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FROM THE EDITORIAL BOARD

Dear readers,

Like a mother is proud of her children and students of their plants, we hereby proudly present to you the 15th edition of RAMS. After months of hard work, we have now finalised this edition to once again fuel the passion for research of (bio)medical sciences. We have tried to combine both innovative and scientifically challenging topics to increase the knowledge and reading pleasure of our readers. You will find that this edition is filled with various articles with a broad range of different topics. We would first like to introduce you to the post-orgasmic illness syndrome, what is it and can it be treated? Another topic that will be discussed is whether skipping breakfast is healthy or not since there is much debate, but no one knows the answer to it. Furthermore, have you always wondered what it is like to work at one of the most recognisable scientific journal in the world? You will be able to get a glimpse by reading an interview with a reviewer from Nature! The scientific articles will cover malaria versus the common flu and Parkinson's disease. While these are familiar topics, there is still so much that we do not know. This, to me, is the beauty of RAMS. In only a few pages, we aim to educate you as much as possible to not only increase your knowledge but also increase your enthusiasm for research.

I wish you a lot of joy while reading. Hopefully, you will learn something new on each page you turn and will be inspired and motivated to keep on expanding your knowledge everywhere you go!

Yours faithfully,

Larissa Govers,
Editorial Editor-In-Chief

INDEX

POST-ORGASMIC ILLNESS SYNDROME IN MEN: A SHORT INSIGHT

Quentin Marsman[1]

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Insights

A 20-year-old man was hesitant to visit the physician. Starting early adolescence, he had experienced some strange complaints, including burning eyes, an intense feeling of warmth all over his body and aching muscles. The symptoms were very unpleasant, mainly because they were present for up to a week at a time. Up until now, he had had around ten episodes of these complaints. However, he could not point his finger at a possible cause. He had just recently started masturbating, so his only thought was that perhaps this had something to do with the complaints. He hoped that the complaints would fade over time, but they did not. Eventually, he decided to visit the physician. The physician was clueless, since he had never seen such a case. Likewise, Waldinger and Schweitzer came across these complaints and became the first to describe men with these symptoms in literature [1]. Published in 2002, they named the syndrome post-orgasmic illness syndrome (POIS).

Introduction

Sexual intercourse is a wonderful event happening between two people. However, contrary to what movies make us believe, this dance is not always flawless. Several processes could go wrong during intercourse. In men, who will be the focal point of this article, premature ejaculation is the most prevalent sexual dysfunction. Studies have found a prevalence of around 20 to 30%, although this percentage could be higher due to the embarrassment of both patient and physician and a lack of awareness [2]. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, premature ejaculation is defined as an ejaculation within one minute of vaginal penetration, causing significant distress [3]. Another orgasm disorder in men is delayed orgasm. The World Health Organisation defines delayed orgasm as 'the persistent or recurrent difficulty, delay in, or absence of gaining orgasm, although the presence of enough sexual stimulation' [4]. Post-orgasmic illness syndrome (POIS) is another condition related to orgasm. The National Institutes of Health Office of Rare Disease Research in the United States of America recognises POIS as a rare condition [5]. The condition seems to occur only in men, as there is no available literature on POIS in women as of this date. The amount of literature researching this condition is limited. In this review, an overview of POIS will be given. Successively, history, diagnosis, pathophysiology, treatment and consequences of the condition will be highlighted.

POIS: a short history

In 2002, Waldinger and Schweitzer were the first to suggest the name post-orgasmic illness syndrome as a cluster of symptoms [5, 6]. In their case report, the two men described flu-like complaints followed by cognitive problems, which lasted for about five to seven days [1]. The flu-like complaints included symptoms such as myalgia, fatigue, intense warmth throughout the body and local signs of allergy, such as sore throat, postnasal drip, skin erythema and burning eyes [1, 5]. The mental problems were characterised as decreased concentration and an irritated mood [5, 7]. The onset of symptoms was a few seconds to hours after sexual activity in these patients. Following this publication, a gradually increasing group of men recognised the symptoms and reported to be relieved that the condition had finally got a name [7].

In 2011, Waldinger *et al.* published a second article on POIS describing 45 cases in Dutch Caucasian males [8]. In this article, it appeared that two types of POIS exist: a primary type, in which POIS starts at puberty or adolescence when a male has his first ejaculations, and a secondary type, in which the disorder has its onset later in life [7]. The distribution of the two types in these 45 men was almost half: 49% with the primary type and 51% with the secondary [7]. The prevalence and incidence of POIS are unknown due to a lack of studies [5]. Currently, 57 cases of POIS have been reported; of those, 47 were published by Waldinger *et al.* in 2002 and 2011 [6].

Diagnosis

As the presentation of POIS comprises a wide spectrum of symptoms, Waldinger *et al.* proposed five preliminary diagnostic criteria for POIS (Figure 1) [8]. Patients have POIS when three or more of these criteria are met [9]. The first criterion requires having one or more symptoms, like the sensation of a flu-like state, irritability or concentration problems [5-7]. This criterion is further divided into seven clusters of symptoms: general, flu-like, head, eyes, nose, throat and muscle (Figure 1) [5-7]. Criterion two states that all symptoms should occur immediately or within a few hours after ejaculation initiated by coitus, masturbation or spontaneously during sleep [5-7]. According to criterion three, these symptoms must occur in over 90% of ejaculation events [5-7]. The fourth criterion states that the symptoms last for around two to seven days and the last criterion required the symptoms to disappear spontaneously [5-7].

Since these criteria were first proposed, literature has consistently used these criteria to diagnose and report cases [6]. In 2019, Strashny was the first to assess the validity of the criteria. Published in Nature, he performed a self-report study among 127 men with self-reported POIS. He found that of those 127 men almost all fulfil a majority of the criteria and even a large minority had all five [9]. He proposed to broaden the third criterion to 'in at least one ejaculatory setting', as this was seen most of the times [6]. A limitation of his study is the lack of verification of his findings through examination by a clinician.

Pathophysiology

Little is known about the pathophysiology of POIS. Since it is a rare syndrome, only few studies have investigated this condition [6]. Nevertheless, there are a few hypotheses for the pathophysiology.

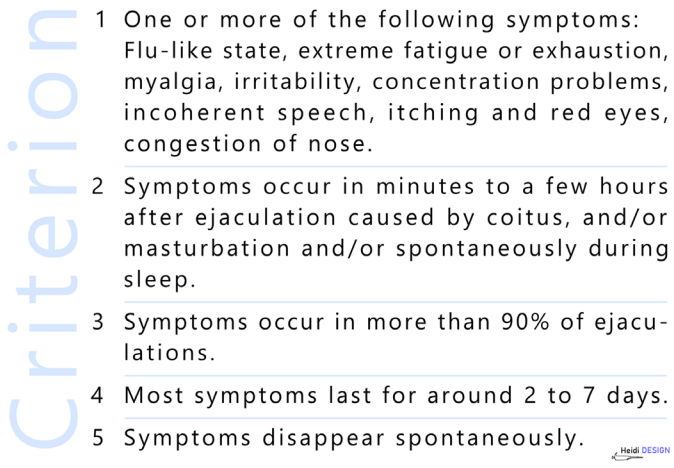

Figure 1: Criteria for diagnosis of POIS

Patients are diagnosed with POIS when three or more of the criteria are met [5-7].

The first hypothesis was suggested by Waldinger *et al.* in their papers from 2011 [8, 10]. In the first of these two articles, they suggest that POIS is an autoimmune or allergic disease, in which the body reacts to its semen via Type-I and Type-IV reactions right after ejaculation [8]. The successful treatment of two men with hyposensitisation with autologous semen in their second article supports this hypothesis [10]. Kim *et al.* added to this hypothesis by finding an increased serum concentration of serum-specific IgE antibodies [11].

Contrary to the theory of Waldinger *et al.* and Kim *et al.*, Jiang *et al.* were not convinced that IgE-mediated semen allergy accounts for the symptoms associated with POIS. In their 2015 study, they investigated one Chinese man with POIS and indeed found positive skin reactions after autologous seminal fluid injection, just like Waldinger *et al.* [12]. However, they found no detectable serum concentrations of specific IgE antibodies, making a possible contribution of IgE in the mechanism of POIS less likely [12]. They compared POIS with opioid withdrawal, due to similarity in the manifestations of both. They suggested that orgasms consume large quantities of endogenous opioids in POIS patients [12].

In a case report, Ashby and Goldmeier proposed a different hypothesis in which POIS is driven by a disorder in the cytokine or neuroendocrine response [13]. The fact that the administration of prophylactic diclofenac, a non-steroidal anti-inflammatory drug, improved the symptoms of patients supported their hypothesis [6].

Lastly, Bignami *et al.* suggested POIS could be the manifestation of a dysregulation of the autonomic nervous system as ejaculation triggers sympathetic activity and, therefore, a release in norepinephrine [14].

Treatment

POIS is a rare condition where underdiagnosis and under-reporting are highly likely [5]. Currently, there are no recognised treatment modalities for POIS [5]. Until now, patients with POIS have been treated with antihistamines, selective serotonin reuptake inhibitors and benzodiazepines [15]. In a case report, Ashby and Goldmeier observed an 80% improvement of symptoms after treatment with diclofenac [13]. In 2011, Waldinger *et al.* successfully treated two Dutchmen with hyposensitisation therapy using autologous semen leading to 60 and 90% improvement of symptoms [10]. In 2017, Gerber proposed flooding as a treatment mechanism, in which patients are advised to keep masturbating just like normal despite the symptoms present [16]. As a result, a desensitisation to the stimulus can be attained. It was shown to be successful in one patient, which indicates the requirement for more research.

Burden of POIS

POIS has some severe mental and psychosocial consequences. Due to the fear of ejaculation and the associated symptoms, many patients with POIS decrease the frequency of their ejaculation or abstain from it all together [5, 6]. This can lead to an internal struggle, disturbing the sexual life of the patient. The associated decrease in concentration and alertness can have consequences for their work or study, requiring precise planning of intercourse to prevent these symptoms from interfering with these essential daily activities [5, 6]. Young people with POIS might have doubts when in search of a romantic partner, as they fear refusal of their partner due to their sexual abstinence [7].

Conclusion

In short, POIS was first mentioned in 2002 as a cluster of symptoms, including flu-like symptoms and cognitive problems. Since then, an increasing group of men reported their symptoms and more literature on this disease emerged. Five diagnostic criteria were proposed. The pathophysiology remains generally unclear, but there are a few proposed theories. There are no recognised treatment modalities for POIS, but hyposensitisation therapy, diclofenac and a number of other drugs have been shown successfully in individual cases. Furthermore, POIS causes a significant burden for the patient, as their sexual life is disturbed. POIS is a rare but debilitating disease in which a lot of research needs to be done to treat these patients sufficiently.

Acknowledgements

RAMS would like to thank sexologist Marianne Vergeer, MSc, Radboud university medical center, Nijmegen, the Netherlands, for providing the author of this article with feedback.

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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 bachelor's!

We challenge you!

Question 1:

The embryonal 'tube-within-a-tube body plan' arises due to the curving of the embryonic disc. With a congenital condition in which the inner tube has locally no lumen, the child will …

A. Miss a cavity (ventricle) in the brains.
B. Have an obstruction in the aorta.
C. Have an obstruction in the intestines.
D. Have regulatory captures in the abdomen.

(Topic from Q5-2 MGZ From cell to tissue, 2018)

Question 2

Every year, patients with diabetes are investigated on having microvascular complications. Besides an investigation of the eyes and kidneys, there is also an investigation of the …

A. Liver
B. Feet
C. Heart

(Topic from Q3 MGZ Diabetes, 2019)

The answers to these questions can be found on page 9 in this journal.

MYTH OR SCIENCE:
IS SKIPPING BREAKFAST GOOD FOR YOU?

Femke Janssen[1]

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Critical Appraisal

'Breakfast is the most important meal of the day' is a well-known phrase. In line with this, Adelle Davis, considered as the most famous nutritionist in the early to mid-20th century, popularised the following mantra: '*Eat breakfast like a king, lunch like a prince and dinner like a pauper*', since breakfast would energise one for the day to come [1]. In the Netherlands, however, almost one in five women and even one in three men aged 19 to 50 years old do not eat breakfast on a daily basis. This percentage is lower in people aged over 50. In this population group, 87% of females and 82% of males consume breakfast daily [2]. Contradictory to the previous statement, some nutritionists state that skipping breakfast is not so bad at all [3]. Thus, disagreement exists on whether skipping breakfast is desirable. Therefore, this article aims to explore whether skipping breakfast in the morning is healthy for you or not.

Introduction

If one wants to maintain body mass, it is vital to consume enough energy throughout the day to keep a good balance between daily energy expenditure and consumption. This balance is essential since enough energy should be present for dietary-induced thermogenesis, energy usage in the resting metabolic rate and activity-induced thermogenesis (e.g. daily life activities), which make up the three components of daily energy expenditure [4]. A healthy food pattern requires the recommended intake of several nutrients in the food. These nutrients include proteins, fats and lipids, carbohydrates, several vitamins, minerals and trace elements [5]. When looking to maintain body mass, one should neither eat too much nor too little. Vegetables, fruit, legumes, fish, wholemeal products, nuts and few animal products are all characteristic food products of a healthy diet [6]. In the Netherlands, breakfast provides 14% of the total daily energy intake, compared to lunch (21%), dinner (36%) and in-between meals (30%) [7]. However, almost one in five women and even one in three men aged 19 to 50 years old do not consume breakfast on a daily basis. This percentage is lower in people aged over 50. In this population group, 13% of females and 18% of males skip their daily breakfast [2]. One reason for this breakfast skipping behaviour is lack of time before going to work in the morning [8]. Although some nutritionists advocate that skipping breakfast is not as bad as we think it is, official nutrition guidelines to date recommend that we do not skip our breakfast [9]. So, what should we believe? Is skipping breakfast in the morning recommended or not, or does it perhaps not make a difference at all?

Pros and cons of daily breakfast consumption

Eating your breakfast in the morning has been found to have several advantages over skipping your daily breakfast meal. First of all, Giovannini *et al.* suggest in their paper that eating breakfast lowers the risk of several chronic diseases [10]. This article suggests that skipping breakfast may lead to the upregulation of appetite, which could possibly lead to weight gain and alterations in risk factors for cardiovascular disease and diabetes, as well as that it may have an association with a poorer overall quality of the diet. This article cites studies which report that an increased meal frequency induces changes in metabolism in favour of risk factors for chronic diseases and thereby lowers the risk of chronic diseases.

Furthermore, two cross-sectional studies found that eating breakfast reduces overweight and obesity [11, 12]. According to the first study, this finding could possibly be explained by a more equal distribution of energy intake across meals throughout the day when not skipping breakfast. According to the second study, it is suggested that breakfast skippers tend to eat more foods containing low nutrient or high energy density or they may consume more discretionary energy at other meals. In addition, this article suggests that skipping your breakfast may lead to excess hunger, which could lead to overeating and subsequently result in both the consumption of larger food portions and increased eating frequency.

Although there is evidence in favour of eating your breakfast, scientifically underpinned evidence for skipping your breakfast also exists. The studies described above indicating that breakfast skipping is associated with both chronic diseases as well as overweight and obesity were all observational studies. Because of this, a causal relationship between breakfast skipping and weight status/chronic disease risk is hard to establish. It could, for example, have been the case that people who eat breakfast already tend to have a healthier diet containing more fibres and micronutrients and that these people are also likely to be more physically active [13, 14]. Conversely, breakfast-skipping individuals are more likely to have an unhealthy lifestyle, including smoking behaviour, excess alcohol consumption and a low physical activity level [15].

In addition, some people advocate for the fact that eating breakfast boosts your metabolism at the beginning of the day. Though this sounds quite logical, this has not been proven, since a randomised crossover design study evaluating the effect of breakfast skipping on energy metabolism found no differences in calories burned over 24 hours between people who skip and who do not skip breakfast [16]. This could possibly be explained by the aforementioned components of energy expenditure: because of dietary-induced thermogenesis, it is true that eating breakfast or any other meal raises the metabolic rate. However, this dietary-induced fraction is always a fraction of the energy content of the meal and so for the immediate energy balance, the ingested energy will not completely be expended by this dietary-induced thermogenesis, since the resting metabolic rate and activity-induced thermogenesis also use energy [4].

Moreover, as discussed earlier on, it has been debated that you can become so hungry when skipping breakfast that you tend to overeat at other meals of the day, resulting in weight gain. However, some studies investigating the relationship between breakfast consumption and energy intake have shown that skipping your breakfast may even reduce your total calorie

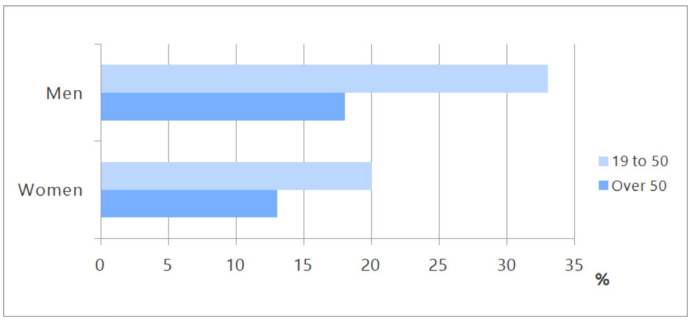

Figure 1: Percentages of daily breakfast skipping behaviour per age category for males and females.

intake per day by up to 400 calories, despite the fact that hunger rating and intake at lunch significantly increased after breakfast skipping [17-19]. Thus, these studies conclude that skipping breakfast does not necessarily result in compensation for the missing energy. Yet, a randomised controlled trial of high quality compared recommendations on whether to eat or skip breakfast in overweight and obese individuals and they found that there was no difference in weight between the groups after four months [20]. These results were supported by a couple of other studies [13, 21]. Additionally, breakfast skipping can result in lower energy intake across the day, and it also seems to result in lower physical activity thermogenesis [22]. Thus, there is no conclusive statement on the effect on weight after skipping breakfast.

Conclusion

Although some observational studies conclude that breakfast consumption causes less overweight and obesity as well as that it lowers the risk of several chronic diseases, these statements can be refuted by the fact that the studies that opted these findings are observational and thus no causal inference is possible. This means that no statement can be made on whether or not eating breakfast really has the potential to reduce overweight/obesity and the risk of chronic diseases.

Moreover, this article found that there were no differences in calories burned over 24 hours between breakfast-skippers and breakfast-consumers as well as that no definite statement can be made on whether or not breakfast skipping results in weight gain or weight loss. This could be explained by evidence that indicates that breakfast consumption may result in an increased energy expenditure and intake, as well as higher physical activity thermogenesis.

In conclusion, skipping breakfast is not especially bad or good for you. Since the evidence suggests that neither your metabolism is boosted by eating breakfast, nor does skipping breakfast automatically lead to overeating, it can be concluded that it just depends on what you eat during the rest of the day. So, feeling hungry in the morning? Grab some breakfast. Are you not in the mood for food? No worries, just skip it!

Acknowledgements

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INSIGHTS GAINED FROM NATURE EDITOR PEP PAMIES

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Interview

In November 2019, RAMS attended the ENABLE congress in Nijmegen with the aim to gain knowledge on open access. One of the participants of the plenary debate was Pep Pàmies, PhD, who is the chief editor of the scientific journal Nature Biomedical Engineering. Since editors can be seen as the guardians of good science and publications, we interviewed Pàmies after the plenary debate to find out how we, as students, can also become good editors and ensure good science.

The plenary debate discussed whether articles should be published in open access. We asked his opinion regarding the matter. He told us that the publishing model of open access has already been proven to be successful and that people want this model. He enlightened us: 'The problem is making it work since there are different fields of science'. This is an obstacle to overcome since scientific fields other than the (bio)medical field have different habits and a different workflow. Furthermore, due to practical problems such as finances, the speed on which we move towards open access is really slow.

Students only have limited experience with publishing models, but can already prepare themselves to become a good editor or reviewer. This is something we should all aspire to become, since we will all have to critically assess scientific articles. What makes an editor a good editor? Pàmies' answer to the question was short but sweet: 'You are a good editor if you recognise good work and scientific relevance'. However, a good reviewer has to provide more. A good reviewer has to study whether the work is valid and if the evidence is proper. Furthermore, a reviewer must assist the editor in whether the science is properly exposed or depicted and whether the article is nicely constructed. Lastly, he added: 'A good reviewer is constructive'. This is something we should all keep in mind when critically appraising articles.

To finalise the insights gained from Pep Pàmies, we asked him what he learned during his time as an editor. His answer was quite surprising. From his point-of-view it is crucial to recognise the constraints of people that do research over the world: differences in people, environments, luck, religion and different findings are things to keep in mind, and therefore you cannot treat all the people the same.

We hope you have gained insights from our interview with Pep Pàmies, chief editor Nature Biomedical Engineering, and remember:

> *"The more you know, the more you realise there is to know."*
>
> - Pep Pàmies, PhD

CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1:
C. Have an obstruction in the intestines

As a result of body folding, the tube-within-a-tube body plan is established. This plan consists of an embryo body design composed of two main tubes: an outer ectodermal tube forming the skin and an inner endodermal tube forming the gut.

For further reading:
Schoenwolf, G.C., *et al. Fourth week: Forming the embryo* in Larsen's Human Embryology, Vol. 5e. (Churchill Livingstone, Philadelphia, 2009)

During the exam, 63% of the participants answered this question correctly.

The exam questions can be found back on page 6 in this journal.

Answer question 2:
B. Feet

Diabetic foot problems are responsible for nearly 50% of all diabetes-related hospital admissions. The blood flow to the feet is assessed clinically and with Doppler ultrasound. Femoral angiography is used to localise areas of occlusion amenable to bypass surgery or angioplasty. Relatively few patients fall into this category.

For further reading:
Gale, E.A.M. and Anderson, J.V. *Diabetes mellitus and other disorders of metabolism* in Kumar and Clark's Clinical Medicine, Vol. 9 (Elsevier Ltd, the Netherlands, 2017)

During the exam, 92% of the participants answered this question correctly.

ZEBRAS OF MEDICINE
CAUGHT A FLU IN THE TROPICS? IT MIGHT BE MALARIA

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Abstract

Review

Background: Malaria (*Plasmodium spp.*) and influenza viruses both cast a significant burden of disease on the world's population. Since *Plasmodium spp.* remains endemic in many countries, it can infect many people on a global scale while influenza infects many patients during each influenza season. Malaria and influenza overlap in terms of clinical symptoms. Since malaria is deadly when untreated, misdiagnosis as influenza should be prevented in order for correct treatment to be initiated on time.

Objective: This review sets out to compare malaria with influenza in terms of clinical presentation, diagnosis and treatment.

Clinical presentation: Malaria and influenza show similar symptoms. However, both diseases have their own distinct symptoms due to their disease-causing pathogens. Infection with *Plasmodium spp.* Results in the possibility of regular fever peaks as a result of the multiplication-release-invasion cycle of the parasite. Symptoms that are seen during an influenza infection and not during a *Plasmodium spp.* infection are severe respiratory symptoms.

Diagnosis: Since the pathogens differ from each other in terms of replication, size and endemic areas, the diagnosis of the pathogens also differ. Diagnosis of malaria is based on case history, clinical observations and diagnostic tests. Influenza does not always need a diagnosis unless the patient is hospitalised, severely ill or at risk for severe infections for correct treatment. Influenza can be diagnosed using antibody tests, cell culture tests or reverse-transcriptase polymerase chain reaction, of which the latter is most frequently performed.

Treatment: Malaria can be treated using a combination of artemether and a drug that inhibits the formation of 'hemozoin' so that the toxic 'heme' accumulates in the parasitic vacuole, such as mefloquine. Influenza can be treated using different antiviral drugs. Currently, there is an ongoing discussion on the value of the treatment of viral infections, since resistance against antiviral medication can occur.

Conclusion: The disease causing pathogens *Plasmodium spp.* and influenza viruses differ a lot in terms of disease-causing pathogen and epidemiology. The diagnosis differs based on this information, such as case history and blood examination for malaria. The treatment of both diseases differ due to the causes of disease. Since malaria is deadly when untreated, physicians should be aware of the disease if a patient's case history does not rule out malaria.

KEYWORDS: plasmodium, misdiagnosis, symptoms, flu

Introduction

Both malaria and influenza cast a major burden of disease on humanity. According to the World Health Organization, roughly half of the world population is at risk of a malaria infection, which is caused by *Plasmodium* species parasites and transmitted by *Anopheles* species mosquitoes [1]. It should be kept in mind that the disease we know as 'malaria' is caused by a group of Plasmodium parasites, with each of those varying in severity of disease and where the parasite is endemic [2]. Malaria causes an estimated 1.2 million deaths each year, based on World Health Organization reports [2]. Although in many temperate zones near- or complete elimination of malaria has been established, this does not count for influenza [2]. Furthermore, the near- or complete elimination of malaria is expected to be reversed due to climate change [3]. Influenza viruses continue to be a season-dependent threat on a global scale to both humans and animals [4]. Humans and many animals of all age groups can get infected with these highly contagious viruses and severe disease states can occur [4]. Highly pathogenic strains of Influenza have emerged while this was not predicted, such as the 'Spanish flu', which killed globally 20 to 40 million people [4]. Early diagnosis of malaria is essential for adequate treatment, as well as effective disease management [5]. However, misdiagnosis of influenza might occur due to the overlapping symptoms of malaria and influenza and physicians might not think of malaria due to the (near-) complete elimination of malaria in their country, which might cause misdiagnosis of malaria [5, 6]. This review sets out to compare malaria to influenza in terms of clinical presentation, diagnosis and treatment.

Clinical presentation

Malaria is caused mainly by four species of *Plasmodium*: *P. falciparum*, *P. ovale*, *P. vivax* and *P. malariae*. Once the parasite gets into the bloodstream after a replication cycle in the liver, it infects red blood cells for replication, which spread across the body and the organs [2]. Symptoms can develop between six to eight days after the bite of an infected mosquito. Once the parasites have replicated in the red blood cells, this will result in cell lysis. The parasites released in the blood will subsequently infect other red blood cells. As a result of this multiplication-release-invasion cycle, sharp increases in body temperature are seen [2]. Since parasite-infected blood cells accumulate in various organs, such as the heart, brain, lungs and kidneys, a variety of other symptoms are frequently seen. The symptoms typically experienced are very flu-like: Fever, shivering, cough, pain in the joints, headache, diarrhoea, vomiting and convulsions [2]. Due to several pathogenic processes, such as jaundice, kidney failure and severe anaemia, this disease is severe and often fatal [2].

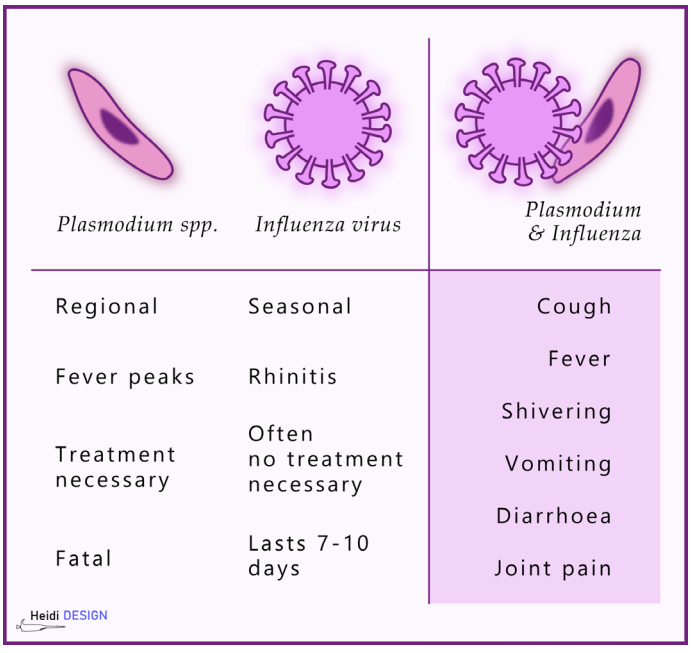

Figure 1: Characteristics and symptoms of Plasmodium and influenza

In contrast to malaria, influenza is not caused by a parasite infection and does not cause periodic fever spikes. Influenza viruses usually cause respiratory disease and are transmitted by aerosol droplets. The replication of the viruses in epithelial cells and enhanced mucus production causes a runny nose and a cough. The onset of systemic symptoms is seen much earlier than in malaria: after an incubation time of approximately two days [4]. During the incubation period, the virus can already be transmitted to another host. Influenza infection is typically recognised by the systemic symptoms, such as fever, myalgia, headaches and severe malaise, as well as respiratory symptoms: coughing, sore throat and rhinitis, which can last for seven to ten days. Coughing and overall malaise can persist for up to two weeks [4]. The symptoms of malaria and flu can thus be very alike, but the incubation periods and specific symptoms (such as periodic fever peaks) differ between the two pathogens. The most crucial difference in quick diagnosis is that a malaria infection occurs in endemic areas and that influenza infections occur during the influenza season. Therefore, the case history of a patient is essential to rule out malaria quickly.

Diagnosis

The diagnosis of malaria and influenza differ since there is a difference in pathogens, replication methods, size and endemic areas [2]. Malaria is diagnosed using case history (whether the patient has been in a malaria-endemic area), clinical observations and diagnostic tests [2]. These diagnostic tests include microscopic examination of blood and polymerase chain reaction (to demonstrate the presence of parasite DNA) [2]. The blood for microscopic examination is ideally collected when the patient's temperature is rising, as that is when the highest number of parasites are likely to be found. Thick blood drops are used for routine diagnosis due to the high sensitivity [2]. Influenza is diagnosed using accurate and rapid tests, as this is essential for effective management of disease, such as isolation measures and exclusion of a bacterial infection [4]. Antibody tests on serum, cell culture tests or reverse-transcriptase polymerase chain reaction can be used, of which the latter can be used for strain typing [4]. These tests should be done within days after onset of symptoms since the virus replication and illness progresses rapidly [4]. Malaria diagnosis is important in every infected individual due to the severity of the disease. Influenza does not cause severe disease states in many patients and is, therefore, not always diagnosed using the pre-mentioned tests. Only people who are at risk of developing severe disease states are usually diagnosed in such manners, such as hospitalized patients.

Treatment

The different species of *Plasmodium* differ in drug response and diagnosing the right pathogen is important [2]. Prevention of infected mosquito bites is the first step of malaria prevention. If one is nonetheless infected, several treatment options are available [3]. Uncomplicated infections are mainly treated with a combination of artemether (inhibits DNA and protein synthesis of the parasite) and a drug, such as mefloquine, that inhibits the formation of 'hemozoin' so that the toxic 'heme' accumulates in the parasitic vacuole [3]. These drugs can be ingested orally. When severe malaria occurs, intravenous or intramuscular artesunate for at least 24 hours can be administrated. When oral ingestion is tolerated again, this treatment is followed up by three days of artemisinin-based combination therapy [3].

Four different antiviral drugs are recommended for the treatment of influenza: oseltamivir, zanamivir, peramivir and baloxavir [7]. Although these drugs should be administered early to prevent disease progression, the efficacy is sometimes limited [7]. These drugs can either be used as a treatment to inhibit viral replication while they can also be used as chemoprophylaxis (prophylaxis in the form of medication) [7]. Each year, there are three strains predicted to emerge, and a vaccine is prepared for these three strains. People at risk can receive this vaccine, although this vaccine is not always effective if a strain emerges different than the predicted strains [7].

Conclusion

Malaria and influenza both infect many people and can cause severe disease states. However, the disease outcomes differ between the two diseases when untreated. Treatment is always necessary for malaria, whereas this is not always the case for influenza infections. The pathogens are diagnosed in a different manner due to the epidemiological, replication, and species differences. One key difference in symptoms is the periodic fever spikes seen with malaria and the continuous fever that is present with influenza. For this reason, an important question that physicians should ask when a patient presents with flu-like symptoms is whether the patient has been in a malaria-endemic area, to exclude malaria as a possible cause of symptoms.

Acknowledgements

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PARKINSON'S DISEASE: A CLEARER ROAD TO A RELIABLE DIAGNOSTIC TEST?

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Innovation

Parkinson's disease (PD) is one of the most common neurodegenerative diseases with a mean prevalence of 1350/100,000 in the Netherlands [1]. Several symptoms of the disease, like bradykinesia, rigidity, tremor and depression, facilitate a substantial decrease in the quality of life of PD patients [1]. It is important to have a correct diagnosis for the reasons that 1) the progress of therapeutic interventions that may stop or slow the disease can be monitored, 2) intervening at the onset of disease is of importance for symptomatic therapy options, and 3) distinguishing between PD and other diseases is crucial, since there might be differences in prognosis or treatment responses [2, 3]. To date, however, the current methods of diagnosing PD remain unsatisfying [4]. Therefore, this review will first discuss the current state of art in the diagnosis of PD and its limitations and thereafter it will discuss a promising new diagnostic test.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases with a mean prevalence of 1,350/100,000 in the Netherlands [1]. Symptoms include motor symptoms like bradykinesia, rigidity and tremor, as well as mental symptoms, like depression or psychosis. These symptoms all substantially impair quality of life of PD patients. Moreover, the financial burden of PD disease rises with the increasing longevity in the population, which leads to a higher incidence of PD cases with age [1]. In short, PD is due to degeneration of dopamine producing neurons in the substantia nigra pars compacta, resulting in an insufficient dopaminergic input in the basal ganglia. Subsequently, there is less stimulation from the thalamus to the premotor cortex, which causes motor symptoms (Figure 1) [5]. The exact cause of PD is unknown, but is expected to be the result of environmental exposures, ageing and genetic susceptibility [6]. Currently, there is no cure available for PD, but there are treatments that aim to treat the symptoms [5, 6]. A correct diagnosis of PD is important for monitoring the progress of therapeutic interventions that may stop or slow the disease, and to intervene at the onset of disease, which might be helpful in terms of providing symptomatic therapy to elevate disease symptoms in patients [2]. However, current diagnosis in the early stages of PD remains relatively suboptimal for the reason that diagnostic accuracy is only 82.7% [4]. This review will first discuss the current state of the art in the diagnosis of PD and its limitations and thereafter it will discuss a promising new diagnostic test.

Current practice

Current diagnosis of PD is mainly clinical [4, 7]. A precise diagnosis of PD is important for prognostic, therapeutic, clinical, pharmacologic and epidemiologic purposes [4]. At present, however, it is a challenge to diagnose PD with certainty, as the clinical presentation of PD is heterogenous and overlaps with various other syndromes. Examples are progressive supranuclear palsy, essential tremor and the parkinsonian variant of multiple system atrophy, commonly referred to as MSA-P [8]. It is of importance to distinguish between these diseases because of the differences in prognosis and responses to treatment [3]. Especially difficult is early diagnosis, since symptoms of possible alternative diagnoses have not yet emerged and response to dopaminergic treatment is less defined [9]. Consequently, misdiagnosis is common and early diagnosis remains difficult and inadequate [4, 7]. Therefore, the United Kingdom Parkinson's Disease Society Brain Bank has determined some criteria, thereby standardising the diagnosis of PD and increasing the diagnostic accuracy even up to 90% [10, 11]. However, it has been suggested that this percentage is the best that can be achieved with clinical assessment [11].

Furthermore, neuroimaging techniques, such as MRI, PET and SPECT, are used to study patterns in the brain. These techniques make it possible to detect premotor disease, monitor disease progression and provide insight in the effects of therapies modifying the disease. Advances in MRI make it possible to separate PD patients from healthy subjects and show a great promise to do the same in PD patients and other akinetic-rigid syndromes [12, 13]. These techniques can be useful measuring the distribution and degree of atrophy in the brain [8] and can provide information about anatomical and functional connectivity changes in PD patients [14]. However, none of these techniques are recommended for routine use in clinical practice [8]. To date, there are no definitive biomarkers for the diagnosis of PD. Reliable biomarkers are needed to discriminate PD from other syndromes [15], since PD is a disease with an ambiguous clinical picture [16].

A promising new diagnostic test

PD is characterised by the accumulation of Lewy bodies, which are composed of misfolded alpha-synucleins [17]. There is increasing evidence that these abnormal formed proteins are harmful to dopaminergic neurons, thereby contributing to neuronal cell death [18-20]. Extensive research has been done over the past years investigating the role of alpha-synuclein in the cerebrospinal fluid (CSF) as a potential biomarker in the diagnosis of PD. Thus far, results were promising but inconclusive [21]. A few years ago, a novel assay has been developed that detects tiny amounts of aggregates of misfolded alpha-synucleins in the CSF [22]. If a high concentration of proteins is added to the CSF, the misfolded alpha-synucleins will misfold the well-folded proteins, which initiates fibril formation [23]. Thereafter, the proteins start emitting light, indicating that there are misfolded alpha-synucleins present in the CSF [23]. Early detection of misfolded proteins in people with an unclear form of PD assures a quite reliable diagnosis. Up until now, the test has a high sensitivity and specificity, but has only been assessed in confirmed clinical cases and not in equivocal cases [16].

Researchers from Nijmegen and Edinburgh have, therefore, recently evaluated the use of this new test in uncertain, but suspected, cases of parkinsonism. For this, they used CSF samples from patients with suspicion of parkinsonism at the time of lumbar puncture. They found a sensitivity of 75%, a specificity of 95 to 98% and positive predictive values of 93%, with the latter two being high, indicating that the vast majority of patients without diagnosis of parkinsonism and a positive test score will have an underlying alpha-synucleinopathy. One restriction of this test is that it cannot differentiate between PD and multiple system atrophy patients. To overcome this, a combination of biomarkers will probably be necessary. However, this is a promising new test with the potential to become a useful diagnostic tool to help discriminate between alpha-synucleinopathies and other parkinsonian syndromes [16].

Conclusion

To summarise, the current diagnosis of PD is mainly based on clinical examination and imaging techniques can provide additional information about structural and anatomical changes in the brain. However, these diagnostic tools are not optimal. Thus, researchers have been searching for biomarkers as a reliable diagnostic tool for PD. Lately, a new test detecting misfolded alpha-synucleins in the CSF has shown great potential. If similar results are observed in other studies, it can be a valuable addition to diagnostics for PD.

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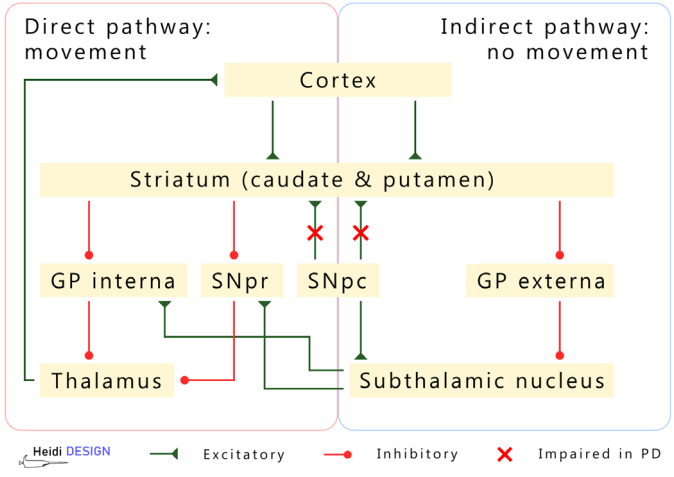

Figure 1: Movement regulating pathways in the basal ganglia in the normal and diseased state

Cells in the Substantia Nigra pars compacta (SNpc) produce dopamine. These cells project on neurons in the striatum (consisting of the caudate and putamen). In the direct pathway (left), excitation of the striatum results in more inhibition of the globus pallidus interna (GP interna) and substantia nigra pars reticularis (SNpr), which in turn leads to less inhibition of the thalamus and thus more activation of movement. In the indirect pathway (right), excitation of the striatum leads to more inhibition of the globus pallidus externa (GP externa), whereafter the subthalamic nucleus is less inhibited and thus more active. This results in more excitation of both the GP interna and SNpr, eventually resulting in inhibition of the thalamus and thereby movement inhibition. In case of PD, the dopaminergic cells in the SNpc degenerate. In both pathways there is less stimulation of the striatum, ultimately resulting in less movement initiation because of over-activity of the indirect pathway and underactivity of the direct pathway.

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RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

Nena Rokx[1]

Summary

With over 3,000 publications per year, scientific research is a cornerstone of the Radboud university medical center [1]. In this section, recent high-impact papers with an impact factor higher than five – published by researchers from the Radboudumc – will be discussed.

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Precision medicine in cancer and hereditary diseases

Mutations in our DNA can disrupt protein synthesis. These mutations may result in truncated proteins when a single base pair is substituted by a premature stop codon. Therefore, these proteins are not able to work as intended. This type of mutation is called a nonsense mutation and they can contribute to hereditary diseases and different types of cancer. To prevent the formation of truncated proteins, human cells perform a quality control process on the RNA by recognition and removal of mRNAs containing nonsense mutations. This process is called nonsense-mediated mRNA decay (NMD). In collaboration with the Institute for Research in Biomedicine, Barcelona, Spain and the Centre for Genomic Regulation, Barcelona, Spain, Rik Lindeboom and Michiel Vermeulen, theme cancer development, Radboudumc have developed a resource, NMDetective, to better understand and predict the effect of NMD on human disease [2]. The NMDetective database describes every possible nonsense mutation that can occur in the human genome and an algorithm identifies which mutations in the genome are susceptible to NMD. Using NMDetective, thousands of genetic variants that give rise to hereditary diseases in humans were analysed and this showed that, in many cases, NMD activity was predicted to lead to greater severity of the disease. This is a surprising result and suggests that pharmacological NMD inhibition could slow the progression of many different genetic diseases. NMDetective could be used in a precision medicine approach to distinguish which patients would benefit from NMD inhibition therapy by determination of the responsible mutation for the disease and the effect of NMD on this mutation. The researchers also investigated the role of NMD in cancer and the interaction between the tumour and the immune system. They found that NMD can hide mutations that would otherwise trigger the immune system. This is because tumours, in general, contain many genetic mutations that would make all sort of altered proteins. These proteins should be picked up, identified and destroyed by the immune system. However, many of these proteins are not produced because of NMD and, therefore, the immune system does not recognise the tumour. NMDetective can be used to analyse the mutations present in the tumour and the algorithm can distinguish between mutations that will and will not activate NMD. Tumours containing mutations that escape NMD will respond better to immunotherapy than tumours containing mutations that do not escape NMD. In tumours containing mutations susceptible to NMD, inactivation of NMD can help the immune system to better recognise tumour cells and, therefore, improve the immunotherapy response. Further development and possible clinical use of NMDetective might contribute to personalised healthcare and therapies targeted on the genetic profile of the disease. This study was published in Nature Genetics (impact factor of 27).

How to stop malaria

Around 216 million people are infected with malaria every year and in recent years an increase in this number was observed. Worldwide, malaria causes 400,000 deaths a year. *Plasmodium falciparum*, a single-celled parasite, is the cause of the deadliest form of malaria, transmitted by mosquitoes. Over the years, malaria has become resistant to several kinds of drugs. However, investigators from the Radboudumc, in collaboration with researchers from the United States of America, the United Kingdom, Switzerland and Spain, found that a psoriasis drug appears to be effective against malaria [3]. The drug is a pantothenamide molecule that closely resembles pantothenenic acid, vitamin B5, which is an essential nutrient for the *Plasmodium falciparum*. The parasite will use the drug in its metabolism and it will be converted into coenzyme A analogs that are highly potent against the malaria parasite. In fact, the drug interferes with the metabolism of the malaria parasite, causing it to die. In this way, the drug is active against the parasite stages that cause clinical disease and that drive onward transmission via mosquitos. Production of the drug is cheap and quick and targets a biochemical pathway that is not covered by currently marketed drugs. Therefore, it meets all the criteria for a possible new drug against malaria. However, preclinical models should be used for further evaluation of efficacy and safety. In a few years this drug can hopefully contribute to elimination of this deadly disease. This study was published in Science Translational Medicine (impact factor of 17).

Productivity loss due to menstruation-related symptoms

Women can have diverse and widespread menstruation-related symptoms such as heavy menstrual bleeding or premenstrual mood disturbances. A large, survey-based, cross-sectional cohort study by Mark Schoep, Department of Obstetrics and Gynaecology, Radboudumc and Hospital Rijnstate, Arnhem and Eddy Adang, Department of Health Evidence, Radboudumc, investigated the impact of these menstruation-related symptoms on work and school productivity [4]. The two main outcomes of the study were absenteeism and presenteeism, with absenteeism being defined as the total amount of time off work or away from school and presenteeism being defined as the loss of productivity while present at a job or school. In total, 32,784 Dutch women between the ages 15 and 45 were recruited to fill in a comprehensive online questionnaire, including questions about each woman's basic characteristics, menstrual symptoms and absenteeism and presenteeism. Of all women, 4,514 (13.8%) reported absenteeism during their menstrual periods with a mean of 1.3 days a year and 1,108 (3.4%) reporting absenteeism every or almost every menstrual cycle. However, only 20.1% (n=908) of the women told their employer or school that they were ill because of menstruation-related symptoms. More than 80% (n=26,438) women reported presenteeism and decreased productivity with a mean of 23.3 days per year. In total, 22,154 (67.7%) women wished they had greater flexibility in their tasks and working hours at work or school during their periods. The results of this study were published in BMJ Open (impact factor of 2.4). In conclusion, presenteeism because of menstruation-related symptoms is a more prominent contributor to a loss of productivity than absenteeism and it seems like the real impact of these symptoms is underestimated.

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RAMS

Word from the Board

Dear reader,

Thank you for reading the fifteenth edition of RAMS. This is the second release this academic year, which once more contains excellent articles from our editorial team and (bio)medical students alike. I want to thank everyone involved for their contributions to this journal.

With the start of 2020, we all stood at the precipice of a novel decade. Some see a grim future, filled with strife and uncertainty. Others see chances and opportunities, or better yet, create their own. With innovations in technology and engineering, moulded by those with the vision to realise their dreams, the future of healthcare seems to have a lot of unknowns in store for us. The quick advancement of milestones in healthcare has left many medical professionals struggling to keep up. But once more, where some see obstacles, others will see ways to accomplish their goals. This new, cutting-edge world will need fresh faces who nonetheless know what they are doing.

And that is where you come in, the (bio)medical students of today, the professionals of tomorrow. RAMS hopes to present you with a platform on which you can grow and develop your scientific proficiency. We hope to give you the experience to keep ahead in this world of rapid development. We hope that you will want to do this together. We will be there, will you join us in our journey into the future?

On behalf of the board of RAMS,

Eric Knijnenburg

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