The many faces of psychosis

Impact

BACKGROUND AND AIM

Approximately 3% of all individuals are diagnosed with a psychotic disorder during their lifetime, with a peak prevalence during adolescence (1). Psychotic disorders are characterized by one or more psychotic episodes in which (a combination of) several symptoms, among them hallucinations, delusions, disorganized speech, anhedonia, a lack of motivation and cognitive impairment, may be experienced. In some cases, patients experience these symptoms throughout their entire life, leading to chronic illness (2). Psychotic disorders may have a great impact on the life of individuals, their environment and society. It is known that patients with a psychotic disorder experience a lower quality of life and score lower on social functioning (3). Furthermore, comorbidity within the cardiovascular and metabolic field is common (4). Finally, the life expectancy of these patients is lower compared to healthy individuals (5, 6, 7). Timely diagnosis and appropriate treatment have been associated with better outcomes, fewer relapses and a better quality of life (8). Treatment usually consists of a combination of antipsychotic drugs and cognitive behavioral therapy, with a main focus on reducing psychotic symptoms, in combination with Individual Placement and Support (IPS, (9, 10)) to enhance societal participation. However, these treatment options do not sufficiently reduce the experienced symptoms in all patients and in many patients, the origin of their psychotic symptoms is difficult to determine. While often it is not known why patients experience these psychotic symptoms, in a small subgroup of patients, these might be the result of a defined biological underlying cause. Among these biological, and often treatable, underlying causes of psychosis are inborn errors of metabolism (IEMs) and autoimmune encephalitis. IEMs are genetically inherited disorders characterized by deficits in metabolic enzymes or transport enzymes, leading to an accumulation or decreased excretion of proteins, carbohydrates and lipids. Autoimmune encephalitis is characterized by the presence of autoantibodies that target receptors, proteins or ion channels in the brain and spinal cord (11, 12). Rather than simply reducing the psychotic symptoms with standard treatments as described above, this subgroup of patients would likely benefit more from treating the underlying biological cause. Although significant advances have been made in the understanding and diagnosing of these rare, yet treatable forms of psychosis, many questions remain to be answered. The present thesis aimed to increase the current knowledge of these rare forms of psychosis by investigating methods to identify and classify patients with such rare forms.

Identifying and classifying patients with such an underlying cause within psychiatric care as soon as possible is important as it may prevent diagnostic delay. In order to do so, it is necessary to define the clinical manifestation of these patients objectively, by executing a thorough neuropsychological, cognitive and neurological assessment, both in the clinic and as part of research. One of the main findings of this thesis included that, although previous studies focused on these biological underlying causes before, both standardized interviews and rating scales are often still lacking. Hence, some symptoms are recognized, while other less specific symptoms, may be overlooked. Therefore, to ensure that symptoms are recognized as much as possible, assessments should follow the structure of standardized interviews and standardized rating scales. In addition, using standardized interviews and rating scales allows us to compare across different cohorts and studies, which is difficult if the methodology between studies differs greatly. This will enable us to determine the generalizability of our findings, replicate results better, identify inconsistencies and determine whether observed findings need further investigation.

Another main finding of the research conducted as part of this thesis is the wide variety of neuropsychiatric symptoms associated with these rare disorders. Consequently, patients are diagnosed with a variety of psychiatric diagnoses as well. Previously it was thought that psychotic symptoms played the largest part in the clinical manifestation of IEMs and that patients were most commonly diagnosed with a psychotic disorder. However, our research showed that these patients also suffer from other psychiatric symptoms and hence were also diagnosed with affective disorders, depressive disorders, anxiety disorders, ADHD, autism and OCD. Although isolated psychotic symptoms have been described in patients with a biological cause as well, comorbidity within psychiatric disorders is common and these observed symptoms are usually described as part of several disorders when DSM criteria are taken into account. Hence, our findings support a dimensional nature of psychopathology, rather than relying on categorical, diagnosis-specific labels. Consequently, our findings support the recent consensus that the underlying neural mechanisms of these disorders may overlap and that a focus on the underlying dimensions and processes is important, thus favoring a transdiagnostic approach (13, 14).

In addition to the lack of using standardized clinical scales and interviews, laboratory protocols are not standardized either, and each laboratory or study often includes a different technique or the same technique with different parameters. Hence, a lot of improvement is still necessary to ensure that the diagnostic process includes both the latest and most accurate techniques and that findings are validated by using different methods.

Furthermore, established techniques within research are often not yet integrated within routine diagnostic care, especially in the case of rare causes such as IEMs or the presence of autoantibodies. This may be due to a variety of reasons, among them the lack of knowledge, a lack of time to incorporate new techniques within routine diagnostics and the fact that new techniques may be more expensive, even though new techniques have been shown to be more effective. However, it may still be worthwhile to further explore the possibility to incorporate new techniques, as it may reduce patient burden and enable precision diagnosis. For example, when patients with these underlying biological causes can be identified by adding safe and simple tests to routine clinical diagnostics, such as next generation sequencing (NGS) and immunohistochemistry, clinicians may be able to tailor treatment to individual patients and hence, provide personalized treatment. Furthermore, exploring the possibility to use biomarkers, such as lipids, within psychiatry may further help to personalize treatment in the future, shifting to "precision psychiatry" (9). With this approach, a subgroup of patients may experience a better quality of life and social functioning in the future.

SCIENTIFIC IMPACT

Although the used laboratory techniques in this thesis are common within research nowadays, there is no standardized protocol used among different laboratories due to several reasons. A lack of using such a standardized protocol may be the result of variability in available resources and equipment at an institute, a preference for specific techniques or reagents, a lack of consensus on the best method or protocol used for a particular experiment or because laboratories often develop or adapt methods to suit their defined research goals. While standardized protocols can help to improve reproducibility and reliability in research, the dynamic nature of science often results in adapting a protocol or developing a new protocol by each laboratory individually. For both immunohistochemistry and cell based assays, in-house, as well as commercially available assays, are used (12, 15, 16). Although the original protocol to detect autoantibodies by immunohistochemistry has been established by Dalmau and colleagues in 2007 (17), our experience with immunohistochemistry over the years showed that further optimization yielded better results. Hence, the results of this thesis contribute to more optimized and hopefully, standardized laboratory protocols in the future. Furthermore, this thesis emphasizes the need to use a (stepwise) combination of techniques necessary to achieve the best result. Accordingly, first, a general screening should be done to assess the possible presence of autoantibodies using immunohistochemistry. Then, it should be determined to which specific antigen autoantibodies bind using cell based assays (as these only detect autoantibodies for a limited number of antigens). Finally, it should be confirmed that the

observed autoantibodies bind to the surface of neurons using primary neurons in a cell culture.

Moreover, this thesis aimed to combine a more clinical approach with laboratory findings and concluded that it is necessary to continue doing so in the future. Combining both fields is essential to gather a more comprehensive picture of the clinical manifestation of patients with a biological cause, to increase diagnostic accuracy and prevent diagnostic delay and/or misdiagnosis and to allow personalized treatment in the future. For this purpose, different fields need to work in a more collaborative manner such as in specialized clinics in which the different fields are all situated. For example, as proposed in **chapter 3**, joint clinics may help different disciplines to work together and to provide timely diagnosis and treatment. In addition to receiving an earlier diagnosis and appropriate treatment, all different disciplines in-house may also be beneficial for patients in that further testing after the initial diagnosis can be efficiently done in such a joint clinic. These joint clinics may also act as a place where these patients receive help in various forms such as different kinds of treatments and even help with daily living activities. Hence, there is one location where the patient can go, both during and after the diagnostic process. However, setting up these specialized centers may be a challenge in terms of organization, costs and time investment. Alternatively, a close collaboration between the clinic and research could be established, in which samples of patients that are tested by commercially available kits as part of routine diagnostics are screened for the presence of autoantibodies by immunohistochemistry, as described in **chapter 4**. Additionally, if necessary, more specific cell based assays could be performed by the research laboratory. Such collaboration, as established between the immunodiagnostic department of the Maastricht University Medical Center (MUMC+) and our research laboratory within Maastricht University, may serve as an example.

INDIVIDUAL AND SOCIETAL IMPACT

The results of this thesis contribute to a shift to a more transdiagnostic approach in psychiatry, including a more prominent role for underlying biology. Although patients do not directly benefit from the results of our study unless they were tested positive and these findings turn out to be clinically relevant and a different treatment strategy is proposed by the treating clinician, patients will benefit from our findings in the future. In the case of IEMs, patients would benefit greatly if NGS is applied within routine clinical diagnostics to detect variants of genes that are associated with (treatable) IEMs by the use of only one blood tube, as this decreases the burden on the patients during the diagnostic process massively. For the presence of autoantibodies, patients would benefit if collaborations between clinical diagnostic and research laboratories in the short term would be established, as combining

in-house immunohistochemistry (research) with the commercially available cell based assays (clinical diagnostics) would increase the sensitivity and false negative results are less likely. Although rare, patients would benefit individually greatly if IEMs or autoantibodies are detected early because this would reduce the risks of complications, increase the chances of a successful recovery or better disease management, leading to better outcomes and an improved quality of life overall. Additionally, this would reduce the burden on caregivers. Finally, when diagnostic delay can be prevented it will also reduce healthcare costs, as the need for expensive medical tests, interventions and hospitalizations may be reduced.

DISSEMINATION OF KNOWLEDGE

Although several steps have been made to disseminate the achieved knowledge of this thesis, future plans have been made as well. For example, we presented our work at collaborating mental health institutions, national and international conferences and symposia. This includes presenting our work at Get the VIBE in 2019 in Eindhoven and at Complement UK in 2022 in London. Additionally, we were involved in several guest lectures about autoimmunity and psychiatric symptoms. Interestingly, several clinicians have sent samples of patients (anonymously) with suspected autoimmunity for us to screen for the presence of autoantibodies after presenting our work, which suggests that presenting our work throughout the Netherlands and beyond is important to raise awareness among clinicians. Additionally, it is important to raise awareness about which current methods are available to screen for these different biological underlying disorders, including their strengths and limitations. We also presented our work at and were involved in the organization of Psychology Unwrapped in 2020, an informal event that focused on raising awareness and minimizing the stigma around mental health. In the future, we will continue to present our work at conferences and symposia, both national and international. Additionally, we hope to contribute to raising awareness by incorporating the topic of psychiatric manifestation due to underlying causes such IEMs and the presence of autoantibodies within education or clinical training. Finally, we strive to work towards clinical implementation by introducing the proposed screener as part of **chapter 2** within psychiatric care. By doing so, we aim to raise awareness among (future) clinicians working within psychiatry.

FUTURE RESEARCH AND SUGGESTIONS FOR IMPROVEMENT

In conclusion, future research within the field of these biological causes should focus on assessing patients by standardized interviews and include (dimensional) clinical scales to objectively assess the severity of the psychiatric symptoms. On the molecular level, several complementary techniques should be combined and optimized (e.g., immunohistochemistry, cell based assays, primary cell culture) to achieve the highest sensitivity and to validate the observed results, as proposed in **chapter 4**. Thereby, a diagnostic delay may be prevented and patients may receive appropriate treatment sooner.

REFERENCES

1. Perala J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsa E, Pirkola S, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry. 2007;64(1):19-28.
2. Heilbronner U, Samara M, Leucht S, Falkai P, Schulze TG. The Longitudinal Course of Schizophrenia Across the Lifespan: Clinical, Cognitive, and Neurobiological Aspects. Harv Rev Psychiatry. 2016;24(2):118-28.
3. Broussard B, Kelley ME, Wan CR, Cristofaro SL, Crisafio A, Haggard PJ, et al. Demographic, socio-environmental, and substance-related predictors of duration of untreated psychosis (DUP). Schizophr Res. 2013;148(1-3):93-8.
4. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. Annu Rev Clin Psychol. 2014;10:425-48.
5. Fekadu A, Medhin G, Kebede D, Alem A, Cleare AJ, Prince M, et al. Excess mortality in severe mental illness: 10-year population-based cohort study in rural Ethiopia. Br J Psychiatry. 2015;206(4):289-96.
6. Simon GE, Stewart C, Yarborough BJ, Lynch F, Coleman KJ, Beck A, et al. Mortality Rates After the First Diagnosis of Psychotic Disorder in Adolescents and Young Adults. JAMA Psychiatry. 2018;75(3):254-60.
7. Teferra S, Shibre T, Fekadu A, Medhin G, Wakwoya A, Alem A, et al. Five-year mortality in a cohort of people with schizophrenia in Ethiopia. BMC Psychiatry. 2011;11:165.
8. Marshall M, Lockwood A, Lewis S, Fiander M. Essential elements of an early intervention service for psychosis: the opinions of expert clinicians. BMC Psychiatry. 2004;4:17.
9. Drake RE, Bond GR, Becker DR. IPS supported employment: An evidence-based approach to supported employment. New York: Oxford University Press; 2012.
10. Bond GR, Drake RE, Becker DR. Generalizability of the Individual Placement and Support (IPS) model of supported employment outside the US. World psychiatry : official journal of the World Psychiatric Association (WPA). 2012;11(1):32-9.
11. Lancaster E. The Diagnosis and Treatment of Autoimmune Encephalitis. J Clin Neurol. 2016;12(1):1-13.
12. Pruss H. Autoantibodies in neurological disease. Nat Rev Immunol. 2021;21(12):798-813.
13. Dalgleish T, Black M, Johnston D, Bevan A. Transdiagnostic approaches to mental health problems: Current status and future directions. J Consult Clin Psychol. 2020;88(3):179-95.
14. van Amelsvoort TAMJ, Klaassen MC, van den Heuvel OA. Transdiagnostische psychiatrie: concept in ontwikkeling. Tijdschrift voor psychiatrie. 2018;60.
15. Nagata N, Kanazawa N, Mitsuhata T, Iizuka M, Nagashima M, Nakamura M, et al. Neuronal surface antigen-specific immunostaining pattern on a rat brain immunohistochemistry in autoimmune encephalitis. Front Immunol. 2022;13:1066830.
16. van Coevorden-Hameete MH, Titulaer MJ, Schreurs MWJ, de Graaff E, Smitt PAES, Hoogenraad CC. Detection and Characterization of Autoantibodies to Neuronal Cell-Surface Antigens in the Central Nervous System. Front Mol Neurosci. 2016;9.
17. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61(1):25-36.