RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

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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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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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