ELEVENTH EDITION - SEPTEMBER 2018

RAMS

Radboud Annals of Medical Students

EDITORIAL EDITION

Radboudumc

COLOPHON

Edition	Eleventh
Date of publication	September 2018
Place of publication	Nijmegen

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Delivery code: M230.01.106
ramsresearch.nl

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FROM THE EDITORIAL BOARD

Dear readers,

The immune system is an exemplary topic for the complexity of balance. We must know how to defend ourselves from pathogens and malignant cells but learn to accept what means us no harm like commensal bacteria and our own organs. To me, it is fascinating to see how something that was developed to protect us, can be just the thing that damages us. Aberrant clearance, too much of the wrong humoral or cellular immune response or an immune response to the wrong stimuli; these are all things that can lead to immense damage to our bodies. Read that again but replace everything about the immune system by elements of our standard of care, and we are still talking about a topic which is captivating to me for its complicated balance. Despite the Hippocratic Oath, which is historically taken by physicians, those who mean us no harm, sometimes do just that.

The base of modern medicine is scientific research. However, many medical operations are performed without supporting scientific evidence for their effectiveness and relevance. Although the first steps to improve this situation have currently been taken, a great deal of improvement is still warranted. A bigger role for research in the base of medical attention could aid in this.

In my opinion, research is an excellent tool for the expression of ambition, enthusiasm, and curiosity. However, to me, taking part in research does not only mean furthering scientific knowledge in my field of interest out of ambition, enthusiasm and curiosity. By taking part in research, I also hope to contribute to better therapies for the patients of tomorrow and more rapid and accurate ways of diagnosing them. Having more medical doctors involved in biomedical research could aid in this. Therefore, I would like to invite you to take part in research yourself. The fact that you are reading this edition of RAMS is a good start.

In this eleventh edition of Radboud Annals of Medical Students (RAMS), we present you a collection of articles by and for (bio)medical students. This edition is special, as we here present to you a collection of editorial articles. Here, you will read about the efficacy of cranberries in urinary tract infections, the value of doing a PhD and the learning curve in surgery. Moreover, in this edition you will find interesting articles about the impact soccer can have on the brain, conversion disorder and the (lack of) added value of Ritalin on learning efficacy. You will also read about the topic of our cover photo: Takotsubo cardiomyopathy, or better known as the broken heart syndrome.

Enjoy reading this edition of RAMS and know that taking part in research and RAMS is only an e-mail away.

Yours faithfully,

Rosalie Kempkes
Editorial Editor-in-Chief

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MYTH OR SCIENCE?
CRANBERRIES: TO PEE OR NOT TO PEE?

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Critical Appraisal

Dysuria, polyuria, and urinary urgency. These three symptoms combined should ring a bell with all medical students: they are typically seen in patients with cystitis. Cystitis and other urinary tract infections (UTIs) are common; 40% of all women develop at least one UTI episode in their life [1]. Fortunately, an UTI can be cleared rapidly without therapeutic interference or, if needed, cured by antibiotics. "Problem solved", one could think. But with the increasing development of antimicrobial resistance among micro-organisms, it seems feasible to look for other options to treat persistent UTIs or to prevent them altogether. Cranberries are sometimes already being advised for the prevention of UTIs, but is there truly a proven benefit for its use?

Classification and epidemiology of UTIs

Urinary tract infections (UTIs) are the most common bacterial infections and the most frequent reason for women to consult their general practitioner. UTIs are more prevalent in women than in men. The incidence of cystitis in women is 70 new episodes per 1,000 women every year, whereas in men the incidence is 10 new episodes per 1,000 men every year. This can be explained by examining the anatomical differences in the urinary tract between women and men. The urethra of women is shorter, and the meatus lies in closer proximity to the anus, resulting in a higher risk of bacterial transmission from faeces to the urinary tract. Consequently, most UTIs are caused by colonisation of the bladder by the bacterial contaminant *Escherichia coli*. UTIs can be divided by anatomical location into lower UTIs and upper UTIs. In addition, UTIs can be further categorised into complicated or uncomplicated UTIs. Infections of the bladder, prostate or urethra are characterised as a lower UTI. Infections of the ureter or the kidneys constitute the upper UTIs. A UTI is regarded as uncomplicated only if the patient is a healthy, non-pregnant female with cystitis. All other cases are automatically characterised as complicated UTIs. Isolated cystitis can progress to an upper UTI, like pyelonephritis. Another complication of cystitis is acute prostatitis. The incidence of these two complications is lower than that of cystitis. Pyelonephritis has an incidence of 1 out of 1,000 males and 2 out of 1,000 females every year. The incidence of acute prostatitis is 2 out of 1,000 males every year [2]. The latter can present as an isolated infection, although generally an associated cystitis is found.

Treatment of UTIs

The first step in the first-line treatment of uncomplicated UTI is conservative. It is advised to drink plenty of water to generate an optimal urine flow and use analgesics if necessary [3]. If this does not clear the infection within a week or the patient experiences too much pain, the general practitioner will proceed to the second step of the protocol, i.e. the initiation of antibiotic therapy [4]. Nitrofurantoin 100 mg twice a day for five days in a row is the first choice antibiotic. If ineffective, an one-time oral dose of 3,000 mg fosfomycin can be prescribed. When the UTI is still persistent, a patient might be given trimethoprim 300 mg one time a day for three days. This order of antibiotics is included in the protocol based on the prevalence of *E. coli* resistance to these antibiotics. Nitrofurantoin shows the lowest resistance and is thereby the antibiotic of first choice. As the infection appears to be more persistent and more potent, broad-spectrum antibiotics are prescribed. This should not be done in an earlier stadium in order to limit the development of antibiotic resistance in the population. Moreover, a urine culture including antibiogram should be obtained in any patient not responding to the initial antibiotic therapy. Patients with recurrent cystitis can have an indication for prophylaxis in the form of cranberry products (drink or tablets) or antibiotics like nitrofurantoin or trimethoprim [5]. Antibiotics are effective in the treatment of UTI infections but have some disadvantages. Using antibiotics as a treatment can not only cause antibiotic resistance but can also cause a disbalance of the microbiome. Antibiotic treatment is also associated with increased oxidative stress which might lead to side effects such as ototoxicity, nephrotoxicity, and tendinopathy [6]. Limiting its use is therefore desirable. Cranberries do not contribute to the development of bacterial resistance. But is there any evidence that cranberry products reduce the incidence of UTI? And would it be a suitable candidate to reduce the use of antibiotics?

Cranberries and cystitis

A systematic review published in 2017, including 7 randomised controlled trials, revealed that cranberries reduce the risk of UTI by 26% in healthy nonpregnant women above 18 years with a history of UTI [7]. The authors concluded that cranberries may be effective in preventing UTI recurrence in generally healthy women. However, the studies used in this systematic review were small, two studies had more than 300 participants. Larger, high-quality studies are needed to confirm this hypothesis. A randomised controlled trial from 2017 examined whether highly standardised cranberry extract oral supplementation is effective as prophylaxis in young healthy boys and girls with recurrent UTIs [1]. Thirty-six subjects aged 12-18 years with recurrent UTI and negative experiences with different antibiotics were included. Exclusion criteria were defined as chronic clinical conditions or risk factors, immunological diseases, concomitant infections of any nature, active (micro- or macroscopic) haematuria, treatment with antibiotics or corticosteroid for any reason in the last 6 months, allergy, or intolerance to cranberries. A urinary culture was performed in all participants, and only those with negative cultures and thus without signs of active infection or bacteriuria were included. The participants were divided into two groups: one group received only the standard preventive management and the other group received the standard preventive management with the addition of oral cranberry extract. Standard preventive management consisted of lifestyle and hygiene instructions. The 120 mg oral cranberry extract was used for 60 days. The number of UTIs in the two months before inclusion was compared with the number of UTIs in the two-month follow-up period. In addition, the number of symptom-free subjects during the registry period was evaluated. The group with standard preventive management showed no decrease in the number of UTIs. The supplemented group, however, showed a noteworthy decrease in the number of UTI and reported fewer symptoms during the registry period (63.1% compared to 23.5% in the control group).

The supplement consisted of 36 mg of proanthocyanins (PACs) which are thought to be the active substance in cranberries. PACs seem to act against pathogens by preventing bacterial adhesion to the uroepithelium and co-aggregation, decreasing biofilm formation and/or reducing inflammation. Fruits are rich in PACs but this is mostly the B-type PACs. Cranberries are rich in A-type PACs which are thought to be most effective in the exertion of its preventive effect within the urinary tract [8]. For example, the *E. coli* is in possession of P-fimbriae that the bacterium uses to bind to the urinary tract epithelium (Figure 1). A-type PACs seem to prevent this binding by decreasing the adhesion forces of the bacteria by shortening the P-fimbriae on the bacterial cell [9].

The results of the randomised controlled trial support the effect of PACs in the prevention of UTIs in subjects who suffer from recurrent UTIs. Unfortunately, the subject group was small and is thereby not the larger high-quality study the authors of the systematic review were looking for. On top of that, the follow-up period was only two months, which is very brief for the follow-up of these chronically recurrent patients.

Conclusions

Cranberries are currently being used as prophylaxis for patients with recurrent UTIs. Although the evidence for the efficacy of cranberries is not enough to conclude the prophylactic effect, it seems that cranberries may play a role in the prevention of UTIs in healthy individuals suffering from recurrent UTIs. More evidence will be needed to confirm the prophylactic effect of cranberries in UTIs, as well as in the more complex patients with relevant comorbidity. Until then, though, we should assume that it works.

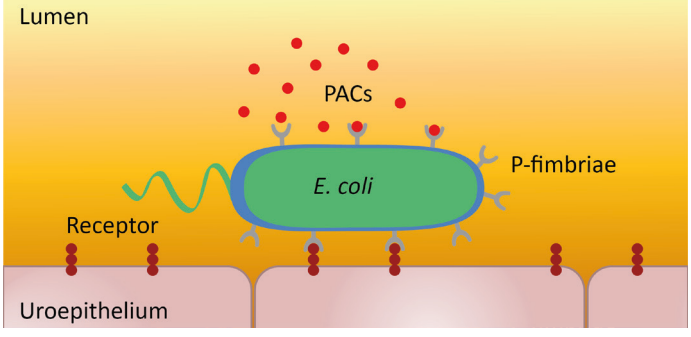

Figure 1: Binding of E. coli to the urinary tract*. The binding of the P-fimbriae to the urinary tract can be prevented by proanthocyanins (PACs). Without the binding, the bacteria cannot hold onto the urinary tract and will be excreted more easily in the urine. This prevents the colonisation of the bacteria in the urinary tract and thereby preventing urinary tract infections (UTIs).*

Acknowledgements

RAMS would like to thank F.J.P. (Hans) van Valenberg, MD, PhD-candidate, Department of Urology, Radboud university medical center Nijmegen, The Netherlands for supplying the author of this article with feedback on what was written in this article.

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JOIN SCIENCE TO HAVE A SIGNIFICANT IMPACT ON HEALTHCARE

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Interview

Each year, approximately 200 PhD students from Radboudumc defend their PhD thesis and obtain the honorary title of "dr.", resulting in them finally being able to call themselves "Doctor of Philosophy". A PhD is a unique academic title that proves that the belonger of this title has successfully participated in advanced academic work. It is a good method to distinguish oneself, as it is attempted by comparatively few students after graduation. Moreover, it is a good opportunity to have a significant impact on healthcare, as the belongers of this title in the medical sciences have performed work which greatly aids the understanding of human disease and health. Thus, it is no surprise that performing research in the career of the young doctor is becoming more of a rite of passage than an exception.

Philosophiae Doctor

PhD is the Latin abbreviation of "Philosophiae Doctor". It is an advanced postgraduate degree involving three or more years of independent research on an original topic. A PhD is carried out with the support from one or more expert academic supervisors; the promotor being the principal supervisor. The end result is a thesis that offers a significant original contribution to knowledge leading to innovative implementations or lays down a basis for further research. Often, a PhD-position is obtained by applying for an open position, or internal via previous internships or connections. Here in Nijmegen, it is also possible to compete for a position in a unique way, namely via the PhD research proposal competition. This competition was brought to life by the Radboud University and Radboud university medical center in 2009. It offers master students the possibility of designing their own PhD, which is a unique opportunity in the sense that the students have the chance to devise and write their own PhD research project, in collaboration with a department of the Radboud university medical center. Students who win the competition receive a grant which is sufficient to carry out their self-written project for the next three or four years. Currently, each year, five to six students can start their own PhD project. But what does doing a PhD entail? Editors of RAMS interviewed three winners of the PhD competition from previous years, Thijs Landman (2017), Daan Viering (2018) and Jeroen Slaats (2016), to find out how they value performing a PhD and how they perceived their road to their self-written PhD-research.

Choosing a field of interest

It can be difficult to decide in which department and research topic you would like to do a PhD in but knowing the fields that interest you can help. During his bachelor's, Thijs Landman participated in the disciplinary honours programme. In the context of this programme, he performed some small-scale research at different institutes, such as the Donders Institute and the Radboud Institute for Molecular Life Sciences (RIMLS). Eventually, he performed research in the field of Physiology on ischemic conditioning for six months as part of his master's research internship. Halfway through his master's programme, a former mentor contacted him, asking whether he wanted to participate in the PhD-competition as his previous experience would make him a suitable candidate. Thijs took an interest in this and chose to further pioneer the field of ischemic conditioning, but this time combining it with the newer insights in its use in cerebrovascular accidents (CVAs). With the help of his current promotor, he produced a research proposal. In 2016 Thijs got selected and since December 2017 he has been receiving funding for his research. "Without this course of events, I would not be doing a PhD right now". He continues to explain the importance of engaging in research early on in your studies. "Preferably start in your bachelor's, because of time management." Also, early experience gives you an advantage in getting a PhD because the regular medical curriculum does not allow for obtaining much experience by itself.

Daan Viering's previously performed research on the genetic causes of hypomagnesemia was in the context of the disciplinary honours programme he performed at the Department for Physiology and partially in London. At first, he doubted whether he wanted to continue within magnesium research or work on another subject. Now, he chose a subject within physiology which is more directly applicable to more patients than his previous research. Starting this year, Daan will study the role of mitochondrial biogenesis in the pathophysiology of hypertension. "This subject will definitely keep me interested for three to four years: we are still far from unravelling the cause of essential hypertension." Daan is drawn to fundamental research because he feels like more boundaries can be pushed when you are still at the beginning of the research. This first part can be the base for many diagnostic or therapeutic strategies in the future. Next to a fundamental research aspect, it was important for him, being a future doctor, to incorporate a clinical aspect in his research proposal as well. "It is of great importance to me to eventually get to the relevance of the research for your patient." Last but not least, the positive working atmosphere Daan experienced at the departments before were of great importance for choosing this field of research. "My supervisor was willing to check my work in the evening hours, this was a great help for me!"

Jeroen Slaats wanted to participate in the competition with the same lab he did his internship with but on a slightly different topic. "The research topic I am working on now is not the same as when I did my internship here. During my internship, I got to know the research topics of my colleagues and I quickly decided that one of those was the one I wanted to continue in. "To participate in the competition, you need a professor from a research group willing to supervise you during the competition and your PhD, which supports your project and ideas. "At a certain moment, I went to my professor and told him I wanted to participate and which research topic I wanted to explore. Fortunately, my professor was enthusiastic as well and together we participated in the competition. Participating is not something you do alone, you do it together with your supervisor who will help you with writing the proposal."

Current limitations

Thijs was in doubt whether he wanted to do a PhD as he chose to study medicine to become a clinician, not a researcher. Four years of research seemed like a pretty long period. Looking back, he was largely motivated to complete a PhD to gain an advantage when applying for future jobs, which he admittingly says is not the most valid reason to start a PhD. Later, while writing the proposal, he found himself enjoying the process way more than he had previously expected. Reading the scientific literature on his topic, Thijs found himself becoming a lot more enthusiastic. Now he also realises that it is a path of personal development. Furthermore, he now acknowledges that you are still young when you finish your master's. Therefore, gradually becoming a clinician by first expanding your knowledge of research can be beneficial. Thijs humbly explains: "I do not think I will become a better doctor per se, but I can become the type of doctor I want to be: critical of the research underlying medical guidelines."

Daan's interest in research was raised early in his studies. In his second year of Medicine, he already performed his first research internship. "I have known that I wanted to do a PhD project for years." Daan really enjoys taking the time to dig and dive into a topic. Discovering new things and experimenting is something he wants to do besides his beloved patient communication. "I am curious by nature and want to find out the mechanism behind a disease. Within a PhD trajectory, I can really get to the bottom of this." Daan first heard of the PhD competition from an acquaintance when he was waiting to start his masters. In March 2017 he discussed the idea to apply for the competition with the supervisor of his previous internship, Jeroen de Baaij. The first deadline for a concept proposal was in September. When you get selected to further develop your proposal, you get approximately 1,5 months to write a full research proposal. "I started too late, which resulted in a race against the clock," Daan laughingly admits. At the time, Daan was also busy with his clinical internships, so he was designated to his weekends and evenings to meet the deadline. In the last week, there was a major setback, "The design for the clinical part of the study was considered unsuitable by an expert". Therefore, Daan and his supervisor had to think quickly for a new method and apply rigorous changes to the study design. "The end result was much better, therefore this was totally worth the hours of sleep I missed. These unforeseen scenarios are part of scientific research."

Jeroen's primary motivation to do research is not to help patients. "Of course, being able to help patients with your research is something you want to achieve, but curiosity and the ambition to investigate certain questions is my primary motivation. That you want to know how something works. It is important to be enthusiastic about problems and wanting to solve them. For me, that is what truly motivates me. I can become very enthusiastic by discovering new things and solving the puzzle." He already noticed this during his first internship in his bachelors, which is why he chose the research master Molecular Mechanisms of Disease, here at Radboud University. As part of his master's studies, Jeroen had already written several research proposals.

The obstacles to doing a PhD

"At some moments it might be a little dull," Thijs admits. It will take some time before the trial starts and most of the preparations are already done. Meanwhile, he is expanding his knowledge by studying more literature, but he would rather start putting it into practice. "It is also about keeping a daily routine to stay mentally fit, so that I will be ready when the trial starts." Besides studying literature, there are still some e-mails to be sent concerning preparations and sending those can be a bit frustrating. "It can take days before I get a reply to my e-mails. Luckily, the professor forwards important e-mails and not surprisingly he gets a reply the next day!" Most importantly, Thijs mentions that it is important to be very critical about whether your research topic is interesting to you. "Otherwise, four years can be a very long time."

"I like living in Nijmegen, so I do not mind being bound to the Radboud university medical center. However, when you do not want to stay in Nijmegen this could be an obstacle for entering the PhD competition," Daan says. However, the PhD competition is obviously not the only way to obtain a PhD position. You can find a PhD programme that fits you when you are willing to spend enough time and energy in it. Secondly, Daan mentions that by doing a PhD within the format of the PhD competition, you have to start with your PhD traject within a certain period of time. The downside to this is that you postpone your development towards becoming a medical doctor.

When asked which parts of his PhD he enjoys less, Jeroen answered kiddingly: "There are only enjoyable things about doing a PhD." After a few seconds of silence, he concedes. "Doing research can be very frustrating." He explained that often expectations will not be realised, results are disappointing, and many experiments do not work out. "As a researcher, you need unjustified optimism. Even if twenty things go wrong or you are behind schedule, you still need to think: "If I try it this way, it will work". He reveals that currently, after his first year of his PhD, he is already behind schedule. However, Jeroen did not seem distraught or anxious about this. "That is PhD-life," he shrugged. "Eventually it will work out." These negative aspects disappear once a discovery is made. "When you finally discover great or unexpected findings, it boosts your motivation enormously," he said enthusiastically. "Champagne will be flowing and none of the disappointments and frustrations will matter anymore."

The perks of doing a PhD

"It all takes a lot of work, but you are the one putting your knowledge and literature searches into practice, that makes it a lot of fun!" Thijs also believes that, after a study in medicine, there is still a lot more to learn about statistics and methodology. Additionally, Thijs looks forward to attending interesting conferences or to link a business trip to his research. "It is not only about the PhD itself, having a PhD creates new possibilities and further developes your personality." Moreover, after receiving the title, it could be easier to combine his job as a clinician with research, working in an academic hospital and to teach at a university.

The PhD competition is a wonderful opportunity to fund your PhD-trajectory. Daan thinks the advantage of bringing in the money yourself is the freedom you get in coming up with your own research question and design. Because of his research experience, Daan is already noticing that it is easier for him to critically read scientific articles than for students without this experience. His former position in RAMS also contributed to the improvement of this skill. As mentioned earlier, Daan stresses that performing a PhD gives you the opportunity to delve into a topic.

Doing a PhD most likely means that now and then you will spend evenings and weekends working. However, despite the irregular working hours, Jeroen considers his work as a hobby and regards the irregularity as an advantage. "You can decide for yourself how you want to spend your time, it is very flexible," he said cheerfully. "As long as you finish your work and show progress, nobody cares what time you start or finish the day, or if you work from home. Admittedly, not everyone works as much outside the regular working hours, but I do not mind working during weekends." Jeroen's impatience to get the results of his experiments are often the reason he spends evenings or weekends working. Aside from the flexibility, Jeroen enjoys other activities that accompany doing a PhD, like attending workshops to improve, for instance, his writing skills. "During a PhD, you do not just learn to do research. You learn to communicate and to present. What I also enjoy is being critical towards research of yourself

and others." Besides acquiring experience in writing research proposals, at the start of the PhD-trajectory, you are up-to-date with the literature in the field and familiar with the project.t

The road ahead

Thijs anticipated his PhD to be a lot of work right away but for now, life is pretty laid back as he is waiting for the trial to start; the calm before the storm so to say. "At the beginning, the trial will be a lot of "hands-on" work for everything to go as planned, such as the inclusion of patients and pressuring the cuffs". Later on, Thijs can use the electronic health records to gather the information needed from roughly 200 patients. He can then focus on smaller scale research projects, such as the autoregulation of perfusion in the brain. Eventually, he would like to work at the Emergency Department as a dedicated doctor and boost research in this field of work because in the Netherlands it is relatively new specialisation.

Halfway November 2018, Daan will officially start with his PhD. However, preparations such as applying for the ethics committee to be allowed to work with animals and obtain patient samples will keep him tied up for a while. "What does my future look like careerwise?" Daan wonders. "Well, in the short term I hope that part of my PhD-trajectory will take place abroad and in the long term I am hoping to become an physian in Internal Medicine."

Jeroen is not sure yet what he wants to do after his PhD. "Maybe you can tell me?" he said jokingly. We suggest a postdoc. "Perhaps I will be a permadoc, a permanent postdoc." In the academic world, it is not common to be a permanent postdoc. However, apart from becoming a postdoc after a PhD, there are numerous alternatives. "The advantage of doing a PhD is that you learn so much that it does not limit you to a future career in the academic world. It is possible to do research as part of a company, or apply for a job in marketing." As Jeroen still – or only – has three years to go before he finishes his PhD, he has plenty of time to trouble his head about it.

Thijs Landman

Being fresh out of medical school, Thijs Landman is about to start his clinical trial on remote ischemic postconditioning in patients with an ischemic cerebrovascular accident (CVA) at the Department of Physiology. The technique of ischemic conditioning, first described in 1986, boils down to exposing tissue to shorts periods of hypoxia, which results in a smaller sized infarction when an actual ischemic event takes place. This can be pre-conditioning when it is performed before the ischemic event, or post-conditioning when done afterwards. Right now, "remote" ischemic conditioning is being tested in a major trial in Cardiology. "Remote" means that hypoxia will not be induced locally, but in a distant tissue, usually by inflating a cuff around the upper arm (just like when you are taking someone's blood pressure). Small-scale research suggests that it might also reduce ischemia after a CVA. Thijs is going to test this in a clinical trial. The hypothesis is that the remote postconditioning produces a systemic anti-inflammatory response. This in turn, reduces the penumbra, an area of ischemic but still viable brain tissue, around the actual infarction. Hopefully, this very patient-friendly intervention will reduce the size of the definite infarction size.

Jeroen Slaats

More than two years ago, Jeroen, former student Molecular Mechanisms of Disease, decided to compete in the PhD proposal competition and subsequently was one of the winners. Now, Jeroen is a PhD student at the Department of Cell Biology at the Radboud Institute for Molecular Life Sciences. He investigates how cancer cells mislead the immune system in different parts of a tumour in order to prevent immune recognition and killing of these cancer cells. Jeroen uses various microscopy techniques to visualize these processes. Even though he started approximately a year ago with his PhD and receives a salary each month, he admits he still feels like a student, saying: "It is called being a PhD student for a reason."

Daan Viering

Daan will start his research on hypertension at the Department of Physiology half November 2018, after finishing his clinical internships. Hypertension has a high prevalence within the population. For most of the people with hypertension there is no identifiable cause found for their high blood pressure, which is labelled as essential hypertension. There is evidence pointing towards a role for the mitochondria in causing essential hypertension. In his PhD project, Daan hopes to clarify the role of mitochondrial biogenesis in the pathophysiology of hypertension. This may lead towards innovative prevention and treatment strategies. Daan's research includes *in vitro* studies, *in vivo* experiments in mice and clinical experiments on humans.

Small overview of the competition

1. The first step in participating in this competition is finding a topic you would like to do research on for four years. Once you have found a research group and professor willing to guide you during the process, you start writing a pre-proposal. This pre-proposal comprises of your CV and a summary of your project proposal. The emphasis is laid on your CV, which should convince the jury of your abilities and motivation and show that you are a suitable candidate.

2. From all students that submitted a pre-proposal, approximately 10 will be allowed to proceed to the next round, in which you have to write the full research proposal. The time to write the full research proposal is limited and involves frequent meetings with your supervisor.

3. All students that write a full proposal will need to defend it in front of a jury. In 5 minutes, you need to explain the content and relevance of your proposal, after which questions will be asked. Hereafter, five to six winners will be announced that will receive a grant.

Checklist

- ☑ Perform research earlier in your studies, for example as part of the honours programme.
- ☑ Write an article, for example a short review, for RAMS to get familiar with the reviewing process.
- ☑ Contact a department and brainstorm together.
- ☑ Start writing your research proposal early enough.
- ☑ Identify your field of interest and make sure to choose a subject of research that will keep you interested for several years.
- ☑ Your topic should provide for at least 4 publications.

EXAM QUESTIONS

As RAMS aims to enlighten both students and professionals, we would like to present you two exam questions. Find out if you can remember what you have learned during your bachelors!

We challenge you!

Question 1

An alpinist resides at high altitude for several weeks and is, therefore, able to deliver better sports performances. This difference can be attributed to a change in his erythroid progenitor cells. What is this change?

A. Dysplasia
B. Hyperplasia
C. Hypertrophy
D. Metaplasia

(Topic: Farmatoxocology, Module Q6 Movement and Flow 2017)

Question 2

A 70-year-old patient has a slow ventricular rhythm. The ECG exhibits normal QRS-complexes but with no connection to the P-wave. Apparently, there is a total AV block with a narrow ventricular escape rhythm. Where does this escape rhythm originate from in this case?

A. Bundle of His
B. Left bundle
C. Purkinje fibres
D. Right bundle

(Topic: Heart, Blood and Gas Exchange, Module Q6 Movement and Flow 2017)

The answers to these questions can be found on page 25 in this journal.

THE LEARNING CURVE IN SURGERY

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Opinion

From an early age onwards, we are exploring, investigating and discovering. We are learning. Then we go to primary school, secondary school and sometimes eventually enrol in university or college. During all these diverse phases of our lives, we continue to learn. The learning process does not stop there, especially in the (bio)medical field. Obviously, this learning process is often accompanied by trial and error, and that is no different in the surgical field. The performance of a surgeon tends to improve with experience, as described by the theory of the learning curve. But what does this learning curve entail? What are the consequences for surgeons, patients, and the implication of new surgical techniques?

The learning curve was first described in the field of aviation. An aeronautical engineer noticed that the efficiency of aeroplane production increased together with experience within a workforce, while the production costs decreased. Later on, a similar phenomenon was described and studied in many medical specialities. As many of the most severe complications occur in the field of surgery, research on the learning curve of surgeons is highly appreciated [1].

The focus of the assessment of the learning curve within surgical procedures is in most cases a minimal access technique (in which one or more small incisions are made instead of a large incision), such as laparoscopic cholecystectomy or hernia repair. Many different learning related parameters are measured here. There is also discussion about what is a strong proxy for learning and what is a weak proxy and cannot relate to the proficiency of a surgeon. Measurements of learning related to a certain surgical technique can be divided into two categories: measures of the surgical process and measures related to patient outcome. Operative time, radicality of tumour resection and haemorrhage during surgery are some examples of surgical process parameters. Patient outcomes are more often postoperative, such as (long-term) survival, length of hospital stay and postoperative infections. For every surgical technique, different measurements of learning are studied to estimate the course of the learning curve [2].

The surgical learning curve nowadays is different from the learning curve that was depicted years ago. In the past, the introduction of a new surgical technique was limited. If a new technique was introduced, it often was very different from the previously used technique and it led to a substantial difference in effectiveness (Figure 1). The learning curve was often small while effectiveness was reached over a short period of time. Over time the complexity of surgical interventions has drastically increased. A more complex technique has led to longer learning curves (Figure 2). On top of that, new surgical techniques are implemented at a much higher rate and the effectiveness of the new interventions have become smaller. The increased complexity also increased the learning associated morbidity, since it takes more time and more practice to reach proficiency level.

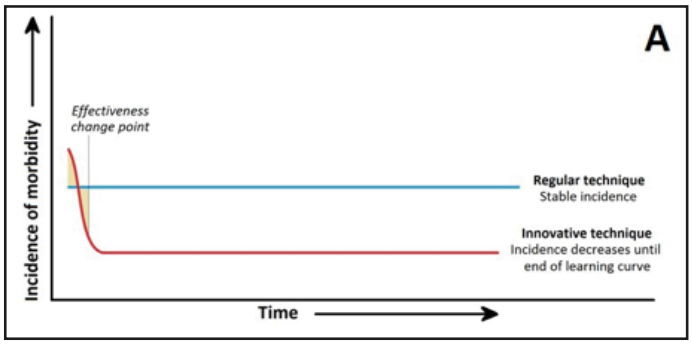

Figure 1: The learning curve as pictured over the last years. *This learning curve is short and has a large post-proficiency difference in effectiveness, which means the new technique was effective after only a small period of time.*

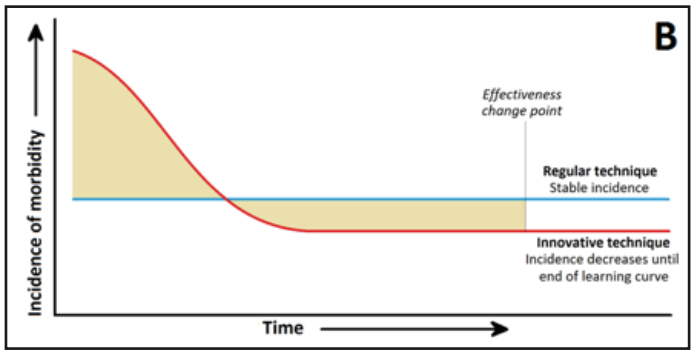

Figure 2: The learning curve nowadays. *Newly introduced surgical techniques are of increased complexity, this leads to longer learning curves and it takes more time before the innovative technique becomes effective. At the same time, the post-proficiency difference in effectiveness is smaller, because there are more and more new surgical techniques that get introduced but they only lead to a minor improvement in surgical outcome.*

It is stated that, in patients who are operated on early after implementation of a new technique, there might be an increased risk of associated morbidity. Highly relevant is the morbidity that is associated with completing the learning curve. Multiple studies recommend that new surgical techniques should be closely monitored because often there is a high learning associated morbidity [3,4]. It is still a point of discussion on how this morbidity can be decreased. It is thought that a better and more intensive preoperative training should be implemented. On top of that, not only the surgeon should be trained, but the whole surgical team [5]. However, data on the reduction of learning curve associated morbidity is scarce.

Van Workum et al. have studied the learning curve and its associated morbidity in minimally invasive esophagectomy (MIE) and show what

the importance can be for patients. In their study, they focused on the burden of learning associated morbidity. This burden is something that is often not taken into consideration when calculating the length of the learning curve. Van Workum et al. conducted a multicenter study on MIE in four European expert centers. After an MIE, an anastomosis is constructed, which can lead to multiple complications such as leakage. This anastomotic leakage was the primary outcome parameter in this study. They found that the incidence of anastomotic leakage decreased from 28.9% at the start of the learning curve to 1.3% after the learning curve was completed. The mean length of the learning curve was found to be 119 cases. But most importantly, 36 patients (10.1% of all patients operated on) had anastomotic leakage that was associated with the learning curve. The researchers conclude that these leakages could have been prevented if the patients were operated by surgeons who already had completed the learning curve [6]. Therefore, it is important to keep in mind what the impact of the learning curve can be on patients.

Conclusion

To conclude, the learning curve in surgery remains a topic much in need of continuous research. The learning curve associated with morbidity can have serious implications for patients. It is still unclear how we can best reduce this learning curve associated morbidity. Further research is necessary to evaluate different learning curves for new surgical techniques and how patient safety can be increased during the learning curve.

Acknowledgements

RAMS would like to thank Frans van Workum, MD from the Department of Surgery of the Radboud university medical center Nijmegen for supplying more extensive insights into this topic and for providing feedback on this article and its figures.

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ZEBRAS OF MEDICINE

TAKOTSUBO CARDIOMYOPATHY: AN INTRODUCTION TO THE BROKEN HEART SYNDROME

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Abstract

Review

BACKGROUND: Takotsubo cardiomyopathy (TTC) is an acute disorder characterised by reversible left ventricular dysfunction. It mostly affects post-menopausal women and is often seen following severe emotional or physical stress.
OBJECTIVE: This review aims to summarize the current knowledge on TTC, thereby informing the reader about the existence and management of the condition and how it can be distinguished from a standard acute myocardial infarction (AMI).
RESULTS: TTC mimics the clinical presentation of an AMI, as symptoms include sudden onset of chest pain and dyspnoea, but at coronary angiography no coronary occlusion is present. Characteristic of TTC is a balloon-like left ventricle (LV) dysfunction at LV angiography. Complications include cardiac arrest, shock, and thrombus formation. An ECG, cardiac biomarkers, echocardiography or LV angiography, and coronary angiography are needed to confirm the diagnosis. The pathophysiology is still unclear, but hypotheses focus on stress-induced catecholamine cardiotoxicity and a generalized dysfunction of the coronary microvessels. It is unclear yet why women are 9-10x more affected than men. Treatment of TTC consists of medication to restore LV function, but studies have shown that the long-term survival is comparable to that of patients who have suffered from an AMI.
CONCLUSIONS: TTC is a variant type of AMI that occurs more frequently in women than men and mimics the symptoms of an AMI. Its pathophysiology is still not well understood, therefore further research is necessary.

KEYWORDS: left ventricular dysfunction, emotional stress, infarction, cardiology

Introduction

Takotsubo cardiomyopathy (TTC) is a disorder characterised by reversible left ventricular dysfunction [1]. They named the disorder takotsubo-like cardiomyopathy, because the shape of the left ventricle during presentation was similar to that of a Japanese octopus-trapping pot (a takotsubo). Since it was first described in 1990, it has become a widely accepted diagnosis in cardiology [2]. Other terms include *transient left ventricular apical ballooning syndrome* and *broken heart syndrome*. The last term refers to the fact that TTC is often seen following an episode of severe physical or emotional stress, which includes the metaphorical breaking of someone's heart. Its clinical presentation is strikingly similar to that of an acute myocardial infarction (AMI), but the underlying pathophysiology differs. It is estimated that 2% of all patients suspected of suffering from an AMI have TTC [3]. This review aims to inform the reader about the existence and management of TTC and how it can be distinguished from a standard AMI.

Takotsubo cardiomyopathy

The clinical presentation of TTC is very similar to that of an AMI [4]. It is often seen following an episode of severe physical or emotional stress. The triggering event differs greatly among patients and could be anything from a sudden financial loss to having a pre-existing condition such as cancer [3]. The predominant symptoms of patients are chest pain (60-75%), similar to that of an AMI, and dyspnoea (47%). Syncope is less common. Heart failure at onset, presenting as acute pulmonary oedema, occurs in 11-28% of the patients. Other complications such as cardiac arrest, cardiogenic shock, ventricular arrhythmias, and thrombus formation are rare but do happen [1]. Sudden death occurs in 3% of the patients [5]. The total number of patients suffering from complications is estimated to be 18.9% [5]. TTC is mostly a transient condition. Once the critical phase has passed and the patient has survived, left ventricular (LV) function often normalises within weeks, although LV function does not normalise in all patients [6].

Diagnostic tests

Because of the similarities between TTC and AMI, most of the diagnostic tools following a clinical suspicion of AMI or TTC are identical. Further investigation requires an ECG, measurement of cardiac biomarkers, echocardiography, and coronary angiography with LV angiography. We will describe the results as seen in TTC.

Firstly, ECG findings include ST-segment elevation and depression or repolarization abnormalities. Other findings include QT-interval prolongation, T-wave inversion, abnormal Q-waves, and non-specific ST-abnormalities [7]. Secondly, measurement of cardiac biomarkers of myonecrosis shows elevated levels of troponin, creatinine kinase, and brain natriuretic peptide (BNP) (including NT-Pro BNP) [8]. Thirdly, the role of echocardiography in diagnosing TTC was assessed. The study concluded that echocardiography should be the first imaging technique to be used, although in clinical practice an LV angiography is often the first confirmation of the diagnosis. Echocardiography can also be used to evaluate complications of TTC such as heart failure and is mostly used to evaluate LV function afterwards. Lastly, coronary angiography shows no signs of coronary occlusion [9].

Diagnostic criteria

In 2004 a set of diagnostic criteria for diagnosing TTC were proposed and were re-evaluated in 2008 [4,10]. These have become known as the Mayo Clinic criteria for the diagnosing of TTC and are the most widely known. Many other criteria have been developed but there is no worldwide consensus. A recent article has proposed a new set of international

diagnostic criteria called the InterTAK diagnostic criteria [11]. These criteria are as following:

1. Patients show transient left ventricular dysfunction presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution. However, more focal wall motion abnormalities can exist.
2. An emotional, physical or combined trigger can precede the TTC event but is not obligatory.
3. Neurological disorders, as well as pheochromocytoma (a catecholamine-producing tumour), may serve as a trigger.
4. New ECG abnormalities are present. However, rare cases exist without ECG changes.
5. Levels of cardiac biomarkers are moderately elevated in most cases. Significant elevation of BNP is common.
6. Significant coronary artery disease is not a contradiction in TTC.
7. Patients have no evidence of infectious myocarditis.
8. Postmenopausal women are predominantly affected.

Differential diagnosis

There are few diseases that need to be distinguished from TTC. As the InterTAK criteria indicate, infectious myocarditis needs to be excluded, but this will not be discussed here. In this section, the differences between TTC and a standard AMI will be briefly discussed. As said, the presentation of TTC mimics that of an AMI. Thus a physician must rely on the results of his/her diagnostic tests. A severe emotional or physical event prior to the onset of the symptoms is suggestive for TTC. However, a 2016 study retrospectively looked at the ECG of 200 TTC patients and 200 AMI patients. They found that an AMI often has a broader QRS width and more prevalent ST-depressions. TTC more often showed ST elevation without concomitant ST depression or T inversion. Isolated T-inversion was more common in TTC as well. Important to note is that an ECG in TTC often shows signs of multi-vessel pathology, whereas an AMI often shows signs of occlusion of more localized vessels (only the LAD for example). They concluded that ECG on admission proves to be helpful in differentiating between TTC and AMI with high specificity [12]. A study from 2015 also looked at ECG differences and concluded that the consequences of missing the diagnosis of an AMI were too severe. The diagnostic accuracy of the ECG criteria investigated in this retrospective study was insufficient to reliably distinguish patients with TTC from patients with an AMI [13]. Laboratory results show elevated troponin T levels, but peak levels are lower than those seen in an AMI. On the other hand, BNP levels are usually higher in TTC than in ACI [8,9]. The golden standard for differentiating between TTC and a standard AMI remains coronary angiography with LV angiography. A standard (type 1) AMI will show signs of coronary occlusion, whereas TTC will not [13]. A type 2 acute coronary syndrome is due to ischemia resulting from conditions such as anaemia, hypotension or coronary artery spasm. These will not show signs of coronary occlusion, but are beyond the scope of this review.

Pathophysiology

The underlying pathophysiology of TTC is not well understood. The most plausible hypotheses focus on sudden catecholamine cardiotoxicity and a generalized dysfunction of the coronary microvessels. Sex and gender also seem to play an important role.

Catecholamine cardiotoxicity

This hypothesis for the pathophysiology of TTC involves acute catecholamine cardiotoxicity provoked by stress. A study from 2005 showed that catecholamine levels were 2 to 3 times as high in patients suffering from TTC compared to AMI [14]. It is thought that in response to stress, cardiac and extra-cardiac sympathetic nerves release high levels of epinephrine. These reach adrenoreceptors in the heart and in its blood vessels, leading to catecholamine cardiotoxicity and the resulting changes typical in TTC [15]. The fact that similar reversible cardiomyopathy is seen in patients suffering from a pheochromocytoma further supports this hypothesis [16].

Generalized dysfunction of the coronary microvessels

Catecholamines have a strong vasoconstricting effect on the coronary microvasculature. It is hypothesised that high levels of catecholamines, as seen in TTC, lead to a shift in the balance between vasoconstricting and vasodilating factors in the microvasculature. The result is a reduced microvascular blood flow and a reduced coronary flow reserve [11].

Sex- and gender differences

The prevalence of TTC differs importantly between men and women [17]. Up to 90% of all patients affected are postmenopausal women with a mean age of 62 to 76 years. The triggering event differs between men and women as well. Physical stress is more likely to induce TTC in men, whereas the triggering event in women is more likely to be emotional. The clinical presentation, in contrast to AMI, is very similar between the sexes, but men are more likely to suffer from cardiogenic shock and cardiac arrest, resulting in a higher mortality rate in men. Despite these striking differences, the exact nature of the female predominance is not well understood. It is hypothesised that it is related to the lack of oestrogen in post-menopausal women, but there is no clear evidence to support this claim [18].

Treatment

Because of the similarities between TTC and AMI, diagnosis of TTC is often delayed and patients usually receive treatment for ischemic heart disease (AMI). This includes an anti-coagulant, a statin, a betablocker, and an ACE-inhibitor. The standard treatment for an AMI does not seem to improve the outcome of TTC however [5]. Once the diagnosis has been made patients should be treated with an ACE-inhibitor or an angiotensin receptor blocker. Betablockers are widely administered, although there is no clear evidence of a beneficial effect [19]. To reduce the risk of a thromboembolic event, patients could temporarily be treated with an anticoagulant [6]. Further treatment is determined by the complications that may arise during the acute phase. Heart failure, for instance, is treated with ACE-inhibitors, betablocker, diuretics, and nitroglycerine. Inotropes such as adrenaline must be avoided [19].

There is currently no standardized long-term treatment, but ACE-inhibitors or angiotensin receptor blockers are reported to decrease the recurrence rate of TTC. Betablockers do not seem effective. Aspirin and statins are appropriate in patients with coronary atherosclerosis [19].

Prognosis

TTC has a recurrence rate of 10-15% with disease-free intervals ranging from three months to 14 years [6,20]. The second trigger is usually a different physical or emotional one than the first. At first, the survival of TTC was thought to be favourable compared to the survival of an AMI; even being similar to that of the general population [7]. However, recent studies show different results. They concluded that the in-hospital mortality rate of TTC was similar to that of patients who had suffered an AMI (3.7% vs. 5.3%, not statistically significant) [21,22]. Long-term follow-up of patients that survived the acute phase of TTC showed a rate of death per patient-year of 5.6%, which is higher than in the general population.

Conclusion

TTC is a specific type of AMI that mimics a traditional AMI in its clinical presentation. Short-term complications can be severe, even including death. Long-term survival has long been thought to be similar to that of the general population, but recent studies showed it is comparable to the survival of patient that suffered from an AMI. The pathophysiology of TTC and the reason for its predominance among women are still poorly understood. However, emotional and physical stress is strongly related to the onset of TTC. More research is needed to fully understand the pathophysiology.

Acknowledgements

I would like to thank prof. dr. A.H.E.M. Maas, Radboud university medical center, from the Departement of Cardiology, Nijmegen, the Netherlands for proofreading this article.

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IS MILK REALLY GOOD FOR ALL?

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Insights

During rotation in trauma surgery, a patient asked if it was possible that he was more prone to bone fractures because he drank little milk as a child. No one could give him the answer. This kept us wondering: is there a connection between intake of dairy and bone health or bone fractures? We decided to do an analysis on this topic.

Background

During childhood, fractures are common: approximately 30-50% of all children experience fractures [1]. The incidence of fractures is the highest in boys, particular during puberty [2,3]. Several studies demonstrated that impaired bone health is related to the risk of fractures in children [2,4]. Fracture risk at any age is, amongst others, determined by bone mineral mass (the number of minerals in a certain volume of bone), the geometry and microstructure of bone. These factors determine the strength, elasticity and fragility of the bone, which varies between a peak bone mass at the end of puberty to an impaired bone mass in elderly [5]. Major determinants of peak bone mass and strength are genetics and the loading of the bone (by physical activity). However, several factors during childhood and adolescence may affect the process of achieving peak bone mass (Figure 1). Nutrition is one of these factors, with in particular calcium and protein intake [6]. The largest quantity of calcium is obtained from milk and dairy foods. Traditionally, milk and dairy products are said to be good for your bones. The aim of this article is to shed some light on the relationships between milk and dairy products intake and bone health.

Bone growth

Bone consists of minerals (60%), anorganic matrix (30%) and water (10%), which makes it a composite material [7]. The development of the skeleton continues until the end of the second decade of life, when peak bone mass is achieved. Genetic factors make up for 60-80% of the variance in peak bone mass and strength [5]. The remaining influencing factors include nutrition, endocrine status (such as sex hormones, vitamin D, growth hormone and Insuline-like Growth Factor 1 (IGF-1)), intercurrent illness and exposure to a variety of risk factors such as cigarette smoking and excessive alcohol intake [5,6]. Physical activity is another important influence on bone. Research showed that physical activity patterns in adolescence accounted for 10-22% of adult bone variance in a study about health in young women [8]. The structural bone composition and thereby the bone mass is dependent on the dietary supply of calcium, phosphate and protein [2,5,6]. The three aforementioned nutrients require a normal vitamin D status for being integrated into the bone material and their combination reduces bone resorption (i.e. breaking down) and stimulates bone formation [7]. The greatest amount of dietary calcium and other nutrients important for bone health are obtained from milk and dairy foods [6]. Resorption and formation of bone occur during adulthood under control of three types of bone cells [7]. Osteoblasts are the bone forming cells. The osteoblasts form the organic matrix, made of collagen proteins, and deposit the collagen fibres on calcium and phosphate (the two main components of bone mineral crystal). Osteoclasts are the cells that break down the bone by resorbing the mineral and matrix of the bone tissue. The

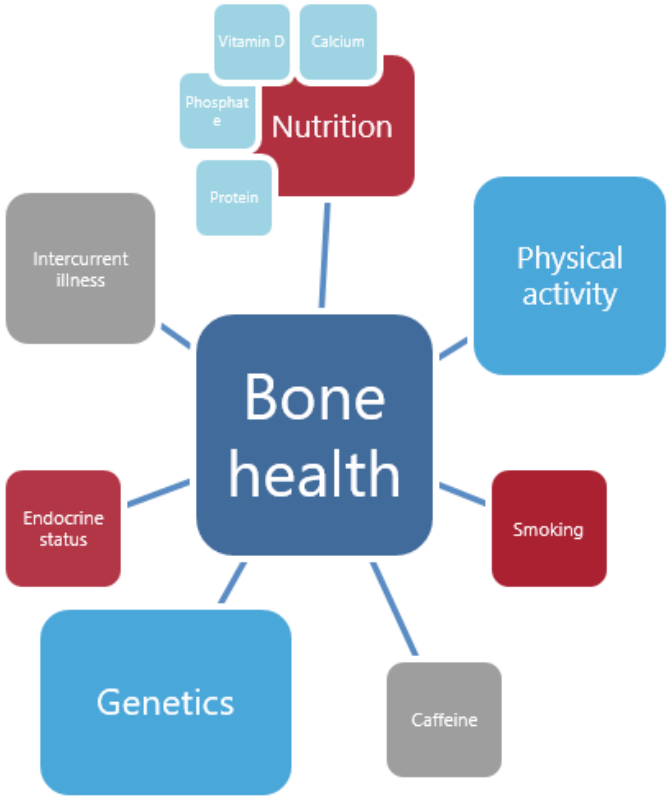

Figure 1: Important factors for bone health.

activity of these cells determines the bone mass and the amount of calcium in the blood. Osteocytes form an interconnected network in bone and regulate the activity of the osteoblast and osteoclast [7]. During physical activity, the osteoblasts are active in bone formation, while during calcium deficiency osteoclasts are active in breaking down the bone to maintain calcium levels in the blood.

Calcium, vitamin D and bone

For a long time, the positive effect of dairy consumption on bone health was attributed to calcium alone [9]. According to Voedingscentrum and U.S. National Institute of Health the recommended amount of calcium is between 200 and 1,200 mg/day [10,11]. This corresponds to one to six glasses of milk per day. However, new evidence shows that dietary phosphate and protein can enhance calcium levels by stimulating intestinal absorption and renal tubular reabsorption of calcium [7,12]. Calcium enters the body through the intestine via two

different mechanisms: an active, vitamin D-dependent transport across the proximal duodenum, and a facilitated diffusion in the small intestine [6]. Several factors influence calcium balance, for instance calcium absorption is modulated by the food source and vitamin D status, which in turn is depending on both dietary intake and production in the skin by exposure to ultraviolet light [13]. Urinary calcium losses are influenced by total dietary (animal) protein, caffeine intake and smoking [14]. An adequate calcium and vitamin D intake increases bone mineral density during skeletal growth and it prevents bone loss and osteoporotic fractures in the elderly [15]. In children aged 3-18, a positive effect of calcium supplementation was shown on total body bone mineral content with daily doses of calcium ranging between 300 and 1,200 mg/day [16]. It is suggested that calcium supplementation may transiently increase bone mineral density by reducing the rate of bone remodelling [11]. In the situation of inadequately low vitamin D and calcium supply, there will be a decrease in the intestinal calcium absorption. This, in turn, causes an overproduction of parathyroid hormone (PTH) [7]. In bone, increased parathyroid hormone stimulates bone resorption, causing calcium levels to rise again. All factors that affect calcium balance, including dietary calcium intake, calcium supplementation and vitamin D, may thus positively affect bone development.

Proteins and bones

Dietary protein provides the body with the necessary amino acids for building the bone matrix and, at the same time, it stimulates IGF-1, which is important for bone formation [17]. IGF-1 is produced by osteoblastic cells [7]. An increase in the circulating level of IGF-1 enhances the renal production of the active form of 1,25-dihydroxy vitamin D, which then stimulates the intestinal absorption of both calcium and phosphate. The tubular reabsorption of phosphate is also increased by IGF-1. This leads to the activity of IGF-1, increases the concentration of calcium and phosphate and influences the bone mineralization process positively [7].

Protein intake in children and adolescents influences bone growth and bone mass accumulation. For example, in a prospective longitudinal study in healthy boys and girls (aged 6-18), dietary intakes were recorded for four years [18]. At the radius shaft, bone mass and size were measured by computerized tomography. The study found a significant positive association between long-term protein intake and bone circumferences, cortical area, bone mineral content and a calculated strength index that indicates bone stability [19]. Overall, protein intake accounted for 4% of the variance in bone variables.

Phosphate and bones

Bone contains about 99% of the total calcium and 80% of the phosphate in the body. Their ratio in bone is 2.2, which is similar to that measured in human milk [7]. Calcium and phosphate both have a structural role in the bone matrix, as well as a positive influence on the activity of bone forming and an inhibitory effect on resorbing cells [20]. Phosphate is involved in the maturation of osteocytes. In the kidney, increased phosphate intake reduces urinary calcium loss and increases calcium balance [7].

Milk and bones

One liter of milk provides calcium, phosphate, vitamins and approximately 35 grams of protein, among which is 'whey protein' that contains growth-promoting elements [21]. Long-term milk avoidance is associated with smaller stature and lower bone mineral mass in growing children. During childhood and adolescence, low milk intake may increase the risk of prepubertal fracture. In children with cow milk allergy, who thus avoided drinking cow milk for a long period, fracture risk was 2.7-fold higher than in a matched birth cohort [22]. A prospective cohort study of self-reported fracture risk at follow-up showed that fracture risk was similar for meat or fish eaters and vegetarians, but was higher in vegans. The percentage of subjects consuming less than 700 mg calcium per day was 15.0% for meat and fish eaters, 18.6% for vegetarians and 76.1% for vegans. This higher fracture risk among vegans would be the consequence of their lower calcium intake [23]. The advantages of dairy consumption are strongest during growth, as shown by a study by Kalkwarf et al. that investigated the effects of milk intake during childhood and adolescence on adult bone density and osteoporotic fractures. The study was conducted in The US on 3,251 non-Hispanic postmenopausal women. In women with low milk intake during childhood (5-12 years of age) and adolescence (13-17 years), a lower bone mass was found in adulthood. Low milk intake during childhood was associated with 11% of osteoporotic fractures in women later in life [24].

Bioactive components of milk may directly affect the bone. For example, milk whey protein suppressed bone resorption and prevented bone loss caused by ovariectomy in aged rats [25]. Both age and ovariectomy decrease oestrogen production, which is an important hormone for bone health. Furthermore, a possible effect of milk is inhibition of bone turnover. A period of 6 weeks in which milk was supplemented to thirty healthy postmenopausal women induced a decrease in several biochemical variables compatible with diminished bone turnover [25].

Are dairy products really that good?

Besides the studies that described positive effects of dairy and calcium intake on bone health, there have been a few articles that concluded otherwise. One of these studies describes that calcium intake could only be responsible for 1% of the interindividual variability in bone mass and that the habitual intake of calcium throughout life is important for bone density, instead of the present dairy intake [14]. In the studies that researched the relationship between fracture risk in children and dairy product intake, one of them found no association between dairy product intake and the occurrence of bone fractures in school-aged children [26]. Another research found that high total calcium intake was associated with reduced fracture incidence, but there was no association with milk consumption alone and fracture risk in 8-16 year olds [27]. This reflects that total calcium intake is more important than intake of milk alone. In a study that assessed total dietary calcium, low bone density was more common in both boys and girls with fractures compared to those without fractures. Girls aged 11-15 years with fractures reported lower average calcium intakes from dairy products currently and between 6-10 years than age-matched controls [28]. In boys, the calcium intake in the groups with and without fractures was similar [29]. Regarding research on the effect of calcium supplementation (300-1,000 mg/day) on bone mineral content and bone mineral density in children and adolescents, there was a 1% - 6% significant increase in bone mineral density or bone mineral content, but the effect did not persist after suppletion was terminated [14]. Results from calcium suppletion trials like these are mostly not mirrored in research that uses total dietary calcium intake or dairy products [14]. Dairy products contain protein, sodium and in some cases supplied vitamin D. These nutrients influence calcium balance and thus bone mineralization, as described earlier. Besides the positive effects on bone, in particular sodium and animal protein tend to increase calcium excretion [14]. Most controlled studies of dairy supplementation show that very low calcium intakes (<400 mg/day) may be harmful to bone development, but increases in dairy or total dietary calcium intake (>400-500 mg/day) are not correlated with or a predictor of bone mineral density or fracture rate in children or adolescents [14,30,31].

Conclusion

Although some studies question the positive effects of dairy on bone health, it is not easy to draw an unambiguous conclusion. The majority of available research states that milk and dairy products are reliable sources of calcium as well as other nutrients important for bone health. The advantages of dairy consumption on bone health are suggested to be the strongest during growth, but bone mineral density and fracture risk are not solely dependent on calcium intake. It appears that there is a minimum of calcium needed for the positive effect on bone mineral density in children with skeletal growth as well as in elderly in preventing osteoporotic fractures. Most western children seem to meet the required amounts and do not need higher milk intake or supplements. In elderly, factors like hormone regulation and activity also play an important role on bone mineral density. It has not been demonstrated that the effect of dairy or calcium consumption persists after consumption is terminated. Still, the answer to the question about the relationship between drinking little milk in childhood and bone fractures and bone health is not that easy. Besides dairy intake, more factors are relevant for bone health. For instance, physical activity, smoking, drinking caffeine and age are important to consider when talking about bone health. Given the many bone influencing factors that also influence each other, it is difficult to design a good study design in which a large group of people varies in only one of these factors. This is important to highlight when explaining this to patients.

Acknowledgements

RAMS would like to thank dr. P. Bisseling, from the Department of Orthopedics at the Sint Maartenskliniek, Nijmegen, The Netherlands and dr. J.M.T. Draaisma, from the Department of Pediatrics of Radboud university medical center, Nijmegen, The Netherlands for providing the authors of this article with insight into the subject and providing feedback on this article.

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HEADING IN THE RIGHT DIRECTION

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Insights

The flying header goal of Robin van Persie in the world cup game against Spain is a special and memorable moment in the Dutch soccer history. However, there are concerns about the possible consequences of heading on the brain and therefore there is even thought about a ban. Will we be able to enjoy such nice goals in the future or does this need to end?

Background

In contrast to other ball games, the unprotected head is purposefully used in playing soccer to deliberately impact the ball and direct it during play. As a result, heading might be harmful to the brain. The Union of European Football Associations (UEFA) and the Royal Dutch Soccer Association (KNVB) started a research on this for youth soccer [1]. During non-professional matches, balls travel at velocities of 80 km per hour or more. On average, players head the ball 6-12 times during competitive games and during practice sessions, this frequency can even reach up to 30 or more headings [2]. The median number of headings a year is 432 [3]. When heading a ball, an average g-force of 16-28 g and peak forces of up to 60 g are established [4,5,6]. Repeatedly heading a ball during soccer is therefore a risk for repetitive minor head injury or repetitive subconcussive head impact (RSHI). As a result, neuronal changes smaller, but similar to those in a concussion appear, without the symptoms of a concussion; immediate but temporary impairment of brain functions, such as thinking, vision, equilibrium, and consciousness [6,7]. In a concussion, due to a head impact neurons will stretch and even tear, causing a disruption in neuronal communication. Additionally, dead neurons will degenerate and release toxins and because of this, other neurons will die too. A subconcussive injury will only damage and not tear neurons (Figure 1). The dysfunction of neurons will stay below the concussion threshold and therefore not severe enough to release symptoms [8]. The act of heading during soccer also increases the risk of a concussion. Compared to other sports (baseball, basketball, field hockey, football, gymnastics, ice hockey, lacrosse, softball, volleyball, and wrestling) this risk of a concussion is higher when playing soccer [9,10]. These two types of head injuries related to heading, RSHI and concussion, can have consequences, and with more than 250 million active players in over 200 countries this might become a serious problem [11]. This raises the question whether heading should be banned in soccer. To investigate this an overview of the short- and long-term consequences of (repeatedly) heading the ball in soccer will be given.

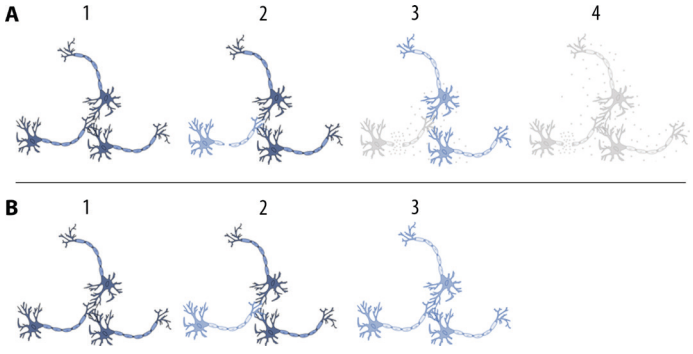

Figure 1: Neuronal mechanisms of a concussion (A) and subconcussive head impacts (B).

A. *The brain consists of a neuronal structure (**A1**) and after a head impact, some neurons will tear (**A2**) causing a disruption in neuronal communication, degeneration of the torn neurons and a release of toxins (**A3**) with the result that other neurons will die too (**A4**). These neuronal changes will give immediate but temporary impairment of brain functions.*

B. *The brain consists of a neuronal structure (**B1**) and after a head impact some neurons will be damaged (**B2**) therefore there will be a disruption in neuronal communication (**B3**). However, the dysfunction of these neurons will stay below the concussion threshold with no symptoms as a result.*

Heading and concussion

A retrospective study using medical history questionnaires of 201 soccer players showed that 62.7% experienced symptoms of a concussion during the previous year [12]. They were asked if they experienced some of the following symptoms in the previous year after being hit on the head playing soccer: knocked unconscious; felt nauseous or vomited; felt confused or disoriented ; experienced dizziness, headaches, memory difficulties, blurred or abnormal vision; or experienced any other symptoms that affected their ability to play soccer or football (e.g., hearing problems, inability to tolerate bright lights) [12]. Concussions related to soccer are more likely to occur in the act of heading than with other aspects of the game [9,13]. There are several contradictory, explanatory mechanisms for the development of these concussions. First, according to a descriptive epidemiology study, the activity most frequently associated with a concussion would be the contact between the head and the ball [14]. In contrast, another study suggests that concussion from heading the ball without other contact to the head appears rare in adult players [9]. Therefore, player-to-player contact in the act of heading would be the most frequent mechanism for a concussion instead of the impact of the ball on the head [9,15]. There are concerns about the short- and long-term effects of these sport-related concussions (SRC) for over 110 years [16,17]. Short-term effects of SRC (0-9 days post-injury) are temporarily significant impairments in neurocognitive performance; memory, reaction time, and visual motor-processing speed [18]. This performance has been measured with a computer-based neuropsychological testing battery. Additionally, players with a history of concussion have more impairments than players with a first concussion [18]. The group of players with a history of concussion is also at risk for lasting deficits, months after the injury [19]. Furthermore, this group is 5.8 times more likely to develop a new concussion than those without a prior concussion [20]. In conclusion, (repetitive) SRC can have short- and long-term consequences on neurocognitive performance. The introduction of an abolishment

on heading will potentially decrease the incidence and therefore the accumulation of SRC, including their potential consequences.

Heading and concussion in children

Children are probably at higher risk of (repetitive) SRC from heading and corresponding consequences. A factor that would play a role in this is the immature brains' susceptibility to injury [2]. The higher risk is also due to a difference in biomechanical factors because of a less developed technique, the size of the head, and less trunk and neck strength to stabilize the head [2,21]. Therefore, in children there is a less efficient energy transfer from the head to the ball and as a result, children would experience relatively greater forces from heading than adults [2,21]. However, there is limited evidence that proves the theory that heading in youth soccer can cause a concussion more easily or more often than in adult soccer [2,21]. In addition, no relation has been found between soccer heading exposure in youth soccer players and concussive symptoms [22].

Consequences of heading for brain function

Exposure to heading has possible consequences on the brain function, more than unintentional head impacts [23]. These consequences comprise a poorer performance on verbal and visual memory, planning, and visuoperceptual processing tasks [24,25]. The studies about this subject vary in the duration of heading exposure; immediate exposure, short-term exposure (<1 year) and long-term exposure (>1 year) and the results can be divided into three groups. In the first group, a negative effect on brain function is found for immediate exposure. An increasing number of headings is negatively associated with cognitive functioning. [24,25]. Nevertheless, no abnormal levels of biochemical markers for brain injury, NF-L, T-tau, GFAP, S-100B, and albuminin, are found in the serum and/or cerebrospinal fluid after immediate exposure to heading. These levels also did not correlate with the number of headings [26]. Moreover, no significant difference in preseason and postseason cognitive performance testing scores is found [27]. This would indicate that these immediate effects are only temporarily and tend to recover. In the second group, it is suggested that there is no effect on brain function; cumulative heading is not or a marginal predictor of poorer cognitive performance [28]. The last group suggests that the association between heading and brain function is a threshold dose-response relationship. A high exposure frequency (>885) to heading in the past year is nonlinearly associated with worse memory performance [3]. This poorer neurocognitive performance is not significantly associated with a history of one or more concussions [3]. The fact that significant cognitive changes only appear with heading above the threshold of 1,800 headings a year, suggests that repair mechanisms cannot manage the cumulative injury that occurs beyond this number of headings [3]. This also suggests that heading below the threshold is safe, with effective intrinsic injury repair mechanisms [3]. However, it is practically impossible to prohibit heading halfway the season for a player that has reached this threshold.

Consequences of heading for brain structure

Besides the potential consequences of heading on the brain function, exposure to heading is associated with several changes in brain structure. After long-term exposure to heading, slight to moderate central atrophy with widening of the lateral ventricles and greater cortical thinning in the right inferolateral, parietal, temporal, and occipital cortex can occur [24,29,30]. Even short-term exposure is, with thresholds in terms of a number of headings, associated with changes in brain structure such as an abnormal microstructure in the temporo-occipital white matter [3,24]. This abnormal white matter structure can be defined as a lower degree of myelination and axonal density assessed with fMRI as changes in fractional anisotropy. The previously mentioned threshold varies between 885-1,550 headings a year and the abnormal white matter microstructure is not explained by a history of concussion [3,24]. Heading below this threshold can therefore be suggested as safe for changes in the brain structure. However, the possible long-term consequences of these aforementioned changes in brain structure are unclear.

Long-term consequences of heading: dementia

It has been suggested that long-term exposure to repetitive, sub-concussive events may result in persistent cognitive impairments [31]. This is underlined by the finding that 30 out of 37 former professional soccer players had mild-to-severe impairment on neuropsychological examination [32]. High numbers of RSHI's possibly also contribute to an increased risk of neurodegenerative diseases including chronic traumatic encephalopathy (CTE) [31]. The clinical features of CTE are variable and consist of a combination of mood and behavioural changes, memory loss, executive dysfunction, slurred speech, parkinsonism, and gait impairment, which typically manifest years after the injuries. CTE is a potential neurodegenerative cause of dementia and motor impairments in retired professional soccer players, with a history of thousands of RSHI's [33]. However, other studies suggest that CTE relates more to acute severe head injuries instead of repetitive heading. This is because the cumulative effects of heading a ball can cause dementia pugilistica, a chronic brain syndrome which is seen in professional boxers [34]. In addition, there are studies that contradict the accelerated cognitive decline due to heading. The suggestion is that once a player ends their career, their risk of harm declines to that of the general population suggesting that neurological changes are potentially reversible [35].

Conclusion

Millions of people worldwide make thousands of soccer headings in their lifetimes with RSHIs and concussions as a consequence. However, there is no conclusive evidence about the possible harmfulness of RSHIs for brain function, brain structure or dementia after long- and short-term exposure to repeatedly heading in soccer. Factors that can play a role in the contradictory results are the rate of exposure, the time between exposures, the vulnerability of individual players and confounding risk factors like behaviour off the field and concussions not related to ball contact [3,29,32]. The high concussion rate related to the act of heading causes temporarily impairments on neurocognitive performance. Should we not better be safe than sorry by banning heading in soccer? However, this would be very radical and the whole sport would change. An approach could be to protect the immature brain from a delayed start with heading. This is advised in the U.S. Youth Soccer recommendations, with heading being taught in controlled settings after the age of 10. In this approach, heading is banned in games until the age of 14 but ideally, the readiness for heading should be determined for each player individual; based on their strength, skill development, and maturation of the brain [36]. In the meantime, more research has to be done to find more conclusive evidence. Until then, we can continue to enjoy beautiful heading goals.

Acknowledgements

RAMS would like to thank prof. dr. J. van der Naalt, neurologist and Professor in Neurotraumatology at the University Medical Center Groningen, The Netherlands and Principal Investigator Traumatic Brain Injury Programme for the Dutch Brain Foundation, for providing insights into the subject and feedback on this article.

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MYTH OR SCIENCE?
A PILL OF RITALIN A DAY KEEPS THE RESITS AWAY

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Critical Appraisal

Joep, reporter for Vox magazine, tested Ritalin in a personal 2-day experiment. Beforehand, he consulted a psychiatrist to get informed on which dosage to take. He tried to learn as many French words as possible, one day with Ritalin and one day without Ritalin. Both days he managed to learn 3 pages of French words and he made four to five mistakes during his tests. Even though the results are almost identical, his experience was not. The day he took Ritalin he felt more focused; no nail biting, no looking at the clock. However, he felt time was flying by as well and he caught himself staring aimlessly at words sometimes. He concludes that he would rather just drink coffee and eat wine gums [1] 22-year-old student Ruben, who shared his story with NWSbeat magazine, claims that methylphenidate (MP) directly improved his study results and that he did not experience any adverse effects in the two years he has been using it. He would recommend it to everyone [2]. Koen Burgerhout from Addiction Institute Bouman of GGZ has a very different opinion on the topic. He describes the increase in MP use amongst students as frightening. He questions the effect of MP on healthy individuals and warns of serious side effects including cardiovascular disease and depression [3].

Introduction

Do you know the feeling that you have to study for an important exam, but you keep scrolling on Facebook or watching Youtube videos? Maybe you have tried natural supplements before such as fish oil, to enhance your concentration [4]. Maybe you have even tried something stronger, such as Ritalin, or its substance name: Methylphenidate (MP). If so, you are not the only one. The Dutch Institute for Responsible Drug Use (Instituut voor Verantwoord Medicijngebruik (IVM)) held a survey in 2017 amongst 400 university and university of applied sciences students and found that 1 in 4 students have used MP to improve concentration while studying. A shocking increase in comparison to 2015, when "only" 1 in 10 students admitted to having used MP [5]. Students obtain this drug from friends who are diagnosed with ADHD, or buy it online for a few bucks. Different opinions exist with regard to the consequences of the use of such drugs. Some argue that, in some ways, MP resembles hard drugs such as cocaine and amphetamine. In contrast, other people compare using MP with drinking coffee [6]. We aimed at figuring out the science behind the use of MP as a cognitive enhancer, by people in doubt of their academic performance.

Medical use of methylphenidate

Attention deficit and hyperactivity disorder (ADHD) is the most common indication for prescribing MP, which is the drug of preference for this disorder. In ADHD there is supposedly a shortage of dopamine in the frontal cortex and the striatum [7]. Dopamine is a chemical that belongs to the catecholamine and phenethylamine families. It plays several important roles in- and outside the central nervous system. One of these roles is as the motivational component in reward-motivation behaviour. Another role is as a local chemical messenger in blood vessels and certain organs, such as the heart. Therefore, dopamine plays a role in dilating the blood vessels of the kidneys, which consequently increases kidney filtration and cardiac output due to a positive-inotropic effect [8]. A shortage in the central nervous system results in decreased concentration, distractibility and impulse control [9]. Consequently, dopamine is one of the most investigated neurotransmitters in the treatment of attention deficit disorders. MP blocks the reuptake of dopamine and norepinephrine. This has a stimulatory effect on the central nervous system, relieves ADHD symptoms on short-term, and increases the activity of the sympathetic autonomic nervous system [8].

MP falls under strict legislation in The Netherlands, which is known as the 'opiumwet'. This law prohibits listed drugs to be smuggled, cultivated, transported, carried or manufactured amongst others [10]. In The United States, the Food and Drug Administration gave MP a 'black box warning'. This is the strongest warning they hand out and it signifies that studies have found a significant risk of serious adverse effects [11]. It must be noted, however, that there are key differences between Ritalin and amphetamine. Amphetamine does not only block the reuptake of dopamine, similar to MP, it also promotes the release of dopamine from vesicles. This release is thought to underlie the strong addictive potential of amphetamine and other hard drugs such as cocaine. Therefore, one can ask themselves whether previously mentioned measures for MP are indeed justified.

Cognitive enhancement

MP is the most used psychostimulant drug for extending the capacity of alertness and cognition in healthy individuals [12]. Several factors increasing its non-medical use (NMU) have been identified. Higher NMU has been reported among males, Caucasians, students engaged in recreational substance use and students in sororities and fraternities. Other factors predicting the use of MP include a history of risky behaviour (like driving under influence) and symptoms of inattention, depression, anxiety, stress, impulsivity and internal restlessness [13]. Perhaps not surprising, since these behaviours are more prevalent in ADHD patients and could be remediated by MP. It thus may be the case that statements of increased academic performance with MP are partly due to underdiagnosed or subclinical ADHD [14]. The same could be hypothesised for depression or anxiety disorders [15]. Anyway, let us look at a recent meta-analysis on this topic, as we are not going to bust or confirm this myth by hypothesis alone.

In 2015, Ilieva et al. obtained a quantitative estimate on the cognitive effects of MP focussing on inhibitory control, working memory, episodic memory as a primary outcome and dosage required to reach an effect as a secondary outcome. Their meta-analysis included 48 studies and 1409 participants. A significant but small positive effect was found with MP regarding inhibitory control/cognitive focus (i.e. looking less out of the window and less slow strolls to the fridge followed by eating food you do not even feel like eating). Also, a small positive effect was found

in the performance of working memory (lasts 30 minutes after learning). This would give you 15 minutes to race through your notes and then your answers in the first 15 minutes of the exam would be slightly better. Not really satisfying, is it? Episodic memory (lasts one hour to one week after learning) performance showed a medium increase with MP. However, both findings for working and episodic memory qualified for possible publication bias. In other words, it is likely that studies that would cancel out these positive results stayed in file drawers [15]. Interestingly, the best stimulatory effect (though questionable) was reached with a low dosage of MP. Unfortunately, this secondary outcome was also confounded (i.e. no firm conclusions can be drawn) in the studies analysed.

A more recent small RCT of 36 students also assessed the students' feeling of well-being during cognitive testing. This was improved by MP, but without significantly improving their cognitive functions. The author's guess is that healthy people do not actually perform better, but they could feel cognitively enhanced, establishing its current popularity [12]. Cropsey et al. continued along this path. They hypothesise that small effects of cognitive enhancers are due to people's expectations of being cognitively enhanced [14]. Therefore, they used a balanced placebo design, using Adderall (an amphetamine, much alike MP). This design has four groups, consisting of two groups who are told the truth (given Adderall/given placebo) and two groups who are deceived (told the opposite of what they receive). Their results showed that the expectation of receiving a stimulant has a positive effect on simple tasks, even more than actual medication, though both effect sizes were small. This might implicate that cognitive enhancement is also moderated by belief (a placebo effect) instead and not entirely by pharmacodynamics.

As stated above, it seems that small positive effects on cognition can be achieved by alternation of dopamine levels in the groups of students that were studied. However, a vital key point is not yet discussed; baseline dopamine levels. This entails that individuals with low dopamine levels can benefit from MP on certain cognitive tasks, while others with high levels of dopamine at baseline will perform worse at the given cognitive tasks. Thus, dopamine has a so-called U-shaped mode of action [16]. Furthermore, it seems that the dopamine level of optimal performance differs amongst the various cognitive functions. For instance, MP increases cognitive focus but this goes at the expense of updating (adapting to potentially changing circumstances) [17].

Negative effects

Considering the results stated in the previous paragraph, the beneficial effects of MP are perhaps somewhat mild. However, the negative effects for occasional MP use are not as well studied and are also depending on usage frequency and dosage. Extensive research has been done on the negative effects of chronic MP use. Lareb, a Dutch center that registers side effects of medication, reported that 75% of patients with ADHD who use MP claim to experience side effects. This results in discontinuation of treatment in 10% of ADHD patients. In general, negative consequences of MP use both prescribed and unprescribed, can be divided into four groups: side effects, abuse, reactions to high doses and complications [18,19].

Side-effects have many different manifestations. Most common (>10%) are insomnia, nervousness, headache, loss of appetite, nausea, and a dry mouth. Furthermore, the side-effects can be aggravated by alcohol and there are interactions with other drugs such as antipsychotics, tricyclic antidepressants, antiepileptica and antihypertensive drugs. It is not indicated after which period of use and at which dose these side-effects occur [18].

Kollins et al. reviewed the abuse potential of MP including 60 studies. They concluded that there is definite abuse potential, since tolerance develops and characteristic stimulant withdrawal symptoms are seen after discontinuation of the drug. These symptoms included insomnia, irritability and depression. Howevers, these effects were minimal or not present in most patients who quit MP by means of a reduction schedule. This study was also conducted with chronic MP users, which questioned if the same applies to occasional users [20].

A high dosage of MP can lead to symptoms such as depression, or anxiety, aggression, emotional liability and headaches. It might also lead to hallucinations and bizarre delusions which could result in dramatic consequences. It must be noted, however, that these effects rarely occur [21]. Complications include raised blood pressure, which possibly places long-term users at risk of heart attacks and stroke. Lareb registered over 1.200 notifications of mild to serious complications after the use of MP [19]. Moreover, stimulant use can also worsen anxiety, depression, psychotic conditions and seizure disorder [18]. Before prescribing MP, a doctor evaluates the patient for these risk factors. If MP is used unprescribed, this evaluation obviously has not taken place. NMU of MP can therefore potentially lead to worsening of psychiatric disorders [11]. Furthermore, there are some studies that suggest that stimulants could influence the user's personality [11,22]. For example, greater focus gained through stimulants could plausibly lead to a loss in creativity, which requires a loosening of mental boundaries [22].

Conclusion

This proclaimed wonder pill seems to influence certain cognitive functions positively, but only in a select group of individuals and possibly at the expense of other cognitive functions. A meta-analysis shows a significant but small positive effect on inhibitory control. Also, it might positively affect working and episodic memory, but these results classified for publication bias. Although confounded, the best effects of MP on cognition were achieved with a low dosage. 10% of ADHD patients discontinue with treatment due to experienced side effects. However, the number of negative effects of unprescribed MP use in students is not known. Nevertheless, these students did not consult a doctor before using MP. Consequently, this could aggravate already existing psychiatric disorders and increase the risk of overdosage. The chance of this is questionable when used occasionally however. Overall, the negative effects seem to be predominant, for the average student, when we look at the current knowledge on this topic. On the individual level this could still mean that some people notice a positive effect. A recent RCT suggests that most of the positive effects felt are moderated by belief of being cognitively enhanced instead of true pharmacodynamics. On the other hand, baseline dopamine levels and the level of dopamine required for a specific cognitive task seem to play an important role, complication the interpretation of study results. It could also be hypothesised that students performing a lot better with MP, indicates underdiagnosed ADHD or personality characteristics within the spectrum.

Acknowledgements

RAMS would like to thank Roshan Cools, professor of Cognitive Neuropsychiatry at the Department of Psychiatry of the Radboud university medical center and principal investigator at the Donders Center for Cognitive Neuroimaging, for providing feedback to the authors of this article.

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TRENDS IN BIOMEDICAL RESEARCH

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Interview

Biomedical research is constantly evolving and new trends arise every year. Targeted cancer strategies, monitoring vital signs of patients with the use of wearables and gene editing or therapy are popular topics worldwide in the last years. Furthermore, the use of deep-learning and artificial intelligence in research has greatly increased and they have also made their entrance in biomedical research. Besides changes in popular topics, changes in conservative trial designs occur more and more as well, which additionally leads to the use of new trial designs, such as an n=1 trial, where every patient is used as its own control. These popular topics and changes all have one corresponding factor: they have a personalised aspect. To find out which research topics are very popular in the Radboudumc and its research institutes, and which ones will become a trend in the upcoming years, we asked dr. Alain van Gool, dr. Paul Smits, dr. René Bindels and dr. Jan Kremer, for their opinion on this subject.

Personalised medicine

Many of you already know that personalised healthcare and innovation are the key elements of the Radboudumc strategy. Personalised healthcare research starts with understanding the disease with the need of the patient as a starting point. It aims at closing the gap between the priorities of the doctor (aims for the best possible treatment), researcher (aims to unravel a certain mechanism for a better therapy) and patient (aims at getting a better quality of life). Dr. Alain van Gool (professor personalised healthcare and head of the Translational Metabolic Laboratory) states that in the last years, technology has rapidly progressed. Nowadays, patients can easily be differentiated based on their molecular biomarkers, adding to the 'precision' in personalised healthcare. However, there is still a lack of options to actually treat these different patients with personalised therapies. Besides the more obvious drug therapies, treatments can also include adaptations in diet or a better balance between work and private life. Dr. van Gool emphasizes that, in terms of personalised healthcare, we are not there yet but progress is expected, particularly in the holistic approach bridging molecule to patient. This personalised healthcare approach in the Radboudumc is unique and is expected to lead to more efficient care and decrease of healthcare costs.

Dr. Alain van Gool

Dr. Paul Smits

Dr. René Bindels

Dr. Jan Kremer

European Reference Networks

The Radboudumc also plays a role in European Reference Networks (ERN), where it is a center of expertise for fourteen rare disorders in Europe such as for rare liver disease, endocrine conditions, and haematological diseases. By combining knowledge and expertise in the Radboudumc with knowledge from other centers, patients will get the most accurate diagnosis and the best treatment possible for their specific disease. In the upcoming years, patient groups from different hospitals (national and international) can be combined into a bigger cohort and can also be used for research purposes, such as gaining a better understanding of the origin of the disease or for designing better drug targets. These ERNs are therefore an example of a perfect mix of diagnostics and research and how this can be carried out more efficiently.

Impressive research within the Radboudumc and its institutes

According to dr. Paul Smits (professor clinical pharmacology, dean and vice chairman of the board from the Radboudumc), the research theme 'Infections diseases and global health' is one of the research themes that impresses worldwide with their research in innate immunology, fungi, tuberculosis and malaria. Dr. Mihai Netea even was awarded the NWO-Spinozapremie (the highest Dutch award in science) in 2016 for his outstanding research on innate immunity. This research theme, therefore, is clearly distinctive in their field in comparison with other national and international research institutes. Besides this theme, also the Donders Institute with their research on Parkinson (coördinated by dr. Bas Bloem), the Department of Genetics with their research on mental defects (coördinated by dr. Han Brunner) and oncology with their research on dendritic cell therapy (coördinated by dr. Carl Figdor, NWO-Spinozapremie award winner in 2006), are strong players in their field.

Future trends

Dr. Smits suspects that research with the use of for example wearables and artificial intelligence will take a great leap. This will lead to a high patient- and community participation and will lead to more and more big data research and innovations. These topics are already very popular worldwide and are currently finding their way in research in the Radboudumc. Dr. René Bindels (scientific director of the RIMLS and professor physiology) feels that besides the earlier mentioned subjects, also deep learning, nanotechnology and the broader use of immune

therapies and cancer diagnostics will become more popular in the next years. He emphasizes, however, that a big part of future trends will rely on curious researchers with accidental discoveries, such as the discovery of penicillin by Alexander Fleming in 1928. Dr. Jan Kremer (professor patient-centeredness and gynaecologist) shares his view that big discoveries are often found by coincidence. He also thinks that more multidisciplinary research has a great potential and that currently, we do not use it enough. Research with collaborations in for example alpha and beta sciences or on the borders of research fields can lead to new, creative perspectives and can lead to the use of mixed research methods such as the combination of quantitative and qualitative research. Also, it is necessary to use new research methods now we know that averaging patients does injustice to the patient's context. This context is very important in personalised research and is certainly a necessary factor for carrying out good quality patient-centered research.

Conclusion

The Radboudumc and its institutes certainly have enough high-quality research, especially due to the unique aspect of personalised healthcare. The main message that these prominent doctors give is that we cannot entirely predict the future trends. So, that is why we advise you, as a student, to embrace your curiosity and be open for multidisciplinary collaborations in your future career.

CORRECT ANSWERS TO THE EXAM QUESTIONS

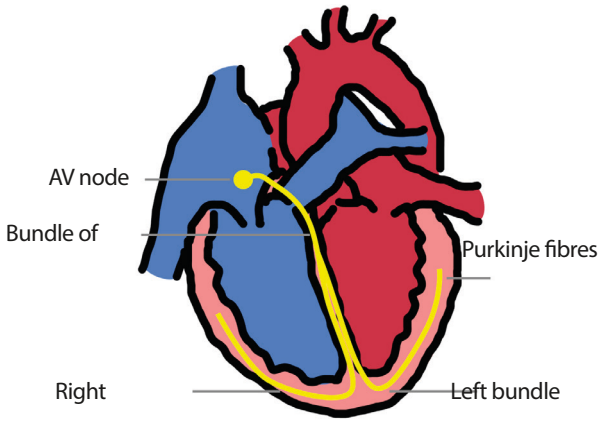
Answer question 1:
B. Hyperplasia

When residing at high altitude for several weeks, the body responds to the lower levels of oxygen in the air by producing Erythropoietin (EPO). EPO stimulates the red blood cell production in the bone marrow. In this process of acclimatization, the amount of haemoglobin in the blood increases as well. This increases the amount of oxygen that can be carried by the blood, explaining the improvement in sports performances. The production of more cells, such as in this case, is called hyperplasia. Hypertrophy is the increase of volume of an organ or tissue due to enlargement of the cells it consists of, without cell proliferation. Metaplasia is the reversible transformation of cells from one differentiated cell type to another, which may be part of a normal maturation process but is also considered to be an early phase of carcinogenesis. Dysplasia is an abnormal development of cell growth and differentiation and is a term used in pathology for an irreversible precancerous stage in cells and tissue [1].

During the exam, 61% of the participants answered this question correctly.

Answer question 2:
A. Bundle of His

The electrical activity of the heart can be recorded in an electrocardiogram (ECG). A normal heart rhythm produces four entities. The QRS-complex represents the ventricular depolarisation and the P-wave represents atrial depolarisation. A patient with a total AV block can still have an escape rhythm, but this will originate from the next pacemaker cells in the conducting system of the heart. As the QRS-complex is still normal, the signal needs to come from the Bundle of His. The QRS-complex would be distorted if the signal originated from different pacemaker cells, as the ventricles would not depolarise in their common way. If the signal would originate from the left bundle, the right bundle or the Purkinje fibres, the right and left ventricles would not depolarise at the same time, which would result in an abnormal QRS-complex [2].



During the exam, 47% of the participants answered this question correctly.

The exam questions can be found back on page 9 in this journal.

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ZEBRAS OF MEDICINE
DIFFICULTIES IN DIAGNOSING: CONVERSION DISORDER

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Abstract

Review

BACKGROUND: Conversion disorder is characterized by symptoms and signs affecting sensory or motor function that cannot be explained by a neurological or other known medical condition. The symptoms can mimic an organic neurological problem which raises the concern of misdiagnosing.
OBJECTIVE: This review will give an overview of the literature on conversion disorder to summarize the current knowledge of this psychiatric disorder with a focus on the signs to discriminate this disorder from an organic neurological problem.
RESULTS: There is a lack of studies with a high level of evidence within the field of the conversion disorder. Some signs seem to indicate whether neurological symptoms are caused by a conversion disorder or neurological problem. However, only the Hoover's sign was found to discriminate between the before mentioned in more than one study. Hypnosis is recommended as a treatment and open communication towards the patient is very important.
CONCLUSIONS: Conversion disorder has been a recognized psychiatric disorder for several years that can have a great impact on a patient's life. More high-quality research is needed to fill the lack of data on the best way to the diagnose and treat this disorder.

KEYWORDS: Functional disorder, hysteria, Hoover's sign, psychiatry, neurology

Introduction

A 22-year old woman presents herself in the emergency room with an acute paresis of her left arm and the inability to open her eyes. Is this a neurological problem? The symptoms may also be caused by a conversion disorder or neurologic symptom disorder. The conversion disorder is characterized by symptoms and signs affecting sensory or motor function that cannot be explained by a neurological or other known medical condition. It was previously classified as a subtype of hysteria. Egyptian physicians 1900 B.C. attributed the symptoms to wandering of the uterus ('hystera' in Greek) within the body. Nowadays, conversion disorder is formally classified as a psychiatric disorder. In the Diagnostical and Statistical Manual of Mental Disorders (DSM-5) conversion disorder is included in the Somatic Symptom Disorders chapter. In the International Classification of Diseases (ICD-10) the disorder is classified within the spectrum of dissociative disorders [1]. Neurologists recently proposed to adopt the disorder within their field of expertise and change its name into 'Functional Neurological Disorders' (FND) [2,3]. This preference so far did not result in a formal listing in one of the classification systems. The similarities between conversion disorder and organic neurologic disorders raise the concern of misdiagnosing. However, the percentage of misdiagnosis is found to be only 4% in a systematic review of 27 studies of FND [4].

This low number suggests that there are observations that can lead to the right diagnosis. In this review, we aim to provide an overview of this challenging disorder. We will discuss the clues in patient history and neurological exam that can point to this diagnosis. Furthermore, we will cover the management and treatment of conversion disorder.

DSM-5

Patients with conversion disorder present themselves with a variety of neurological symptoms: examples are weakness or paralysis, abnormal movements, swallowing symptoms, speech symptoms, seizures, anaesthesia, and visual or hearing disturbances. However, an organic cause is missing. Standard neurologic exam, as well as, laboratory and imaging results are within normal limits. Conversion disorder differs from simulation and factitious disorder in the sense that patients with conversion disorder are not clearly feigning their symptoms. The term "conversion" finds its origin in Freud's psychodynamic theory and refers to the phenomenon of converting an intrapsychic conflict into physical symptoms [5]. The precise prevalence of the disorder is unknown. In 5% of the referrals to neurological clinics this diagnosis is made. The incidence of conversion disorder is 4.6/100,000 per year and is two to three times more common in females [6].

The diagnostic criteria for the conversion disorder are stated in The Diagnostic and Statistical Manual of Mental Disorders (DSM) as listed down below (table 1) [7]. In the most recent version of the DSM, the DSM-5, the criterion that a temporal association between psychological factors and the onset or the worsening of symptoms must be present, which was a part of the DSM-4, has been abandoned. The reason for this being that psychological stressors are not always found [3,8]. Therefore 'with' or 'without psychological stressor' is added as a specifier. A background of childhood trauma is correlated with conversion disorder more frequently than in controls [9,10].

Diagnostic tests

In order to diagnose a patient with conversion disorder, it is not enough to exclude organic pathology: it is not a 'diagnosis of exclusion'. The

Table 1: DSM-5 criteria for the diagnosis of conversion disorder (functional neurlogical disorder) [7]

A.	The patient has ≥1 symptoms of altered voluntary motor or sensory function.
B.	Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.
C.	The symptom or deficit is not better explained by another medical or mental disorder.
D.	The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

diagnosis is far and foremost based on incongruence and inconsistencies. Incongruence means that the symptoms do not fit a known organically determined pattern. An example: the sternocleidomastoid muscle is bilaterally innervated and therefore usually spared within an organic hemiparesis. When patients thus have a paralyzed limb on the left side and also the inability to rotate the head to the left side, this collides with the pattern of muscle weakness one would expect.

The term inconsistency is used for finding different patterns over time or when distracted. For example, a patient has a paralytic arm but when the arm is passively lifted and released it does not fall down immediately. These inconsistencies and incongruences are called positive signs. There are about 40 positive signs described in the literature, however, there is a wide range in sensitivity and specificity for these tests and observations. In general, it is hard to validate them because of the lack of a golden standard for diagnosing functional disorders. We will now discuss frequently observed positive signs in conversion disorder.

La belle indifférence

La belle indifférence is one of the positive signs often described by doctors as an indication of functional neurological disorder. It is defined as 'a relative lack of concern about the nature or implications of the symptoms' [11]. In a systematic review of eleven studies with a total of 356 patients with conversion disorder and 157 patients with organic disease, it was shown that the prevalence of la belle indifférence was 21% in the group of patients with conversion symptoms and 29% in patients with an organic disease. Seven out of the eleven studies concluded that la belle indifférence was not useful for distinguishing patients with FND from patients with organic disease. In the remaining four studies there was no comment on its value [12]. Based on these studies, it can be questioned whether la belle indifférence is a useful clinical sign.

Pronator drift

When performing the pronator drift, also known as the Barré sign, the patient is asked to fully extend both arms with palms facing upwards and eyes closed. In the presence of an upper motor neuron disorder the patient's arm will pronate and a drift can occur. Drifting in absence of this pronation was described by Babinski to be a sign of hysterical paresis. To verify if this drifting in absence of pronation is indeed a positive sign, Daum et al. performed this test in 26 patients with conversion disorder and 28 patients with an organic neurological condition [13]. All patients with conversion disorder were found to have a positive drift without pronation sign, whereas this was only found in two patients of the control group. From this, one can conduct a sensitivity of 100% and specificity of 93% of this sign for conversion disorder. However, the fact that the examiners in this study were not blinded for the diagnosis of the patients should make one cautious in interpreting these percentages.

Hoover's sign

Hoover's sign, first described in 1908 by Charles Hoover, is used to detect a functional paresis of the lower extremity [14]. It is based on the principle of contralateral synergic movement; when the left hip is flexed against resistance, the right leg will involuntarily extend. When there is weakness in voluntarily hip extension, but a normal involuntary hip extension is found when flexing the contralateral hip, it is called a positive Hoover's sign. The involuntarily extension can be perceived by the examiner by placing his hand under the weak leg. In a systematic review the sensitivity of Hoover's sign was found to be 94% and the specificity 99% based on four studies [15,16].

Spinal Injuries Center Test

Another test used to identify lower leg functional weakness is the Spinal Injuries Center test. The patient lies on his back and the examiner passively lifts and flexes the patient's knees on the bed. When the examiner gently releases his hand and the patient maintains the uphold position of the knees, the test is considered positive. In severe paralysis, the affected leg will fall back on the bed immediately. Based on a study with 14 patients with functional leg paresis and a control group of 48 patients, sensitivity and specificity were found to be 100% and 97.9% respectively [17]. The examiners in this study, however, were not blinded for the diagnosis of the patients and the results should therefore be interpreted with caution. Moreover, this test can only be used in patients who present themselves with severe leg paresis.

Excluding organic causes

When uncertainty remains about the diagnosis, MRI images, a lumbar punction or laboratory tests can be used to rule out specific medical disorders. However, clinicians must always keep in mind that additional tests can lead to false positives when there is a low a priori chance. Moreover, doctors must be aware of the existence of the so-called 'functional overlay'; patients can both show functional neurological symptoms and have a neurological disease. For example, about one-third of the patients with Parkinson's disease are found to have functional symptoms [16].

Psychiatric comorbidity

About one-third of patients diagnosed with conversion disorder presenting with motor symptoms also meet criteria for other 'axis I psychiatric diagnoses', and 50% meet criteria for axis II (personality disorder) diagnoses [18].

Management and treatment

There is no specific cure for FND and management is often challenging, but since FND can have a significant impact on quality of life, it is important to have knowledge of the possible treatment options.

The Dutch multidisciplinary guideline for the treatment of SOLK or somatization disorders (2011) recommends hypnosis as treatment for conversion disorder [19]. However, a Cochrane review evaluating evidence for various treatment modalities concluded that more research was required [20]. Several specialised psychiatric clinics in The Netherlands offer treatment programmes for conversion disorder.

It can be very hard for people to accept that no organic cause is found for their symptoms. This not only holds true for the functional neurological disorders but also for functional somatic syndromes such as fibromyalgia and irritable bowel syndrome. Therefore, explaining the diagnosis to patients to the point wherein they get confidence in the diagnosis as well is the first step of treatment. Henningsen et al. suggests that for this first step it is important to reassure the patient with a positive explanation of the functional disorder; show the patient a positive clinical sign, and do not only mention the negative test results. If necessary, symptomatic measures, pain relief for instance, should be used. It is important to keep the patients mobilised, the symptoms will not be improved by bed rest. On the contrary, it is more likely that they will worsen because of deconditioning. Finally, Henningsen et al. states that psychoeducation in the form of advising on illness behaviour should be part of the management of a functional disorder. When this is insufficient one should consider referring to a psychotherapist [21].

Transcranial magnetic stimulation is an upcoming treatment for conversion disorder. It is a neurophysiological technique based on electromagnetic induction. With the use of a short magnetic pulse, an electric current is induced in the brain to stimulate the different brain areas. Controlled trials looking into this new treatment method have not been completed yet, however, preliminary results show some promise

in the seizure type of FND. There are also some case reports wherein transcranial magnetic stimulation was found to reduce the symptoms of FND [22].

Prognosis

The overall prognosis of functional motor symptoms is disadvantageous. In a systematic review of 24 studies, it was shown that in 20 studies over 30% of the patients had the same or even worse symptoms at follow-up. The duration of symptoms is found to be related to delay in seeking treatment and psychiatric comorbidity [23].

It is shown that the quality of life of patients with FND is even worse than for patients with an organic neurological disorder. Patients with FND scored significantly lower on 5 of the 8 domains of the Short Form 36 item scale for health-related quality of life. The five domains are amongst others social functioning and bodily pain [24].

Conclusion

In conclusion, it is challenging to differentiate between a neurological disorder and a functional neurological disorder and crucial to choose the right treatment. In this way, the prognosis for patients such as the 22-year old woman may be significantly improved. Positive signs can help doctors with the diagnosis. For functional neurological symptom disorders it is essential to perform a full medical history and a thorough neurological exam to support your diagnosis with full confidence. In the management of FND open communication and respect towards the patient is key!

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RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

Joost Kools[1], Fleur Strobbe[1], Rosalie Kempkes[2],

Summary

With over 3000 publications per year, scientific research is a cornerstone of the Radboud university medical center [1]. In this section, recent high-impact papers – published by researchers from the Radboudumc – will be discussed.

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[2] Master Student Molecular Mechanisms of Disease, Radboud university medical center, Nijmegen, The Netherlands.

Prophylactic haloperidol does not increase survival in patients with delirium

Delirium is an acute syndrome of the brain which results from an underlying somatic disease. Symptoms include a lower level of consciousness and awareness, confusion, and inattention. It is commonly observed among elderly, especially in patients in the ICU, with a prevalence rate of up to 80%. Although a delirium will resolve spontaneously when the underlying somatic disease has successfully been treated, it is important to recognise and treat the delirium because it can lead to higher complication rates, increased hospitalization length and even mortality. A delirium is currently treated with haloperidol, which can also be used as prophylaxis in non-critical patients, such as those undergoing hip surgery. However, after several scientific trials, it still remained unclear if the prophylactic use of haloperidol is beneficial in the ICU setting.

To investigate this, the biggest placebo-controlled trial ever conducted in this field was conducted in 20 Dutch ICUs, which included 1,800 patients. No significant difference was found in this trial between the haloperidol and the placebo group regarding survival at 28 days and 90 days. Furthermore, no significant difference was found for delirium- and coma-free days, delirium incidence or adverse effects. As this research, which was also conducted at the Radboudumc Department of Intensive Care Medicine, had a major power due to the large research population but no ambiguous results were found, the conclusion is clear: haloperidol as prophylaxis does not reduce mortality in ICU patients [2].

New possible compounds for a vaccine against malaria

Malaria is a disease caused by parasites, which are transferred by mosquitoes among humans. A lot is currently known about the life cycle of these disease-causing parasites, but an effective vaccine has yet to be produced. Vaccines against malaria can be divided into three groups, each aimed at interfering at a different point in the parasites' life cycle: pre-erythrocytic vaccines, blood-stage vaccines and transmission-blocking vaccines. These prevent the parasites from multiplying in the liver, infecting our erythrocytes or from producing sexually active parasites capable of transmitting the infection to mosquitoes, respectively. Infection of our erythrocytes leads to their destruction, leading to the clinical picture referred to as malaria. However, the parasites will not be transferred to humans until they have reached the sexual-stage. Even after the symptoms of malaria are successfully treated and no parasites can be detected in the blood anymore, a patient can still be a carrier of parasites that hide in the liver. This greatly toughens the eradication of malaria and is observed as a major challenge to the development of effective vaccines against malaria. Therefore, the prevention of more people becoming infected with malaria has been the main subject of research.

Teun Bousema from the Department of Medical Microbiology and his colleagues have discovered that the immune system of 1 in 25 malaria patients prevents malaria from spreading by producing antibodies against the sexual-stage malaria parasites. Moreover, they have identified antibodies produced by humans that are capable of preventing the re-emerge of malaria in patients. Bousema and colleagues have thereby identified possible compounds for an effective vaccine, which could greatly help to reduce the disease burden of malaria worldwide [3].

Dye kills malaria parasites

Besides vaccines aimed at preventing malaria, therapies to treat malaria are desperately needed. Currently, malaria parasites are getting increasingly resistant to standard artemisinin-based therapies. Together with the University of California and the Malaria Research and Training Center, Teun Bousema aimed to identify novel therapies for malaria in a study in Mali.

Bousema and colleagues from the Department of Medical Microbiology added methylene blue to the standard of care, artemisinin-based therapy. Methylene blue is a dye often used in biomedical laboratories to distinguish dead cells from living cells. Interestingly, this addition prevented patients from being able to transfer malaria to mosquitoes within 48 hours of receiving the treatment. With artemisinin-based therapy alone, this effect was not reached until one week after initiating treatment. These findings suggest that the use of methylene blue can prevent the spread of malaria shortly after starting treatment. Moreover, adding methylene blue to the current therapy is safe and well tolerated by patients. The only disadvantage? It turns the patient's urine bright blue [7]!

Borrelia burgdorferi causes a change in the glutathione metabolism

The spirochete *Borrelia burgdorferi* causes Lyme's disease when transmitted by the bite of an infected tick. Initially, it often presents with erythema migrans (an expanding area of redness on the skin). If left untreated, Lyme's disease can cause joint, heart and neurological problems. It is hypothesised that these symptoms are caused by the host's immune response to the *Borrelia* infection. This response may also cause the persistence of the symptoms after treatment.

Leo Joosten from the Department of Experimental Internal Medicine and colleagues, among whom Mariska Kerstholt and Hedwig Vrijmoeth, who have studied biomedical sciences and medicine, respectively, published their research about the role of glutathione metabolism in host defence against *Borrelia burgdorferi* infection.

They found a tenfold increase in the levels of the important antioxidant glutathione in monocytes after they were exposed to *B. burgdorferi*. Moreover, they found that glutathione is a critical regulator of the cytokine production, likely by protein glutathionylation, by these immune cells after the exposure to *B. burgdorferi*, while this appeared to have limited effect on the oxidative state of the cell. Their study did not only show the importance of the glutathione metabolisms in vitro but also in vivo, as they also found a prolonged altered glutathione metabolism in patients with Lyme's disease. Joosten and colleagues, therefore, hypothesise that these metabolic infections may persist even after the bacterium has been cleared, which could explain enduring of symptoms in patients over a longer period of time.

This study did not only provide new insights into the pathogenesis of Lyme's disease but also provided a new explanation for the variation and endurance of clinical symptoms, even after successful treatment of the bacterial infection. With this, Joosten and colleagues demonstrate the importance of host-pathogen interactions with the metabolism in human disease [4].

Patient-specific computer models can help to predict fracture risk

It has been widely acknowledged that some cancers can metastasize to the bone and thereby subject patients to an increased risk of pathological bone fractures. The development of these fractures can have a big impact on the patient's quality of life and should be prevented. Therefore, the treatment of metastases is determined by the risk of pathological bone fractures. However, there is currently a lack of accurate tools to guide clinicians to make the correct treatment decision.

Researchers from the Orthopaedic Research lab of the Radboudumc, Department of Orthopaedics, have developed a patient-specific finite element (FE) model for fracture risk prediction. This is a computer model that uses the patient-specific geometry and bone density obtained from a CT-scan to predict the risk of bone fractures. This FE model was validated and compared with the clinical assessments made by experienced doctors in a prospective cohort study. A total of 39 patients with non-fractured femoral metastases that underwent radiation for pain reduction were included. During this study, nine pathological fractures were reported in seven different patients. When looking at the predictions retrospectively, the FE prediction models made for all patients were more accurate in assessing the risk of fractures compared to the assessment made by experienced doctors. This suggests that the FE models can be a valuable tool in daily practice when assessing pathological bone fracture risk [5].

Diving longer because of larger spleens

Human adaptations to extreme environments are a frequently studied subject. Populations adapted to extreme environments enable research to the long-term genetic and physiological consequences of these extreme environments, like hypoxia-tolerance in humans. This is not only scientifically interesting but can also provide clinically relevant insights into the management of hypoxia in patients with, amongst others, COPD or sleep apnea.

Thus far, the phenomenon of hypoxia tolerance had been studied in high-altitude human populations. However, an international group of scientists, including researchers from the Department of Experimental Internal Medicine of the Radboudumc, have recently studied hypoxia tolerance in humans who engage in breath-hold diving. They studied the indigenous Bajau people, also called 'Sea Nomads', who live in Southeast Asia. The Bajau are well known for their breath-hold diving and extraordinary breath-holding abilities. They dive to depths of 70 meters with traditional equipment to catch fish and shellfish. The study compared the genomes of the Bajau to those of nearby populations and found 25 sites on the genome that differed between the groups. One of the variations was on the PDE10A gene. Illardo et al. suggest that natural selection on genetic variants in the PDE10A gene have increased the spleen size in the Bajau population. This larger spleen provides the Bajau with a larger reservoir of oxygenated red blood cells, making it possible for them to hold their breath longer. This insight might motivate novel research to human adaptation to hypoxia tolerance [6].

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RAMS

A Word from the Board of RAMS

Dear reader,

Thank you for reading the eleventh edition of RAMS. I am proud to inform you that this is also the first edition of RAMS in our lustrum year. This year, RAMS will celebrate her fifth anniversary as a journal and organisation.

As I am writing this acknowledgement, I also realise that I do not know what the origin of the word 'lustrum' is. As a member of a scientific journal, this led me to some research of my own. It sounded Latin to me, and this is correct. A lustration, in ancient Rome, was a purification of all the people by means of ceremonies held every five years, originally done by a sacrifice.

We have started a new academic year and with this, new and old students are at the beginning of new challenges. A not so ancient, but nonetheless old saying by First Lady Eleanor Roosevelt goes: 'Do something every day that scares you'. This does not mean that you should start keeping spiders in your home or jumping off of high buildings for no apparent reason. It means stepping out of your comfort zone. A year ago, I stepped out of my comfort zone by applying for a position in a committee that I did not know much about, but I accepted the challenge. Now, I look back at a year full of new faces, experiences and knowledge within RAMS. I hope I can inspire you to step out of your comfort zone, whether it is meeting new people, running that half marathon or joining an organisation. Studying is more than what comes from your textbooks.

Without getting into too many details on facts about ancient traditions or old presidents, I would like to address how honoured I am to be a part of the first lustrum board of RAMS. Not only is it a year of celebrating RAMS, but it is also a year in which to reflect upon the past five years and what we have accomplished. I would like to thank the alumni of RAMS for having stepped out of their comfort zone to achieve this.

After all, the only place where success comes before work is in the dictionary.

On behalf of the Board of RAMS,

Emily Aupers
Chair of RAMS 2018-2019

General Board

RAMS is directed by the general board, which consists of five medical students. As members of the board they frequently meet to make sure all activities run smoothly. Moreover, they are in close contact with the supervisory board and the editorial staff. If you have any questions on general, promotional or financial subjects, please contact the general board of RAMS via voorzitter.rams@ru.nl.

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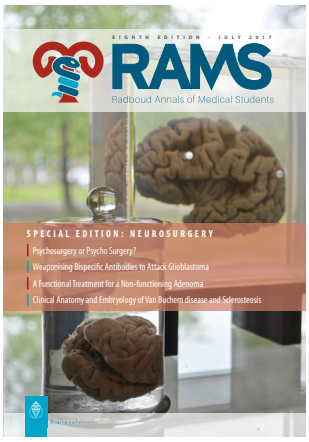

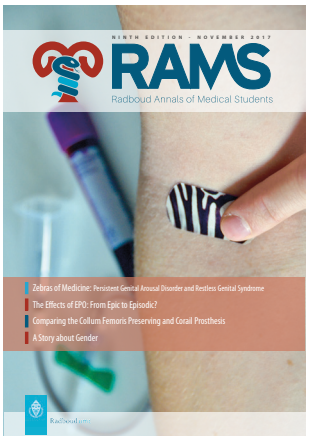

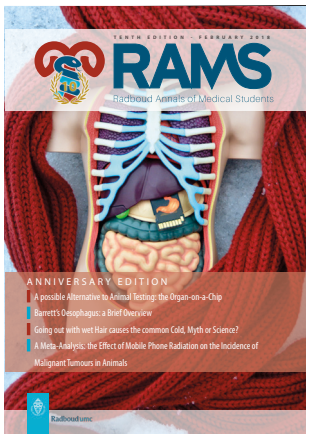

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