does this add?
It is not uncommon that an alternative diagnosis is suspected. The disease CJD can mimic acute Wernicke encephalopathy, which was the case with our patient. We call attention to the importance of recognition of sporadic CJD.

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a neurodegenerative disorder. It is a transmissible prion disease whereby incorrectly folded prion proteins are formed.[1,2] There are several forms of the disease, depending on the prion subtype. Recognition of the disease is exceedingly difficult.[3,4] We describe a 65-year-old man with the sporadic form of CJD mimicking Wernicke encephalopathy.

CASE REPORT

A 65-year-old man was referred to the department of internal medicine by the general practitioner due to complaints of progressive cognitive impairment, which consisted of memory loss, loss of organisation and disorientation. He also had a drunken man's gait and double vision. These complaints had been present for approximately four weeks.

The medical history revealed a myocardial infarction and chronic obstructive pulmonary disease. The patient was not on any medication. He drank 6 units of beer a day. Previously, his alcohol consumption had been considerably higher.

The general physical examination showed no abnormalities. On neurological examination he had nystagmus, a paresis of the right lateral rectus muscle of

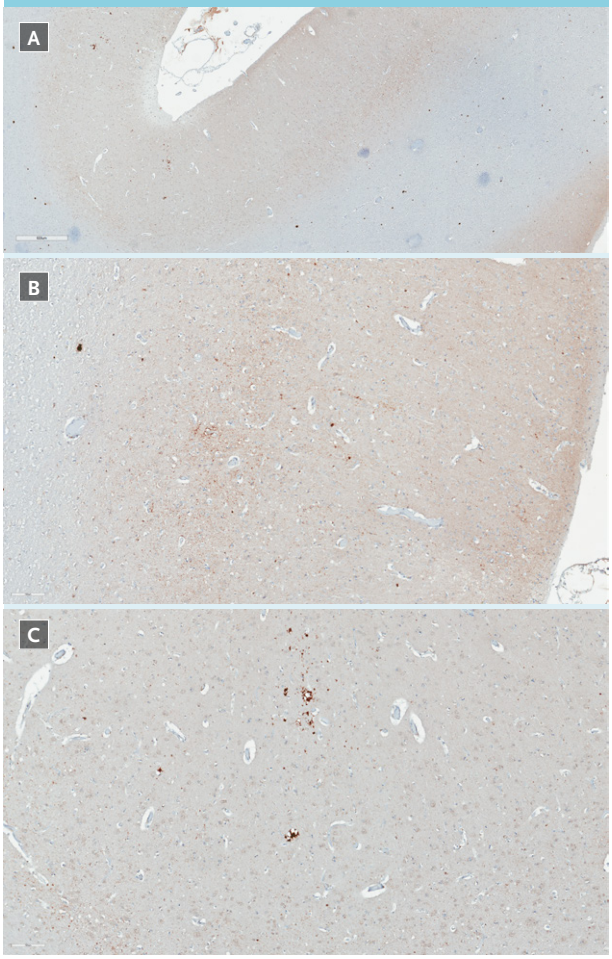
the eye and a wide gait. Additional laboratory tests and a CAT scan of the brain showed no abnormalities. The most obvious diagnosis was acute Wernicke encephalopathy. We treated the patient immediately with thiamine 500 mg three times a day. After two days the paresis of the lateral rectus muscle showed some improvement. We sent the patient home with the advice to take 100 mg thiamine a day. His wife was involved in the care and checked the correct intake of medications.

However, six weeks later the patient's cognitive function had regressed and he was totally dependent in his activities of daily living. He also had a dysarthric speech, nystagmus, ataxia and myoclonus of several muscle groups. The diagnosis of rapidly progressive dementia was made, with the differential diagnosis limbic encephalitis, malignancy or Creutzfeldt Jakob disease (CJD). Meanwhile, the results of the vitamin B1 level proved to be normal, whereupon the diagnosis of acute Wernicke encephalopathy was rejected. Tests for paraneoplastic antibodies were negative and the level of protein 14-3-3 in cerebral spinal fluid (CSF) was still pending. An MRI scan (with diffusion weighted imaging) of the brain gave no new insights. The EEG showed a diffuse encephalopathic pattern with delta waves parieto-temporally and sharp-slow waves without triphasic complexes, which made a neurodegenerative condition more likely.

During the following days there was a rapid progression of the symptoms, as well as hypertonia in the arms and legs. The patient could barely speak. The diagnosis of CJD was most likely and the infaust prognosis was shared with the family members. We contacted the physicians of the Registration Centre of Prion Diseases of the Department of Epidemiology, ErasmusMC Rotterdam, who informed the public health authorities. They contacted the family members to inform them about the importance of performing an autopsy.

The patient died the following day, two months after the first symptoms emerged. During the autopsy of the brain, deposits of prion proteins were found, both synaptic as well as perineural and perivacuolar (*figure 1*). The 14-3-3 protein was detected in CSF. Gene analysis was negative for the familial form of CJD. These findings confirmed the sporadic form of Creutzfeldt-Jakob disease.

Figure 1. *Staining with 3F4-anti-PrP. A. Overview of a sulcus with fine cortical synaptic pattern (brown, fine-grained haze) perivacuolar staining and plaque-like deposits in the white matter. B. Low perineural enhancement. C. Perivacuolar deposits*



Pathogenesis and clinic

CJD is a communicable and fatal neurodegenerative disease caused by accumulation of natural misfolded proteins (prion proteins) in the body, which will deform the central nervous system.[1,5] Neural loss, astrocyte proliferation, spongiform changes and deposition of proteins in the brain tissue will occur.

CJD is divided into multiple forms, depending on the cause and clinical pathological profile (*table 1*). The sporadic form occurs in 85% of all cases of CJD, with an annual worldwide incidence of 1-2 persons/million. It occurs particularly in people between the ages of 50-70 years.[4] The cause is unclear, but there may be a spontaneous change of the structure of prion protein or a spontaneous mutation in the PRNP gene encoding.

Individuals can present with the same symptoms in a different sequence, which makes the disease difficult to recognize in the early stages.[3,6,7] It is not uncommon that an alternative diagnosis is suspected, which was the case with our patient.

There are always signs of a rapidly progressive dementia, developing over a period of several weeks or months, in combination with other symptoms such as cerebellar ataxia, loss of vision and myoclonus. However, the disease can also present with isolated cerebellar ataxia or an isolated loss of vision. Characteristically the symptoms are rapidly progressive. The patient can deteriorate in a matter

Table 1. *CJD divided into multiple forms*

Forms of CJD	Cause	Features
Sporadic form	Unclear: probably a spontaneous mutation in the prion protein	• Occurs at middle-age • Cerebellar ataxia, loss of vision, myoclonus • Median duration of disease is 5 months
Genetic form	Mutations in PRNP gene	• Can mimic the other forms • Dementia often occurs late in the course of disease • Median duration of disease is several years • Family history can be negative • Can occur at younger ages • Often no detectable 14-3-3 proteins in CSF
Iatrogenic form	Iatrogenic transmission of prion protein by invasive medical treatment	• Similar features as the sporadic form
Variant	Ingestion of contaminated products with bovine spongiform encephalopathy	• Occurs at a young age (median age 26 years) • Presents with psychiatric symptoms such as depression, anxiety and social withdrawal • At later stadium there is ataxia, dystonia, chorea, myoclonus. • Median duration of disease is 14 months

of days. Classical symptoms at the end stage of the disease are akinetic mutism and myoclonus, which were present in our patient. The median duration of the disease is four months.[3]

Diagnosis and treatment

As previously described,[8] often the diagnosis cannot be made with certainty during the patient's life. To diagnose CJD with certainty examination of (post-mortem) brain tissue showing the presence of prion proteins in the brain tissues is required. In exceptional cases a brain biopsy is performed while the patient is still alive if there are clear MRI changes, which can be biopsied. The sensitivity of the detection of 14-3-3 protein in CSF (a nonspecific marker of rapid neuronal loss) is 94-97% and the specificity is 84-87%.[9,10] The sensitivity of detection of periodic sharp wave complexes in the EEG is 66% with a specificity of 74%. According to the diagnostic criteria, six weeks after presentation the probable diagnosis 'sporadic CJD' could have been made in our patient due to rapid progressive dementia, visual and cerebellar problems and myoclonus (*table 2*).[11]

To date, there is no curative treatment for this disease and the treatment is only supportive.

Pitfalls

CJD can mimic acute Wernicke encephalopathy with the classical triad of cognitive impairment, nystagmus and ataxia caused by a vitamin B1 deficiency, which is typically seen in malnourished patients, for example in alcohol abusers.[12] In our patient this triad was present. Combined with the alcohol abuse, the diagnosis was plausible. However, the non-significant improvement of the paresis of the lateral rectus muscle after supplementation with thiamine did not seem to support this diagnosis.

With the onset of new symptoms a few weeks later, the diagnosis of CJD became clear, enabling us to inform the family members of the situation.

CONCLUSION

The rarity of CJD and the diverse clinical symptoms make recognition of the disease extremely difficult. Rapid recognition of the disease is important so that the patient and relatives can be informed as early as possible during the course of the disease. It is essential to inform the relatives fully to create awareness that deterioration of their loved one can be expected within a period of weeks without possible treatment. Also of importance for the relatives is the information about whether the CJD is the familial form. Because the diagnosis can only be made with the examination of (post-mortem) brain tissue, family members should be extensively counselled about the importance of performing an autopsy.

ACKNOWLEDGEMENTS

We thank Wim van der Hecke, pathologist at the University Medical Centre Utrecht, the Netherlands for providing *figure 1* and Alice Moonen, palliative care nurse at the Erasmus Medical Centre Rotterdam for critically reviewing the manuscript regarding English grammar and

Table 2. *Diagnostic criteria for sporadic CJD (January 2017) adapted from the university of Edinburgh*[11]

A	Rapidly progressive cognitive impairment
B	– Myoclonus – Visual or cerebellar problems – Pyramidal or extrapyramidal features – Akinetic mutism
C	Typical EEG
D	High signal in caudate/putamen on MRI brain scan

Suspect cases can be diagnosed as 'sporadic CJD' as follows;

Possible
A and two items of B and duration < 2 years

Probable
A and two items of B and typical EEG*
OR
A and two items of B and typical MRI brain scan**
OR
A and two items of B and positive 14-3-3 protein in CSF
OR
Progressive neurological syndrome and positive 'real-time quaking-induced conversion (RT-QuIC)' in CSF or other tissues

Definite
Progressive neurological syndrome and
Neuropathologically or immunocytochemically or biochemically confirmed

*Generalised periodic complexes
**High signal in caudate/putamen on MRI brain scan or at least two cortical regions (temporal, parietal, occipital) either on diffusion weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR).

spelling. Furthermore we would like to thank the family of our patient for granting informed consent to publish this case report.

DISCLOSURES

The authors declare no conflicts of interest. There is no funding or financial support.

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PHOTO QUIZ

An unexpected cause of nausea and vomiting in a patient with metastasised lung cancer

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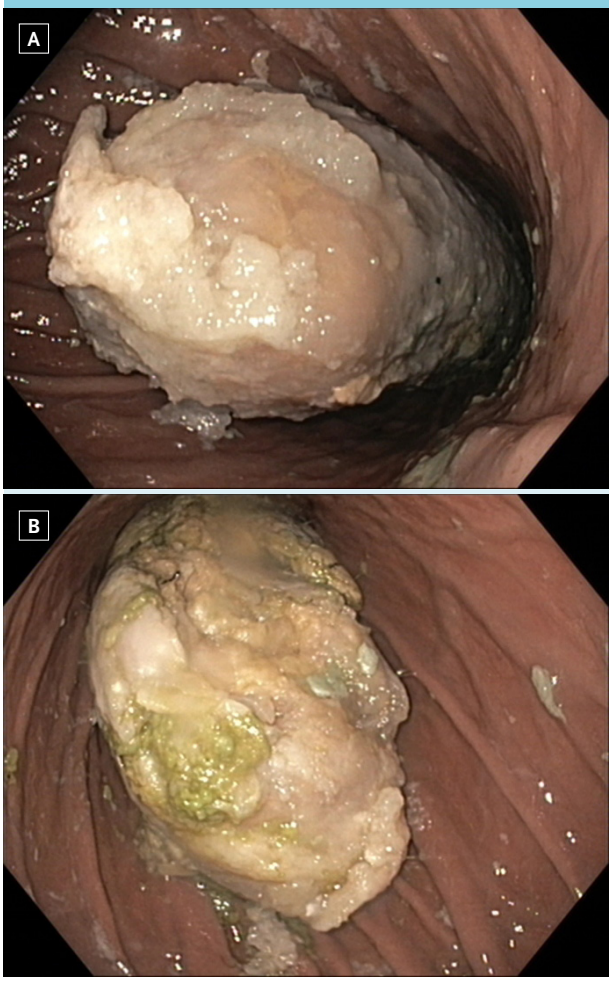
CASE REPORT

A 63-year-old woman with stage-IV adenocarcinoma of the lung, treated with chemo-radiotherapy, was admitted because of persistent vomiting for several weeks, without fever, abdominal pain or a change in bowel habits. She was fed through an enteral feeding tube because of radiation oesophagitis. Her medication list included oramorph, fentanyl (transdermal), esomeprazole, sucralfate, and ondansetron. Besides minor signs of dehydration, no other gross abnormalities were found upon physical examination. Blood analysis revealed an increased C-reactive protein of 71 mg/l, but normal electrolyte levels and renal function. A MRI cerebrum was performed, which showed no signs of cerebral metastases. Next, a gastroscopy was performed (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 216 for the answer to this photo quiz.

Figure 1. *A. Endoscopic inspection of the stomach reveals a large (8x3 cm) bezoar. B. Endoscopic inspection in inversion of the stomach bezoar*



ANSWER TO PHOTO QUIZ (PAGE 215)

AN UNEXPECTED CAUSE OF NAUSEA AND VOMITING IN A PATIENT WITH METASTASISED LUNG CANCER

DIAGNOSIS

Unexpectedly, gastroscopy revealed a large bezoar located in the stomach (8 x 3 cm, *figure 1a, b*). Endoscopic manipulation of the mass was performed to dissect the mass into smaller pieces and allow further passage into the duodenum. Additionally, the patient was treated with domperidone (10 mg orally 4 times a day) and two litres of Coca-Cola in 24 hours. Her symptoms resolved rapidly and she was discharged home two days later.

Bezoars are masses that may be formed from food, medication or hair, which are trapped within the gastrointestinal system.[1] Enteral tube feeding combined with opioids and sucralfate, which the patient used, is associated with development of a bezoar, presumably due to gastric dysmotility and the formation of insoluble complexes between sucralfate and nutritional proteins.[2] A systemic review analysis, largely based on case reports and including 46 patients, revealed that Coca-Cola administration as monotherapy can successfully resolve a phytobezoar in half the cases and in more than 90% when combined with endoscopic intervention. Only a minority of the patients (9%) needed additional surgical intervention to remove the bezoar.[3] The chances of success with cola are higher for phytobezoars, which contain indigestible plant material, than for diospyrobezoars, which are formed from persimmon (sharon fruit and kaki).[1,3] Alternatively, surgical removal or enzymatic digestion may be needed.[2,3]

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PHOTO QUIZ

A gap in memory tape

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CASE REPORT

A 56-year-old right-handed man presented with a three-hour episode of anterograde amnesia and disorientation. He drove ten miles to a horse riding club where he joined his daughter for an hour and drove back home. His family noted that he was confused on return and had repeatedly asked his daughter whether they had been horse riding as planned. He had no memory of driving or spending time at the club.

The patient has no history of epilepsy, head trauma, migraine, or cerebrovascular disease. He was not taking regular medications. He is an ex-smoker having given up smoking 20 years ago.

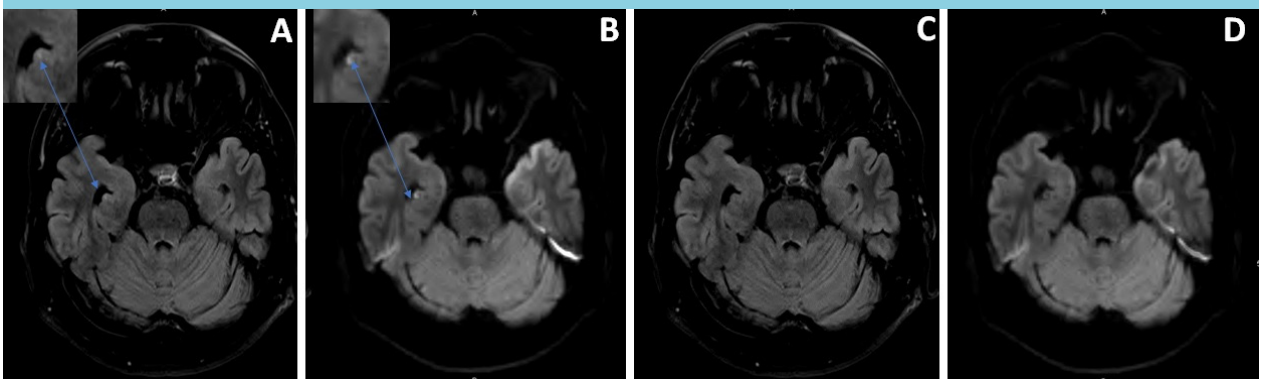
Neurological examination including cognitive function was unremarkable on presentation.

1.5 Tesla magnetic resonance imaging (MRI) of the brain performed four days later revealed right hippocampal restricted diffusion (*figure 1*). Routine blood tests, EEG, Holter monitor, carotid Doppler, and transoesophageal echocardiogram were normal, and the toxicology screen was negative. A repeat MRI two months later showed complete resolution of signal abnormality across all the MRI sequences including T2 and fluid attenuation recovery (FLAIR).

WHAT IS THE DIAGNOSIS?

See page 218 for the answer to this photo quiz.

Figure 1. *A. Axial fluid attenuation recovery (FLAIR) MRI of the brain shows right hippocampal hyperintensity; B. Axial diffusion-weighted imaging (DWI) MRI of the brain shows a hyperintense spot on the right hippocampus; Repeat FLAIR (C) and DWI (D) two months later show resolution of the hyperintensity and the restricted diffusion respectively*



ANSWER TO PHOTO QUIZ (PAGE 217)

A GAP IN MEMORY TAPE

DIAGNOSIS

Based on the clinical scenario alone, a provisional diagnosis of transient global amnesia (TGA) was made and alternative conditions such as acute confusional state, psychogenic amnesia, seizure as well as transient ischaemic attack (TIA) were considered to be possible differential diagnoses. Our clinical suspicion was later confirmed when the MRI showed a typical appearance for TGA (see *figure 1*).

TGA is characterised by sudden anterograde memory impairment of no more than 24 hours and patients recover fully without any long-term consequences. Patients retain personal identification, do not lose consciousness and can function during the episode.

The aetiology of TGA is a matter of continuing debate and although the clinical features are well defined, the exact pathophysiological mechanism remains unclear. Several aetiological possibilities have been suggested including ischaemia, migraine, epileptic phenomena and hippocampal venous congestion.[1] In this text, we provide evidence against the ischaemic hypothesis.

Focal diffusion lesions can be selectively seen in the CA-1 field of the hippocampal cornu ammonis and detection is maximal 48-72 hours after symptom onset.[2] CA-1 neurons are involved in the process of memory stabilisation after its initial acquisition.

Given the diffusion restriction on MRI, TGA is often mislabelled as an acute ischaemic event. Multiple studies, however, have shown evidence against arterial ischaemia as an underlying mechanism in TGA.[3,4] The lack of signal abnormality in FLAIR sequences in repeat imaging (*figure 1*) is against ischaemia as we would expect to see persistent gliotic changes in stroke cases.[4] Secondly, bilateral hippocampal DWI changes are reported in 16.3% of patients with TGA,[5] again making an ischaemic cause unlikely in view of the simultaneous involvement of two different vascular territories. Thirdly, Toledo et al. investigated perfusion MRI in the acute phase of TGA and it was found to be normal.[3]

In summary, TGA is a benign clinical syndrome with a low recurrence rate. No specific treatment is required, however, differentiation from epilepsy and TIA is of paramount importance because these conditions require different diagnostic and therapeutic approach; and have different prognostic implications.

DISCLOSURES

The authors report no disclosures relevant to the manuscript.

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PHOTO QUIZ

What can smudge the 'tough body' corpus callosum?

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CASE REPORT

A 57-year-old lady was admitted acutely to the ICU with progressive confusion and seizures. She had a prolonged history of alcohol excess, complicated by chronic pancreatitis. She was managed symptomatically and received high-dose thiamine supplementation.

Magnetic resonance imaging (MRI) of the brain showed oedema at the left parieto-occipital lobe (*figure 1*), a rounded lesion in the splenium of the corpus callosum (*figure 2A*) and periventricular white matter changes (*figure 2B*). She improved spontaneously. Repeat MRI brain, two weeks after presentation, showed complete resolution of the previously noted oedema at the left parieto-occipital lobe, but the persistence of the corpus callosum lesion and the periventricular white matter changes.

One year later, she represented with complaints of missing and hitting objects on the right side of her visual field, as well as memory loss and unsteady gait. Repeat MRI brain showed the persistence of the previous changes in addition to corpus callosum atrophy.

Figure 1. *T2 and ADC sequences showing oedema at left parieto-occipital lobe (arrows)*

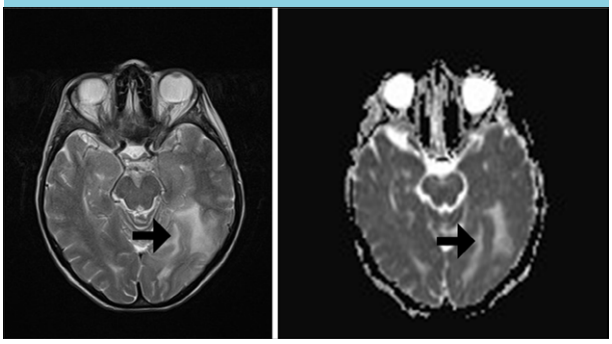
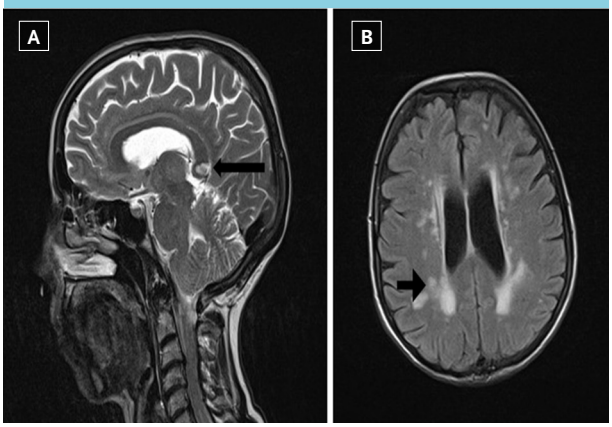


Figure 2. *T2 sequence showing a rounded lesion in the splenium of the corpus callosum (A) and Flair sequence showing periventricular white matter changes (B)*



WHAT IS THE MOST LIKELY DIAGNOSIS?

A. Infarction
B. Susac syndrome
C. Multiple sclerosis
D. Acute disseminated encephalomyelitis
E. Marchiafava-Bignami disease

See page 220 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 219)

WHAT CAN SMUDGE THE 'TOUGH BODY' CORPUS CALLOSUM?

DIAGNOSIS

The clinical presentation and MRI findings are suggestive of Marchiafava-Bignami disease. It is a rare condition, frequently associated with alcoholism. Brain MRI may show callosal, but also extra callosal white matter, and cortical lesions.[1,2] Our case is unique because there was oedema which subsequently resolved on repeat MRI. The course of the disease may be acute, sub-acute, or chronic, and is marked by dementia, spasticity, dysarthria, and inability to walk. Patients may lapse into a coma and die, survive for many years in a demented condition, or occasionally recover. An interhemispheric disconnection syndrome has been reported in survivors.[3]

What else can smudge the 'tough body' corpus callosum? Infarction isolated to the corpus callosum is relatively rare given its robust collateral blood supply. When infarctions occur, the splenium is most often affected, followed by the body and genu. Susac syndrome is an arteriopathy which causes small multifocal snowball-like lesions predominantly involving the central parts of the corpus callosum. Other features of Susac syndrome are encephalopathy, branch retinal artery occlusion and hearing loss. With its predominance of myelinated fibres, the corpus callosum is also affected by demyelinating diseases, such as multiple sclerosis and acute disseminated encephalomyelitis. Callosal lesions in multiple sclerosis tend to be small and involve the inferior aspect. Acute disseminated encephalomyelitis causes larger enhancing lesions that often cross the midline and may reach the upper and lower margins of the corpus callosum.[4]

DISCLOSURES

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

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PHOTO QUIZ

A pulmonary masquerade...

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CASE REPORT

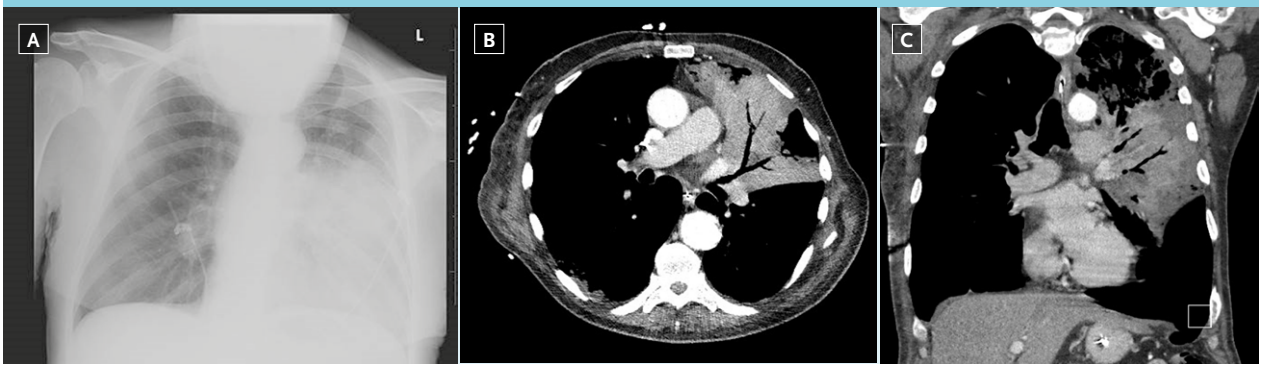
A 66-year-old male was admitted to the intensive care unit in respiratory distress. Medical history revealed type 2 diabetes mellitus, a small right-sided lacunary cerebral infarction and alcohol/nicotine abuse. Known prescribed medications were metformin, folic acid, clopidogrel, pravastatin, fosinopril, amlodipine, ranitidine and hydrochlorothiazide. Physical examination showed a very tachypnoeic patient using the accessory respiratory muscles, respiratory rate 40/minute, $SatO_2$ 85% with 15 litres/minute oxygen on a non-rebreather mask, blood pressure of 160/80 mmHg, heart rate of 100/minute and tympanic temperature of 37.3 °C. Blood gas analysis showed a metabolic compensated respiratory acidosis (pH 7.38, pCO_2 7.0 kPa, HCO^{3-} 30.6 mmol/l, base excess 4.4 mmol/l) and hypoxia (pO_2 8.5 kPa, $SatO_2$ 90%). He was intubated and immediately mechanically ventilated. Laboratory results showed leucocytosis (35 x 10^9/l) and C-reactive protein of 39 mg/l. Chest X-ray (*figure 1, panel A*) showed extensive infiltration of the left upper lobe, suspicious for infectious pneumonia. We suspected a severe case of community-acquired pneumonia and started intravenous treatment with penicillin 6 million units a day and ciprofloxacin 400 mg three times a day.

In the next few days the patient did not improve. Urine testing on *Legionella pneumophila* and *Streptococcus pneumoniae* antigen was negative, as were blood/sputum cultures and PCR testing on bacterial and viral respiratory micro-organisms. CT scan (*figure 1, panel B and C*) showed dense consolidation with air bronchograms, suspicious for necrotising pneumonia. On day 3, a bronchoalveolar lavage (BAL) was performed, which showed no airway obstructions but large quantities of thin, bright, clear-white foamy sputum. Again, all cultures stayed negative. Eosinophilic pneumonia/pneumonitis was excluded by testing the BAL liquid on eosinophil count. His situation worsened and intermittent ventilation in a prone position was needed. Finally he was treated with high-dosed steroids for a 'cryptogenic organising pneumonia'. Again there was no improvement.

WHAT IS YOUR DIAGNOSIS?

See page 222 for the answer to this photo quiz.

Figure 1. *A. Chest X-ray: dense consolidation in the left upper lobe, with positive silhouette sign with the heart and normal appearance of the left hemi-diaphragm; B. CT scan of the chest with intravenous contrast, axial view: consolidation left upper lobe, with air bronchogram; C. Chest CT scan with intravenous contrast, coronal view: consolidation of left upper lobe, with air bronchogram*



ANSWER TO PHOTO QUIZ (PAGE 221)
A PULMONARY MASQUERADE…

DIAGNOSIS

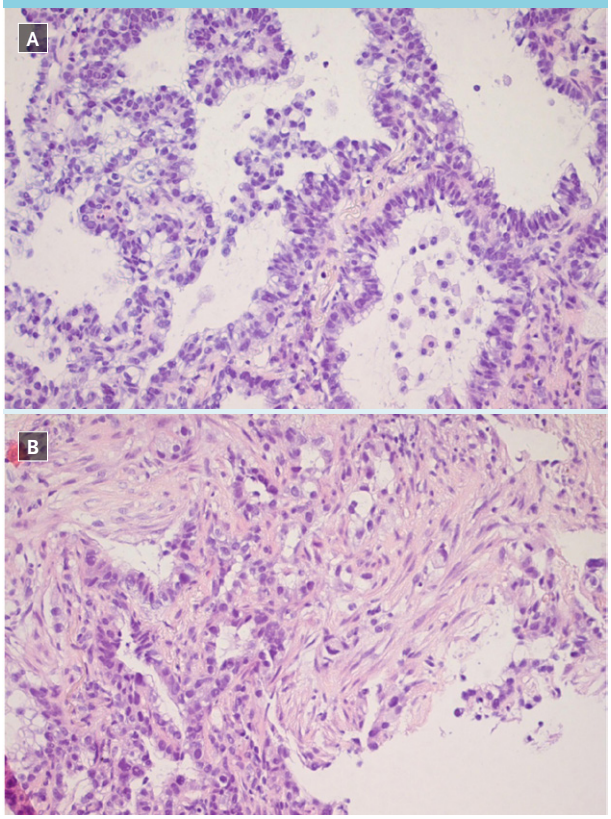
Ultimately transthoracic ultrasound guided 18 G needle biopsy was performed (*figure 2*), revealing a diagnosis and explanation why this patient did not improve despite full ICU treatment: lepidic predominant adenocarcinoma. Unfortunately there were no curative treatment options. Treatment was stopped and he died soon after. The family did not grant permission for autopsy.

Lepidic predominant adenocarcinoma (LPA), known as bronchioloalveolar carcinoma prior to the IASLC/ATS/ERS lung adenocarcinoma classification from 2011,[1,2] is often difficult to differentiate from pneumonia.[3] LPA typically arises in the periphery of the lung, and grows along the alveolar walls, often without destruction of the underlying parenchyma.[3] Because of this so called lepidic growth, radiographic images may be indistinguishable from pneumonia or can appear as ground glass opacity.[2,3] Clinically, 62% of patients with LPA present without symptoms and with only an abnormal chest X-ray. The other 38% present with symptoms of cough, chest pain and sputum production, which in itself can lead to suspicion of infectious pneumonia. Bronchoscopic examination is usually normal.[4] LPA may radiographically and clinically resemble not only pneumonia, but also non-infectious inflammatory processes (hypersensitivity pneumonitis, cryptogenic organising pneumonia, various vasculitic processes).[3] Lack of fever and leucocytosis, with persistence of abnormal radiographic findings should raise suspicion about the correctness of a diagnosis of infectious pneumonia, and a focal or unilateral infiltrate points against many of the other non-malignant diseases mentioned above. Although hard to differentiate from infectious pneumonia, CT findings favouring the diagnosis of invasive adenocarcinoma include an air-filled bronchus within consolidation with stretching, squeezing, sweeping, widening of the branching angle and bulging of the inter-lobar fissure,[5] coexisting nodules and a peripheral distribution of consolidation.[6] An empirical trial of antibiotics and reassessment of clinical/radiographic findings is a reasonable approach. However, histological biopsy is the only means of diagnosing a malignancy and ruling out other aetiologies. Thus biopsy should always be considered when patients do not respond to antibiotics.[3]

DISCLOSURES

The authors have no conflicts of interest to declare.

Figure 2. *A. Microscopic image of lung biopsy showing adenocarcinoma with partially lepidic growth pattern (200x magnification); B. Microscopic image of lung biopsy with multiple foci of stromal invasion (200x magnification)*



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