RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

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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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Metallic implants to synthesise antibacterial drugs

To support or replace diseased tissues, in for example trauma surgery, dental, orthodontic and cardiovascular care, metallic biomaterials are very effective. However, bacterial contamination of the surfaces is a major problem and prophylactic treatment with system antibiotics is common. This preventive treatment does not always have the desired effect and can even be harmful. Therefore, it would be useful to develop methodologies for the localised delivery of antibacterial agents to metallic biomaterials. Marja ter Meer, a PhD candidate at the Department of Radiology and Nuclear Medicine of the Radboudumc, made the serendipitous observation that a grooved alloy wire converted fluorogenic substrates into their fluorescent products [2]. After further research, she discovered that frequently used metallic biomaterials also have the enzymatic ability to degrade glycosidic linkages. This study was published in Chemical Communications (impact factor of six). Based on the results of this study, metallic biomaterials would be able to converse a prodrug, containing a sugar group, into active antibacterial agents by degrading glycosidic linkages. This approach is called enzyme-prodrug therapy. Metallic biomaterials themselves do not have enzymatic activity. However, a version with very small grooves in the metal has high enzymatic activity. In these grooves, iron was deposited, which is found responsible for efficient drug conversion through an unknown mechanism. Unfortunately, metallic biomaterials of pure iron are not stable enough and, therefore, an iron coating would be used. This iron coating was shown to be able to effectively convert a prodrug into antibiotics against many types of bacteria. In this way, less systemic antibiotics can be used, which reduces harm for the rest of the body. In the future, this technique may possibly also be implicated for anti-infection, prohealing, anti-cancer and anti-inflammation purposes [2].

Aggregated N=1 trials in rare diseases

About eight percent of the population suffers from a rare disease during their lifetime. However, for rare diseases, it is often impossible to conduct a Randomised Controlled Trial (RCT), which is seen as the gold standard for drug efficacy, due to the small numbers of patients and substantial heterogeneity. This makes it difficult to draw a reliable conclusion about the efficacy and safety of a potential treatment in a rare disease. Bas Stunnenberg from the department of Neurology and Gert Jan van der Wilt from the department of Health Evidence, both at the Radboudumc, investigated whether an aggregated N-of-1 trial design produces efficacy results consistent with those from a RCT [3]. They investigated this for the efficacy of mexiletine (a sodium channel blocker) in 27 patients with the rare chronic disease nondystrophic myotonia, which is caused by mutations in the skeletal muscle channels. Because of these mutations, there is a delayed relaxation of the muscle after voluntary contraction, so-called myotiona, which results in muscle stiffness. The primary outcome measure was the mean daily self-reported stiffness severity score. In an N=1 trial, an individual patient is treated with mexiletine and with a placebo for specific periods until the efficacy in the patient becomes clear. However, credible methods to combine different N=1 trials, to provide information about the overall effect of the drug on the disease, were unavailable. In this study, they found a way to combine the results of the multiple N=1 trials using a Bayesian hierarchical model. In this model, the results from each patient were aggregated into a sample mean and variance. Thereafter, patients' mean effect sizes were modeled with between-patient variance. Using this method, this study found similar results as an international multicenter crossover RCT from 2012; a reduction in mean daily-reported muscle stiffness. These findings support the efficacy of mexiletine in nondystrophic myotonia patients and the potential of N=1 trials for assessing drug efficacy in chronic rare diseases. Moreover, fewer patients are needed compared to RCTs and aggregated N=1 trials can predict the likelihood of the candidate drug having a clinically meaningful effect on individual patients. This study was published in the Journal of the American Medical Association (impact factor of 48) [3].

Little sharing of brain defects in patients with schizophrenia and bipolar disorder

Psychiatry is now the last area of medicine in which diseases are diagnosed solely on the basis of symptoms. An example of a psychiatric disorder is schizophrenia: diagnosed based on the presence of psychoses and specific behavioural symptoms. However, patients with schizophrenia have an extremely variable representation of their symptoms. To better understand the biology behind schizophrenia and bipolar disorder, Thomas Wolfers from the department of Human Genetics and the Donders Centre for Cognitive Neuroimaging at the Radboudumc investigated how much the brains of individual patients differ from the average patient with the diagnosis of schizophrenia or bipolar disorder [4]. The study performed a cross-sectional design using magnetic resonance imaging data from patients with schizophrenia, bipolar disorder and healthy control individuals. To quantify the brain structural heterogeneity, regional brain alterations at the level of individual participants were mapped in reference to normative brain ageing across the adult lifespan. The results of this study were published in the Journal of the American Medical Association Psychiatry (impact factor of 17). On average, patients with schizophrenia had significantly reduced grey matter in frontal regions, cerebellum and temporal cortex and patients with bipolar disorder primarily had deviations in cerebellar regions. However, only in a few regions, an overlap of more than two percent among patients was observed. These findings suggest that there is no average patient in schizophrenia and bipolar disorders and that it is not possible to stratify schizophrenia and bipolar disorder into biologically more homogeneous subtypes. Therefore, the use of brain imaging techniques to diagnose schizophrenia and bipolar disorders is not possible. This study also supports the notion that mental disorders are complex, with little sharing of causal brain structural defects [4].

References

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