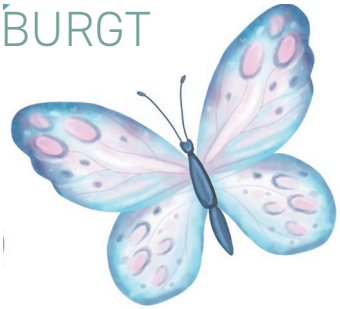
The many faces of psychosis



THE MANY FACES OF PSYCHOSIS

A novel approach to identify and classify rare forms

NIKITA ALANA VAN DE BURGT

The many faces of psychosis

A novel approach to identify and classify rare forms

Nikita Alana van de Burgt

Cover design: Bregje Jaspers
Layout: Nikita van de Burgt
Printed by ProefschriftMaken || www.proefschriftmaken.nl
ISBN: 978-94-6469-567-0

The many faces of psychosis

A novel approach to identify and classify rare forms

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Pamela Habibovic,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op dinsdag 7 november 2023 om 10.00 uur

door

Nikita Alana van de Burgt

Promotors

Prof. dr. Therese van Amelsvoort
Prof. dr. Pilar Martinez-Martinez

Co-promotor

Dr. Nicole Leibold

Beoordelingscommissie

Prof. dr. Bart Rutten (voorzitter)	
Prof. dr. Koen Poesen	Universitair Ziekenhuis Leuven, Belgium
Prof. dr. Clara van Karnebeek	Emma Kinderziekenhuis
Dr. Marielle Vlooswijk	

Al onze dromen kunnen uitkomen… als we de moed hebben om ze na te streven.

Walt Disney

TABLE OF CONTENT

CHAPTER 1

General introduction

"When I began to hear voices, I thought of the voices as from something of that source (aliens)... Well, you see, it's really my subconscious talking. It was really that, and I, of course, know that now."
- John Nash, PhD, Nobel Prize-winning mathematician and main character of *A Beautiful Mind (1)*

PSYCHOSIS AND PSYCHOTIC SPECTRUM DISORDERS

Psychosis is a clinical condition characterized by relatively common symptoms and (partial) loss of contact with reality and often presents in one or more psychotic episodes. These may occur in several neuropsychiatric disorders, neurodevelopmental diseases, and medical conditions and result in disturbed thinking and altered perceptions. Consequently, during a psychotic episode, someone hears, sees and/or believes things that others do not hear, see or believe. Although this usually occurs in medical conditions, experiencing such symptoms once in your lifetime is not uncommon in the general population, with an estimated prevalence between 5 and 28% (2, 3, 4, 5). One of the conditions which is characterized by psychotic episodes are psychotic spectrum disorders. It is estimated that approximately 2-3% of the population has a psychotic spectrum disorder, with a first onset typically during adolescence or early adulthood (6).

Diagnosis of a psychotic spectrum disorder

Currently, psychotic spectrum disorders are diagnosed based on the medical and psychiatric history and current symptoms, and classified according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or the International Statistical Classification of Diseases and Related Health Problems, Eleventh Edition (ICD-11) (7, 8). In order to receive a diagnosis of a psychotic spectrum disorder, several criteria need to be met. First, one of the following symptoms must be present: hallucinations, delusions, disorganized speech, disorganized or catatonic behavior and/or negative symptoms. Hallucinations (i.e., distorted perceptions), delusions (i.e., distorted thought content) and disorganized speech (i.e., distorted language and thought process) are all classified as positive symptoms (7). The most commonly described hallucinations are auditory hallucinations, in which a person hears sounds or voices without an external stimulus (7). However, hallucinations can also be visual, olfactory, gustatory or tactile. Visual hallucinations may be characterized by seeing objects, visual patterns, shapes, people or flashes in the absence of external stimuli.

In contrast, olfactory and gustatory hallucinations may be characterized by detecting smells or tastes in the absence of chemical stimuli, respectively. Sensations of touch or perception

of movement without any physical stimulation may characterize tactile hallucinations. Besides hallucinations, delusions are commonly experienced by patients with a psychotic spectrum disorder. Delusions are characterized by altered, false, and irrational beliefs or ideas that are not based on reality. For example, an individual can believe that they are followed or targeted by someone (e.g., persecutory delusions), that other people can hear their thoughts or read their mind (referred to as thought broadcasting), that someone or something controls their thoughts (called thought control) or that they receive coded information via the tv, radio or other media (i.e., delusions of reference) (7, 9). Negative symptoms are characterized by a decreased ability to experience pleasure (i.e., anhedonia), a decrease in thought and speech (i.e., alogia), a lack of motivation (i.e., avolition), and a flattened mood and emotional expression (i.e., affective flattening) (7, 10). Consequently, individuals often experience social withdrawal, a decrease in daily life functioning and functioning within academia or occupation (11). Although not part of the diagnostic criteria, a psychotic episode is often accompanied by cognitive impairment, including memory and attention deficits and problems with executive functioning (12, 13, 14). Finally, psychomotor disturbances such as catatonia, characterized by abnormal movements, are sometimes observed in patients with a psychotic spectrum disorder as well (15). However, the presence and intensity of symptoms differ widely between patients, resulting in a heterogenous group of disorders that are difficult to diagnose and treat (11).

Second, these symptoms must be present for a significant portion of time and negatively influence daily functioning, e.g., work or academia, relationships or self-care. Depending on the number of symptoms present and the duration of these symptoms, a diagnosis of schizophrenia, schizophreniform disorder, or brief psychotic disorder can be considered (16). Schizophrenia is characterized by symptoms that last for at least six months, of which the hallucinations, delusions, disorganized speech, negative symptoms and sometimes catatonic behavior are present for at least one month. If the symptoms last less than six months, a diagnosis of schizophreniform disorder is established. If the symptoms are present for less than one month, a diagnosis of brief psychotic disorder is considered. However, when a major depressive episode, a manic episode or a combination of both are present, a diagnosis of schizoaffective disorder is considered. When psychotic symptoms do not meet any of the criteria of the psychotic spectrum disorders or when the symptoms are inadequate or contradictory, a diagnosis of psychotic disorder not otherwise specified is established. However, while hallucinations or delusions need to be present to meet the diagnostic criteria, these symptoms can also be a consequence of a medical disorder or direct physiological consequence of a drug or toxin exposure. Psychotic symptoms, such as hallucinations, are symptoms that are not specific to a psychotic spectrum disorder but can occur within other psychiatric and somatic disorders as well.

Treatment of a psychotic spectrum disorder

Treatment of a psychotic spectrum disorder often consists of anti-psychotics, sometimes in combination with other psychotropic medication, cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) (17, 18). Although several treatment options are available, not everybody responds similarly or as expected. This may be because underlying causes are diverse and often not fully known and understood. It is known that several risk factors may contribute to the development of a psychotic spectrum disorder, such as early life stress, exposure to violence, physical or sexual abuse, childhood trauma, low socioeconomic status (SES), substance abuse, viral infections or having a first-degree relative that suffers from a psychotic spectrum disorder (19, 20, 21, 22, 23, 24). Furthermore, several risk genes have been associated with a psychotic spectrum disorder (25, 26). However, not all psychotic spectrum disorders cannot be explained by risk genes or a family history of a psychotic spectrum disorder only (27). Therefore, it is thought that a psychotic spectrum disorder is the consequence of a combination of genetic predisposition and socio-environmental factors.

In addition to the more common gene-environmental interactions underlying the development of a psychotic spectrum disorder, in rare cases, a psychotic episode can be the result of another underlying somatic disease, such as an inborn error of metabolism (IEM) or autoimmune encephalitis. These underlying diseases are individually often rare, however, together they are quite common (28, 29, 30, 31, 32, 33, 34). However, they may not be easily recognized by a psychiatrist or another medical doctor as it may be difficult to distinguish the clinical manifestation from a primary psychotic spectrum disorder. However, identifying patients that have a psychotic episode as a result of such an underlying cause is important, as some of these diseases and causes are treatable by dietary changes, supplementation of specific vitamins or immunomodulatory treatment. Hence, treatment may affect the underlying cause rather than prescribing psychotropic drugs to reduce psychotic symptoms.

Additionally, treatment is most efficient at the earliest psychiatric manifestations (35, 36, 37). Consequently, identifying these patients is crucial to prevent diagnostic delay and provide appropriate and effective treatment. Finally, raising awareness for these underlying causes within psychiatric care in general is crucial as screening for these diseases is not yet part of routine clinical practice and is only executed if suspicion of such a disease is raised by the treating clinician. Taken together, it is essential to determine these underlying causes, raise awareness for them within psychiatric care, and incorporate screening within routine diagnostics.

Based on the current state of knowledge, it seems likely that in a subgroup of patients, psychotic symptoms result from an underlying cause or somatic disease that has not yet been diagnosed or treated. More specifically, these psychotic symptoms may be caused by autoimmune encephalitis or may be the result of an underlying IEM. An altered balance of lipids in the brain may also be related to psychotic symptoms. As these underlying causes have not received a lot of attention yet in research and the clinical practice and are easily overlooked, it is essential to identify biomarkers to correctly diagnose and treat this subgroup of patients with a rare form of psychosis, to prevent diagnostic delay and provide better treatment outcomes in the future.

INBORN ERRORS OF METABOLISM

Inborn errors of metabolism (IEMs) are genetic disorders in which metabolic enzymes or transport proteins do not work correctly. The incidence of IEMs varies, and although these genetic disorders are considered rare, the cumulative incidence is estimated between 1:800 and 1:1000 live births (28, 29, 30, 31). These disorders may manifest due to a mutation in a single gene or a heterozygous mutation in two different genes, which is considered a compound mutation. Often these mutations are acquired via autosomal recessive inheritance, although some mutations can be autosomal dominant or X-linked. These IEMs are classified according to the affected metabolic system or pathway, such as the lysosomes, the mitochondria or the urea cycle. Consequently, these disorders are classified as lysosomal storage disorders, mitochondrial disorders and urea cycle disorders (see Figure 1). In lysosomal storage disorders, substrates such as glycoproteins, mucopolysaccharides, heparan sulfate and sphingolipids accumulate within the lysosomes of the cells. These complex carbohydrates, fats or other substrates cannot be broken down, leading to cellular dysfunction and organ damage. However, carbohydrate, protein- and vitamin- and mineral metabolism can also be affected, depending on the type of IEM. Mutations can also result in defects of the bile acid synthesis or manifest as porphyria, a disorder in which porphyrins and porphyrin precursors build up in the body, mainly affecting the skin and the nervous system (38, 39).

Depending on the biological function of the affected enzyme or protein, the IEM may result in a wide variety of symptoms with a variation in severity as well. Usually, these disorders are severe and detected early in life via newborn screening. However, not all IEMs are included in the screening panels currently used, and the sensitivity to detect IEMs differs significantly (40). Additionally, many of these disorders manifest as late-onset variants, in which symptoms may not be detected until adolescence or adulthood. Usually, these variants are characterized by a predominant presence of neuropsychiatric symptoms rather

than somatic symptoms only. For example, in the case of Wilson's disease, Niemann-Pick disease type C, metachromatic leukodystrophy, and late-onset GM_2 gangliosidosis several case reports described patients in which isolated psychiatric symptoms manifested before any neurological symptoms (See Figure 1) (41). The most commonly described psychiatric symptoms in patients with an IEM included psychosis with or without visual hallucinations, depression, behavioral disturbances and confusion (41). Quite often, atypical symptoms such as catatonia are present and intellectual impairments are commonly described when the medical history is considered.

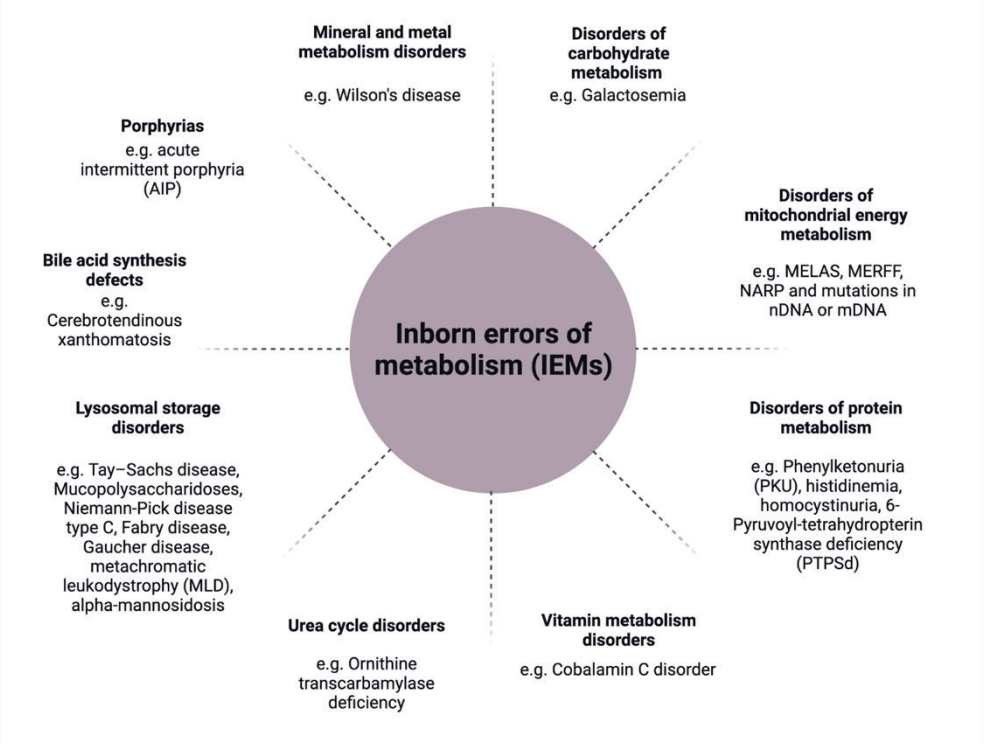


Figure 1 A schematic overview of the different classes of inborn errors of metabolism (IEMs) and the most commonly described IEMs within the psychiatric field. MELAS = Mitochondrial Encephalopathy, Lactic Acidosis and stroke-like episodes, MERFF = Myoclonic Epilepsy with Ragged Red Fibers, NARP = Neuropathy, Ataxia and Retinitis Pigmentosa.

Furthermore, neuropsychiatric symptoms may be the result of autoimmune encephalitis. In the case of this autoimmune disorder, autoantibodies bind to specific receptors in the brain, which are present at the surface of neurons, oligodendrocytes and/or myelin. Additionally, these autoantibodies may bind to proteins or complexes within the cell or at the cell membrane of neurons (see Figure 2). Subsequently, the binding of these autoantibodies may block the function of the affected receptor, protein or complex. Consequently, neurons and other tissues in the brain and the spinal cord cannot work correctly, and cellular functioning may be disrupted. Ultimately, the binding of these antibodies may lead to cell death and inflammation within the brain and/or the spinal cord.

The binding of these autoantibodies can result in a wide variety of symptoms, dependent on which receptor, protein or complex is affected (see Table 1). For example, neuropsychiatric manifestations are primarily associated with the binding of autoantibodies against the N-methyl-D-aspartate receptor (NMDAR, see Figure 2A). However, the binding of autoantibodies against the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), γ-aminobutyric acid type A receptor ($GABA_AR$), γ-aminobutyric acid type B receptor ($GABA_BR$), dipeptyl-peptidase-like protein 6 (DPPX), contactin-associated protein-2 (CASPR2) and leucine-rich glioma-inactivated 1 (LGI1), which are both parts of the voltage-gated potassium channel (VGKC) complex, are associated with neuropsychiatric symptoms as well (see Figure 2B, C). The binding of autoantibodies against glutamic acid decarboxylase (GAD), an enzyme that catalyzes the production of GABA, is also associated with the occurrence of neuropsychiatric symptoms (see Figure 2E) (42, 43, 44, 45, 46, 47, 48, 49, 50, 51). Additionally, autoantibodies binding to Myelin Oligodendrocyte Protein (MOG, see Figure 2D) have recently been associated with neuropsychiatric symptoms in several case reports (52, 53, 54, 55).

The most commonly described neuropsychiatric symptoms associated with these autoantibodies are hallucinations, delusions, confusion, cognitive deficits, depression, anxiety, sleep disorders, personality changes and agitation (see Table 1) (51, 56). Other symptoms that are often observed in these patients are mutism (i.e., inability or unwillingness to speak), seizures, tremors (i.e., involuntary trembling or shaking of the body or limbs) and dyskinesia (i.e., involuntary muscle movement in the face, limbs and legs or other parts of the body) (56). Some patients experience prodromal symptoms such as sudden weight loss, fever, headache, nausea, diarrhea or other gastrointestinal or abdominal symptoms (51, 57).

Like IEMs, autoimmune encephalitis is considered a rare disorder, with an estimated prevalence of 13.7:100,000 in 2014, with a higher prevalence among African Americans, young women, and children (32, 33, 34). In the case of autoantibodies against the NMDAR, it was thought that 4% of the patients present with isolated psychotic symptoms without neurological manifestations (36, 58). Additionally, several case reports described patients positive for several autoantibodies, among them anti-NMDAR, anti-AMPA, anti-TPO, anti-Yo, with (initial) isolated psychotic symptoms as well (58, 59, 60, 61, 62, 63, 64, 65, 66). However, more recent studies that performed systematic screening of autoantibodies in patients with a psychotic disorder, revealed that the percentage of isolated psychotic symptoms among patients with autoantibodies is probably lower, with percentages between 0 and 2% reported (67). Nevertheless, up to 60% of the patients with NMDAR encephalitis are admitted to a psychiatric unit initially (68, 69). It is speculated that subtle neurological symptoms are often present in patients with isolated psychiatric symptoms, but not sufficiently recognized within clinical care (59). Hence, although there is no clear consensus of whether the prevalence of isolated psychotic symptoms among patients with autoimmune encephalitis is correctly estimated, detection of these autoantibodies among these patients as soon as possible remains important, as early treatment results in improved clinical outcome. Currently, patients are only tested in case there is a clinical suspicion of autoimmune encephalitis and testing is not always possible locally or analysis takes several weeks, which may result in diagnostic delay and thus, treatment (70). Additionally, new targets of autoantibodies are still discovered every year.

Table 1 Neuropsychiatric manifestations of autoantibodies against neuronal antigens.

	Associated symptoms		
	Psychiatric	Neurological	Other symptoms
Antigen			
NMDAR (36, 56, 68, 71, 72, 73)	Psychosis (hallucinations, delusions, disorganized behavior), anxiety, depression, agitation, aggressive behavior	Motor retardation, catatonia, seizures, decreased consciousness	Cognitive deficits, sleep disorders
AMPA (65, 74)	Psychosis (not specified), confusion, mood disturbances, agitation	Seizures	Cognitive deficits, sleep disorders
$GABA_AR$ (75, 76, 77)	Psychosis (hallucinations, apathy), confusion, anxiety, depression	Catatonia, seizures	
$GABA_BR$ (78)	Psychosis (not specified), agitation	Catatonia, ataxia, seizures	
GFAP (79, 80, 81)	Psychosis (hallucinations, delusions), depression, confusion, mood disturbances	Ataxia, seizures, weakness in legs, tremor	Cognitive deficits, headache
DPPX (51, 82)	Psychosis (hallucinations, delusions), confusion, depression	Rigidity, myoclonus, ataxia, tremor, seizures	Cognitive deficits, sleep disorders, gastrointestinal or abdominal symptoms
CASPR2 (56, 83, 84, 85)	Psychosis (hallucinations, delusions), confusion, agitation, panic attacks	Seizures, movement disorders, isolated neuromyotonia, Morvan's syndrome	Sleep disorders
LGI1 (56, 86, 87)	Psychosis (hallucinations), confusion, depression	Seizures, movement disorders	Cognitive deficits, sleep disorders
GAD (88, 89, 90, 91)	Psychosis (hallucinations, delusions, disorganized behavior, apathy), depression, anxiety, aggressive behavior	Seizures	Cognitive deficits, sleep disorders
MOG (55, 92, 93)	Psychosis (hallucinations), confusion, personality changes	Blurred or loss of vision, weakness, loss of sensation and numbness in arms and legs, seizures, decreased consciousness	Bladder or gastrointestinal or abdominal symptoms

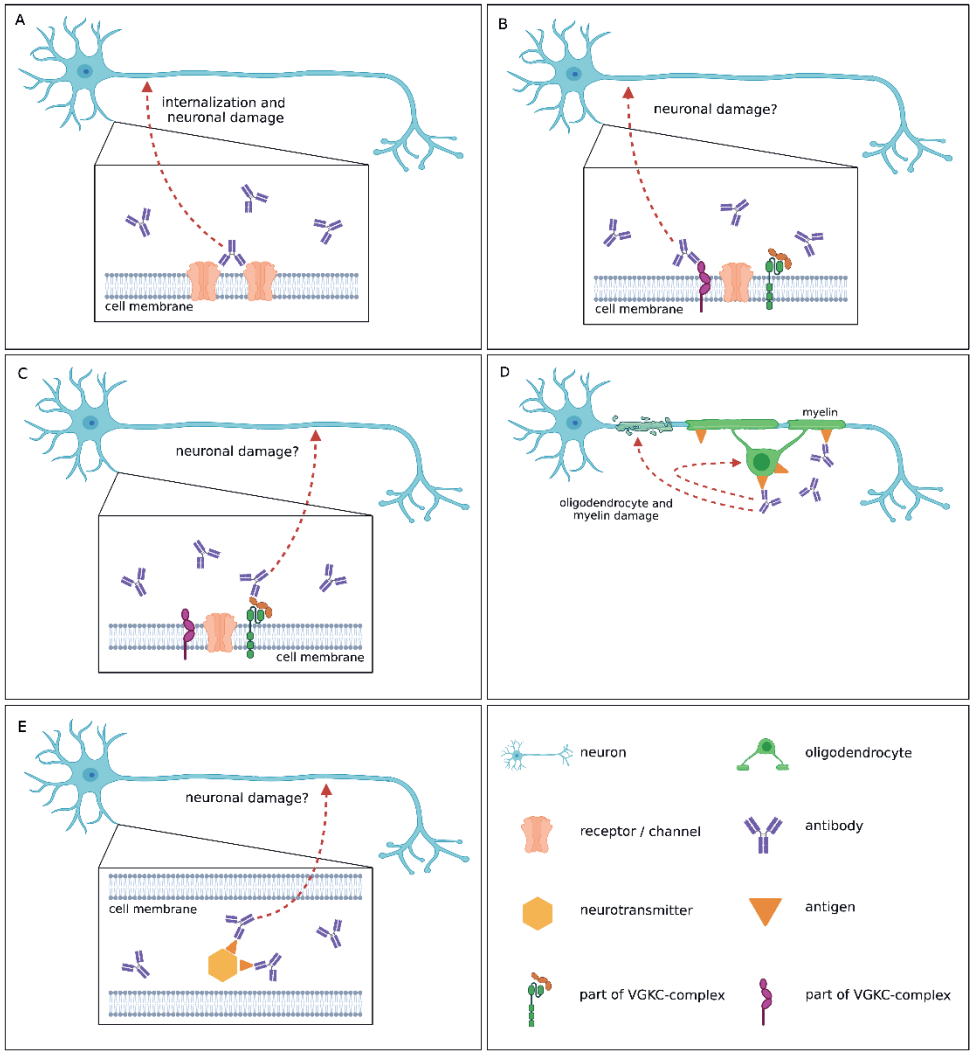


Figure 2 Schematic overview of the binding of autoantibodies against receptors, complexes and proteins in the brain and spinal cord. A) Binding of autoantibodies to neuronal surface receptors, such as the NMDAR. B) Binding of autoantibodies to ion channels/membrane receptors and associated proteins such as LGI-1. C) Binding of autoantibodies to ion channels/membrane receptors and associated proteins, such as CASPR2. D) Binding of autoantibodies against proteins on oligodendrocytes or myelin, such as MOG. E) Binding of autoantibodies against intracellular proteins, such as GAD65.

LIPIDS

In addition to IEMs and autoantibodies, an altered balance in and between different classes of lipids is also associated with psychiatric disorders. Lipids are a complex group of organic molecules that can be classified into several categories, including phospholipids, sphingolipids, glycolipids and di- and triglycerides (94), which can be further divided into several classes (94). For example, phospholipids can be further divided into glycerophospholipids and phosphosphingolipids, of which the latter consists of phosphatidylcholine and phosphatidylethanolamine among others (94). Sphingolipids, on the other hand, can be further divided into ceramides, glycosphingolipids, and sphingomyelins (95, 96). They represent a class of highly conserved lipids and consist of a backbone of sphingoid bases and aliphatic amino alcohols (97) and are synthesized via a pathway that starts with the condensation of serine and palmitoyl coenzyme A, which ultimately leads to the formation of dihydroceramide and ceramide (98) (see Figure 3). Following, sphingomyelin, sphingosine, ceramide-1-phosphate and complex glycosphingolipids such as gangliosides are formed (98).

Lipids, especially sphingo- and phospholipids, are essential for the structure and function of cellular membranes (99, 100). Furthermore, lipids play an important role and function as second messengers in the central nervous system, where they are found in neurons, glial cells, and the vascular compartment of the brain. They modulate various signaling events, including cellular differentiation and proliferation, apoptosis, cytokine production, and synaptic plasticity (94, 95, 101). Consequently, lipids are essential for maintaining normal brain function; hence, lipid levels are tightly regulated (52, 53, 54).

Disruption of lipid metabolism is strongly associated with several diseases that result in neurological, psychiatric, and metabolic symptoms. For example, disruptions have been observed in Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis (102, 103). Furthermore, in the case of neurodegenerative disorders, plasma lipids are even proposed as potential biomarkers for diagnosis, prognosis, and treatment outcome (103). Changes in the lipid metabolism have also been observed in psychiatric disorders, such as schizophrenia, bipolar disorder, and major depressive disorder (102, 103). It is hypothesized that the disruption of lipid metabolism is associated with altered synaptic neurotransmission, a dysfunction of myelin and oligodendrocytes and inflammatory mechanisms. More specifically, changes in the levels of sphingomyelin (SM), ceramide (Cer), phosphatidylcholine (PC), phosphatidylserine (PS) have been associated with several molecular changes in patients with schizophrenia, such as changes in white and grey matter, increased pro-inflammatory cytokines and decreased synaptic and axonal connectivity

(104). Plasma measurements in 265 patients with schizophrenia showed a decrease in phosphatidylcholine diacyl C38:6 (PC ae C38:6) compared to controls (105), although a decrease in this lipid has also been observed in patients with Alzheimer's disease (106). Additionally, an increase in specifically ceramide 34:1 (Cer34:1) was observed in the red blood cells of 20 patients with schizophrenia (107). However, most research so far focused on lipid species as a whole, rather than measuring changes in individual lipid species. Hence, whether these molecular mechanisms are caused by a whole class of lipids or individual lipid species is yet to be determined. Furthermore, whether these changes are different from both control individuals is not yet investigated. Finally, associations have been based on blood samples and post-mortem material and whether these associations hold in cerebrospinal fluid (CSF) is not yet known.

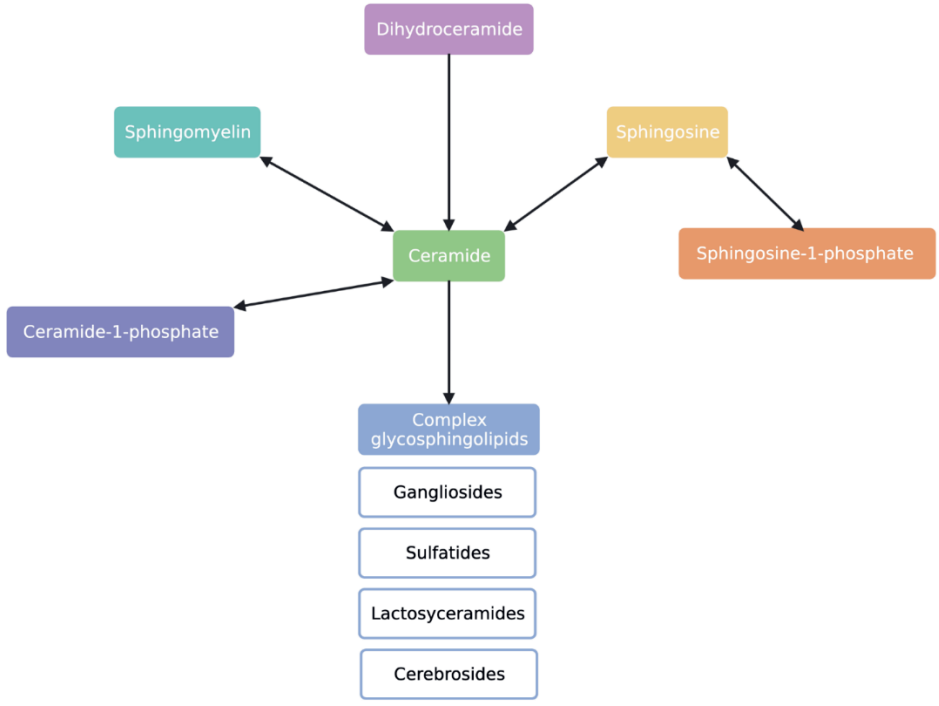


Figure 3 Schematic overview of the pathways of the sphingolipid metabolism. The sphingolipid biosynthesis starts with the condensation of serine and palmitoyl coenzyme A, which leads to the formation of dihydroceramide and ceramide via a series of reactions. Out of ceramide, sphingomyelin, sphingosine, complex glycosphingolipids, and cermide-1-phosphate are formed. The phosphorylation of sphingosine can form sphingosine-1-phosphate.

SCREENING METHODS FOR RARE FORMS OF PSYCHOSIS

Over the previous years, great improvements have been made in regard to detecting these rare forms of psychosis (see Table 2). Currently, late-onset variants of IEMs are usually detected by screening for markers in the blood, urine and cerebrospinal fluid. Additionally, routine diagnostics often include imaging techniques such as ultrasound, Magnetic Resonance Imaging (MRI) and Computed Tomography (CT). However, genetic testing, such as next generation sequencing has been proposed as an alternative for extensive biochemical testing, an approach similar to that of other genetic disorders (108). In order to detect autoantibodies, routine diagnostics usually consists of cell based assays, in which either fixed or live cells are modulated in order to express the antigen of interest. In case autoantibodies against the antigen of interest are present, a fluorescent signal is generated of which the intensity of that signal is compared to that of a (negative) control. However, research has shown that combining several different techniques, including immunohistochemistry, cell based assays and primary hippocampal neurons, may improve the sensitivity and specificity of testing (109). Although immunohistochemistry is not able to detect the presence of autoantibodies directly, it is commonly used to indirectly visualize the binding of autoantibodies to tissue antigens in several autoimmune disorders. However, as immunohistochemistry only enables indirect visualization and cell based assays are not suitable to detect the presence of novel autoantibodies, both methods are limited in their detection rate. Primary hippocampal neurons derived from animal models can be used to determine whether these autoantibodies bind to the surface of neurons and act as a model to study the interaction between these autoantibodies and the neuronal tissue (110, 111). In regard to the measurement of lipids, several methods have been used to detect lipid families and individual lipid species, of which liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) is currently considered to be the gold standard as it is a highly sensitive method to detect small amounts of lipids in complex samples and enables the identification of specific lipid species based on their fragmentation patterns. Consequently, the research of this thesis aims to combine these different techniques with thorough clinical assessment.

Table 2 Screening methods for rare forms of psychosis.

	Screening methods	
	Currently used in diagnostics	Potential better alternatives as studied in this thesis
IEMs	Biochemical testing and imagining techniques	Genetic testing
Autoantibodies	Cell based assays	Combining immunohistochemistry, cell based assays and primary hippocampal neurons
Lipids	n.a.	Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS)

n.a. = not applicable

AIMS AND OUTLINE OF THIS THESIS

Taken together, the purpose of this thesis is to classify, identify and characterize patients with an underlying somatic disease that results in psychosis, estimate the prevalence of these rare forms of psychosis and, ultimately, improve diagnosis and treatment in the future.

For this purpose, this thesis is divided into three parts. Part 1 of this thesis focuses on IEMs and consists of two chapters. **Chapter 2** provides a literature review on the neuropsychiatric manifestation of IEMs. In **chapter 3**, we investigated the prevalence of IEMs in patients with a psychotic spectrum disorder with next generation sequencing.

Part 2 of this thesis focuses on autoantibodies and their clinical characteristics in patients with psychosis and consists of two chapters. **Chapter 4** provides a clinical study in which we investigated the prevalence of autoantibodies and characterized the psychiatric, neuropsychological and neurological symptoms in patients with psychosis. In **chapter 5**, we conducted a systemic assessment of autoantibodies against myelin oligodendrocyte glycoprotein in two independent cohorts of patients with psychosis.

In part 3 of this thesis, the focus shifts to the relationship between lipids and psychotic symptoms. Accordingly, **chapter 6** provides insight into changes in different lipids between patients with psychotic symptoms and controls.

Finally, in **chapter 7**, findings from the presented studies are summarized and integrated. Additionally, implications for clinical practice and future research are concisely discussed.

REFERENCES

1. Nash JF. John Nash's Beautiful Mind/Poisonous Stew/Dame Judi. In: Wallace M, editor. 60 minutes: CBS 2002.
2. Sommer IE, Kahn RS. Psychosis susceptibility syndrome: an alternative name for schizophrenia. Lancet Psychiatry. 2014;1(2):111.
3. Linscott RJ, van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med. 2013;43(6):1133-49.
4. Temmingh H, Stein DJ, Seedat S, Williams DR. The prevalence and correlates of hallucinations in a general population sample: findings from the South African Stress and Health Study. Afr J Psychiatry (Johannesbg). 2011;14(3):211-7.
5. Blom JD. Hallucinations and other sensory deceptions in psychiatric disorders. In: Jardri R, Cachia A, Thomas P, Pins D, editors. The neuroscience of hallucinations. 1 ed. New York, NY: Springer-Verlag New York inc.; 2013. p. 43–58.
6. 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. Archives of general psychiatry. 2007;64(1):19-28.
7. Association AP. Diagnostic and statistical manual of mental disorders. 5th ed. Washinton, DC: American Psychiatric Association; 2013.
8. Harrison JE, Weber S, Jakob R, Chute CG. ICD-11: an international classification of diseases for the twenty-first century. BMC Med Inform Decis Mak. 2021;21(Suppl 6):206.
9. Kiran C, Chaudhury S. Understanding delusions. Ind Psychiatry J. 2009;18(1):3-18.
10. Loas G, Salinas E, Pierson A, Guelfi JD, Samuel-Lajeunesse B. Anhedonia and blunted affect in major depressive disorder. Compr Psychiatry. 1994;35(5):366-72.
11. Mosolov S, Yaltonskaya PA. Concept, classification and clinical differentiation of negative symptoms in schizophrenia. Current therapy of mental disorders. 2020;1:2-12.
12. Rodriguez-Jimenez R, Bagney A, Moreno-Ortega M, Garcia-Navarro C, Aparicio AI, Lopez-Anton R, et al. [Cognitive deficit in schizophrenia: MATRICS Consensus Cognitive Battery]. Rev Neurol. 2012;55(9):549-55.
13. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res. 2004;72(1):41-51.
14. Woodberry KA, Giuliano AJ, Seidman LJ. Premorbid IQ in schizophrenia: a meta-analytic review. Am J Psychiatry. 2008;165(5):579-87.
15. Al-Diwani AAJ, Pollak TA, Irani SR, Lennox BR. Psychosis: an autoimmune disease? Immunology. 2017;152(3):388-401.
16. Anderson KK. Towards a public health approach to psychotic disorders. Lancet Public Health. 2019;4(5):e212-e3.
17. Barron H, Hafizi S, Andreazza AC, Mizrahi R. Neuroinflammation and Oxidative Stress in Psychosis and Psychosis Risk. Int J Mol Sci. 2017;18(3).
18. Sloan G, Hobson J, Leighton J, McFarlane B, Law R. An overview and history of interpersonal psychotherapy. Nurs Stand. 2009;23(26):44-9.
19. Conus P, Cotton S, Schimmelmann BG, McGorry PD, Lambert M. Pretreatment and outcome correlates of sexual and physical trauma in an epidemiological cohort of first-episode psychosis patients. Schizophr Bull. 2010;36(6):1105-14.
20. Buchy L, Cadenhead KS, Cannon TD, Cornblatt BA, McGlashan TH, Perkins DO, et al. Substance use in individuals at clinical high risk of psychosis. Psychological Medicine. 2015;45(11):2275-84.
21. van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: A longitudinal population-based study. American Journal of Epidemiology. 2002;156(4):319-27.
22. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. Nature. 2010;468(7321):203-12.
23. Jones HJ, Stergiakouli E, Tansey KE, Hubbard L, Heron J, Cannon M, et al. Phenotypic Manifestation of Genetic Risk for Schizophrenia During Adolescence in the General Population. Jama Psychiat. 2016;73(3):221-8.

24. Zwicker A, Denovan-Wright EM, Uher R. Gene-environment interplay in the etiology of psychosis. Psychol Med. 2018;48(12):1925-36.
25. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421-7.
26. Bergen SE, Ploner A, Howrigan D, Group CNVA, the Schizophrenia Working Group of the Psychiatric Genomics C, O'Donovan MC, et al. Joint Contributions of Rare Copy Number Variants and Common SNPs to Risk for Schizophrenia. Am J Psychiatry. 2019;176(1):29-35.
27. Gomes FV, Zhu X, Grace AA. Stress during critical periods of development and risk for schizophrenia. Schizophr Res. 2019;213:107-13.
28. Saudubray JM, Garcia-Cazorla A. Inborn Errors of Metabolism Overview: Pathophysiology, Manifestations, Evaluation, and Management. Pediatr Clin North Am. 2018;65(2):179-208.
29. Pampols T. Inherited metabolic rare disease. Adv Exp Med Biol. 2010;686:397-431.
30. Ahrens-Nicklas RC, Slap G, Ficicioglu C. Adolescent presentations of inborn errors of metabolism. J Adolesc Health. 2015;56(5):477-82.
31. Gambello MJ, Li H. Current strategies for the treatment of inborn errors of metabolism. J Genet Genomics. 2018;45(2):61-70.
32. Dubey D, Pittock SJ, Kelly CR, McKeon A, Lopez-Chiriboga AS, Lennon VA, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol. 2018;83(1):166-77.
33. Abbatemarco JR, Yan C, Kunchok A, Rae-Grant A. Antibody-mediated autoimmune encephalitis: A practical approach. Cleve Clin J Med. 2021;88(8):459-71.
34. Gu Y, Zhong M, He L, Li W, Huang Y, Liu J, et al. Epidemiology of Antibody-Positive Autoimmune Encephalitis in Southwest China: A Multicenter Study. Front Immunol. 2019;10:2611.
35. Trakadis YJ, Fulginiti V, Walterfang M. Inborn errors of metabolism associated with psychosis: literature review and case-control study using exome data from 5090 adult individuals. J Inherit Metab Dis. 2018;41(4):613-21.
36. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157-65.
37. Camp KM, Lloyd-Puryear MA, Huntington KL. Nutritional treatment for inborn errors of metabolism: indications, regulations, and availability of medical foods and dietary supplements using phenylketonuria as an example. Mol Genet Metab. 2012;107(1-2):3-9.
38. Wang B. The acute hepatic porphyrias. Transl Gastroenterol Hepatol. 2021;6:24.
39. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute Hepatic Porphyrias: Review and Recent Progress. Hepatol Commun. 2019;3(2):193-206.
40. Mak CM, Lee HC, Chan AY, Lam CW. Inborn errors of metabolism and expanded newborn screening: review and update. Crit Rev Clin Lab Sci. 2013;50(6):142-62.
41. Sedel F, Baumann N, Turpin JC, Lyon-Caen O, Saudubray JM, Cohen D. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J Inherit Metab Dis. 2007;30(5):631-41.
42. Grain R, Lally J, Stubbs B, Malik S, LeMince A, Nicholson TR, et al. Autoantibodies against voltage-gated potassium channel and glutamic acid decarboxylase in psychosis: A systematic review, meta-analysis, and case series. Psychiatry Clin Neurosci. 2017;71(10):678-89.
43. Luo Y, Li J, Jiang F, Tan A, Qin X, Xiao X, et al. Autoimmune Encephalitis With Psychotic Manifestations and Cognitive Impairment Presenting as Schizophrenia: Case Report and Literature Review. Frontiers in Psychiatry. 2022;13.
44. Hansen N, Lipp M, Vogelgsang J, Vukovich R, Zindler T, Luedecke D, et al. Autoantibody-associated psychiatric symptoms and syndromes in adults: A narrative review and proposed diagnostic approach. Brain Behav Immun Health. 2020;9:100154.
45. Broadley J, Seneviratne U, Beech P, Buzzard K, Butzkueven H, O'Brien T, et al. Prognosticating autoimmune encephalitis: A systematic review. J Autoimmun. 2019;96:24-34.
46. Mayorova MA, Butoma BG, Churilov LP, Gilburd B, Petrova NN, Shoenfeld Y. Autoimmune Concept of Schizophrenia: Historical Roots and Current Facets. Psychiatr Danub. 2021;33(1):3-17.

47. Murashko AA, Pavlov KA, Pavlova OV, Gurina OI, Shmukler A. Antibodies against N-Methyl D-Aspartate Receptor in Psychotic Disorders: A Systematic Review. Neuropsychobiology. 2022;81(1):1-18.
48. Diamond B, Huerta PT, Mina-Osorio P, Kowal C, Volpe BT. Losing your nerves? Maybe it's the antibodies. Nature Reviews Immunology. 2009;9(6):449-56.
49. Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neuroloy. 2011;10(8):759-72.
50. Grain R, Lally J, Stubbs B, Malik S, LeMince A, Nicholson TR, et al. Autoantibodies against voltage-gated potassium channel and glutamic acid decarboxylase in psychosis: A systematic review, meta-analysis, and case series. Psychiatry Clinical Neurosciences. 2017;71(10):678-89.
51. Hara M, Arino H, Petit-Pedrol M, Sabater L, Titulaer MJ, Martinez-Hernandez E, et al. DPPX antibody-associated encephalitis: Main syndrome and antibody effects. Neurology. 2017;88(14):1340-8.
52. Singh B, Cruz-Flores S, Chaudhry MR, Piriyawat P, Ponce CP. Psychiatric manifestations of anti-MOG antibody disease. Neuroimmunology Reports. 2022;2:100073.
53. Zhou J, Tan W, Tan SE, Hu J, Chen Z, Wang K. An unusual case of anti-MOG CNS demyelination with concomitant mild anti-NMDAR encephalitis. J Neuroimmunol. 2018;320:107-10.
54. von Zedtwitz K, Matteit I, Michel M, Feige B, Runge K, Denzel D, et al. Anti-MOG autoantibody-associated schizophreniform psychosis. Acta Neuropsychiatr. 2021:1-8.
55. Armangue T, Olive-Cirera G, Martinez-Hernandez E, Sepulveda M, Ruiz-Garcia R, Munoz-Batista M, et al. Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. Lancet Neurol. 2020;19(3):234-46.
56. Herken J, Pruss H. Red Flags: Clinical Signs for Identifying Autoimmune Encephalitis in Psychiatric Patients. Front Psychiatry. 2017;8:25.
57. Wong D, Fries B. Anti-NMDAR encephalitis, a mimicker of acute infectious encephalitis and a review of the literature. IDCases. 2014;1(4):66-7.
58. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-d-aspartate receptor encephalitis. JAMA Neurol. 2013;70(9):1133-9.
59. Baum L, Johnson PMC, Lizano P. Is it psychosis, or an autoimmune encephalitis? Current Psychiatry. 2022;21(8):31-8,44.
60. Endres D, Perlov E, Riering AN, Maier V, Stich O, Dersch R, et al. Steroid-Responsive Chronic Schizophreniform Syndrome in the Context of Mildly Increased Antithyroid Peroxidase Antibodies. Front Psychiatry. 2017;8:64.
61. Endres D, Perlov E, Stich O, Meyer PT, Lutzen N, Tebartz van Elst L. Case report: low-titre anti-Yo reactivity in a female patient with psychotic syndrome and frontoparieto-cerebellar atrophy. BMC Psychiatry. 2015;15:112.
62. Endres D, Rauer S, Kern W, Venhoff N, Maier SJ, Runge K, et al. Psychiatric Presentation of Anti-NMDA Receptor Encephalitis. Front Neurol. 2019;10.
63. Lungen EM, Maier V, Venhoff N, Salzer U, Dersch R, Berger B, et al. Systemic Lupus Erythematosus With Isolated Psychiatric Symptoms and Antinuclear Antibody Detection in the Cerebrospinal Fluid. Frontiers in Psychiatry. 2019;10.
64. van Elst LT, Kloppel S, Rauer S. Voltage-Gated Potassium Channel/LGI1 Antibody-Associated Encephalopathy May Cause Brief Psychotic Disorder. J Clin Psychiat. 2011;72(5):722-3.
65. Hoftberger R, van Sonderen A, Leypoldt F, Houghton D, Geschwind M, Gelfand J, et al. Encephalitis and AMPA receptor antibodies Novel findings in a case series of 22 patients. Neurology. 2015;84(24):2403-12.
66. Graus F, Boronat A, Xifro X, Boix M, Svigelj V, Garcia A, et al. The Expanding Clinical Profile of Anti-Ampa Receptor Encephalitis. Neurology. 2010;74(10):857-9.
67. Hoffmann C, Zong SH, Mane-Damas M, Molenaar PC, Losen M, Titulaer MJ, et al. Absence of Autoantibodies Against Neuronal Surface Antigens in Sera of Patients With Psychotic Disorders. Jama Psychiat. 2020;77(3):322-5.
68. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and Characteristics of Isolated Psychiatric Episodes in Anti-N-Methyl-

D-Aspartate Receptor Encephalitis. Jama Neurology. 2013;70(9):1133-9.
69. Bost C, Pascual O, Honnorat J. Autoimmune encephalitis in psychiatric institutions: current perspectives. Neuropsychiatr Dis Treat. 2016;12:2775-87.
70. Abboud H, Probasco JC, Irani S, Ances B, Benavides DR, Bradshaw M, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. J Neurol Neurosur Ps. 2021;92(7):757-68.
71. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain. 2010;133(Pt 6):1655-67.
72. Weiss D, Kertzscher L, Degering M, Wozniak D, Kluge M. Anti-NMDA receptor encephalitis and overlapping demyelinating disorder in a 20-year old female with borderline personality disorder: proposal of a diagnostic and therapeutic algorithm for autoimmune encephalitis in psychiatric patients "case report". Bmc Psychiatry. 2021;21(1).
73. Mantere O, Saarela M, Kieseppa T, Raij T, Mantyla T, Lindgren M, et al. Anti-neuronal anti-bodies in patients with early psychosis. Schizophr Res. 2018;192:404-7.
74. Yang S, Qin J, Li J, Gao Y, Zhao L, Wu J, et al. Rapidly progressive neurological deterioration in anti-AMPA receptor encephalitis with additional CRMP5 antibodies. Neurol Sci. 2016;37(11):1853-5.
75. Pettingill P, Kramer HB, Coebergh JA, Pettingill R, Maxwell S, Nibber A, et al. Antibodies to GABAA receptor α1 and γ2 subunits: clinical and serologic characterization. Neurology. 2015;84(12):1233-41.
76. Petit-Pedrol M, Armangue T, Peng XY, Bataller L, Cellucci T, Davis R, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABA(A) receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurology. 2014;13(3):276-86.
77. Spatola M, Petit-Pedrol M, Simabukuro MM, Armangue T, Castro FJ, Artigues MIB, et al. Investigations in GABA_A receptor antibody-associated encephalitis. Neurology. 2017;88(11):1012-20.
78. Dogan Onugoren M, Deuretzbacher D, Haensch CA, Hagedorn HJ, Halve S, Isenmann S, et al. Limbic encephalitis due to GABAB and AMPA receptor antibodies: a case series. J Neurol Neurosurg Psychiatry. 2015;86(9):965-72.
79. Endres D, Lerchenmuller V, Runge K, von Zedtwitz K, Nickel K, Urbach H, et al. Anti-astrocytic autoantibody patterns in the cerebrospinal fluid of patients with depression and psychosis. Psychiatry Res. 2022;317:114905.
80. Li J, Wang C, Cao Y, Shi J, Liu H, Zhou M, et al. Autoimmune glial fibrillary acidic protein astrocytopathy mimicking acute disseminated encephalomyelitis: A case report. Medicine (Baltimore). 2021;100(25):e26448.
81. Tomczak A, Su E, Tugizova M, Carlson AM, Kipp LB, Feng H, et al. A case of GFAP-astroglial autoimmunity presenting with reversible parkinsonism. Mult Scler Relat Disord. 2020;39:101900.
82. Balint B, Jarius S, Nagel S, Haberkorn U, Probst C, Blöcker IM, et al. Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. Neurology. 2014;82(17):1521-8.
83. Vynogradova I, Savitski V, Heckmann JG. Hemichorea Associated with CASPR2 Antibody. Tremor Other Hyperkinet Mov (N Y). 2014;4:239.
84. Govert F, Witt K, Erro R, Hellriegel H, Paschen S, Martinez-Hernandez E, et al. Orthostatic myoclonus associated with Caspr2 antibodies. Neurology. 2016;86(14):1353-5.
85. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol. 2011;69(5):892-900.
86. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010;133(9):2734-48.
87. Tofaris GK, Irani SR, Cheeran BJ, Baker IW, Cader ZM, Vincent A. Immunotherapy-responsive chorea as the presenting feature of LGI1-antibody encephalitis. Neurology. 2012;79(2):195-6.

88. Wang JJ, Gong SL, Kong FX, Cai DB, Huang BQ, Zheng HT, et al. Psychotic Symptoms as the Initial Presentation of a Long-Lasting Misdiagnosed Anti-GAD65 Autoimmune Encephalitis: An Emblematic Case and Literature Review. Frontiers in Psychiatry. 2022;13.
89. Gagnon MM, Savard M. Limbic Encephalitis Associated With GAD65 Antibodies: Brief Review of the Relevant literature. Can J Neurol Sci. 2016;43(4):486-93.
90. Najjar S, Pearlman D, Zagzag D, Golfinos J, Devinsky O. Glutamic Acid Decarboxylase Autoantibody Syndrome Presenting as Schizophrenia. Neurologist. 2012;18(2):88-91.
91. Warren N, Freier K, Siskind D, O'Gorman C, Blum S, Gillis D, et al. Anti-glutamic acid decarboxylase antibody screening in first-episode psychosis. Aust Nz J Psychiat. 2022.
92. Gutman JM, Kupersmith M, Galetta S, Kister I. Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in patients with optic neuritis and seizures. J Neurol Sci. 2018;387:170-3.
93. von Zedtwitz K, Matteit I, Michel M, Feige B, Runge K, Denzel D, et al. Anti-MOG autoantibody-associated schizophreniform psychosis. Acta Neuropsychiatr. 2022;34(1):47-54.
94. Tracey TJ, Steyn FJ, Wolvetang EJ, Ngo ST. Neuronal Lipid Metabolism: Multiple Pathways Driving Functional Outcomes in Health and Disease. Front Mol Neurosci. 2018;11:10.
95. Morales A, Lee H, Goni FM, Kolesnick R, Fernandez-Checa JC. Sphingolipids and cell death. Apoptosis. 2007;12(5):923-39.
96. Fahy E, Subramaniam S, Murphy RC, Nishijima M, Raetz CR, Shimizu T, et al. Update of the LIPID MAPS comprehensive classification system for lipids. J Lipid Res. 2009;50 Suppl:S9-14.
97. Merrill AH, Jr. Sphingolipid and glycosphingolipid metabolic pathways in the era of sphingolipidomics. Chem Rev. 2011;111(10):6387-422.
98. Maceyka M, Spiegel S. Sphingolipid metabolites in inflammatory disease. Nature. 2014;510(7503):58-67.
99. Hannun YA, Obeid LM. Principles of bioactive lipid signalling: lessons from sphingolipids. Nat Rev Mol Cell Biol. 2008;9(2):139-50.
100. Dai Y, Tang H, Pang S. The Crucial Roles of Phospholipids in Aging and Lifespan Regulation. Front Physiol. 2021;12:775648.
101. Castillo RI, Rojo LE, Henriquez-Henriquez M, Silva H, Maturana A, Villar MJ, et al. From Molecules to the Clinic: Linking Schizophrenia and Metabolic Syndrome through Sphingolipids Metabolism. Frontiers in neuroscience. 2016;10.
102. Narayan S, Thomas EA. Sphingolipid abnormalities in psychiatric disorders: a missing link in pathology? Front Biosci (Landmark Ed). 2011;16:1797-810.
103. van Kruining D, Luo Q, van Echten-Deckert G, Mielke MM, Bowman A, Ellis S, et al. Sphingolipids as prognostic biomarkers of neurodegeneration, neuroinflammation, and psychiatric diseases and their emerging role in lipidomic investigation methods. Adv Drug Deliver Rev. 2020;159:232-44.
104. Castillo RI, Rojo LE, Henriquez-Henriquez M, Silva H, Maturana A, Villar MJ, et al. From Molecules to the Clinic: Linking Schizophrenia and Metabolic Syndrome through Sphingolipids Metabolism. Front Neurosci. 2016;10:488.
105. He Y, Yu Z, Giegling I, Xie L, Hartmann AM, Prehn C, et al. Schizophrenia shows a unique metabolomics signature in plasma. Transl Psychiat. 2012;2.
106. Chang R, Trushina E, Zhu KX, Zaidi SSA, Lau BM, Kueider-Paisley A, et al. Predictive metabolic networks reveal sex- and APOE genotype-specific metabolic signatures and drivers for precision medicine in Alzheimer's disease. Alzheimers Dement. 2022.
107. Schwarz E, Prabakaran S, Whitfield P, Major H, Leweke FM, Koethe D, et al. High throughput lipidomic profiling of schizophrenia and bipolar disorder brain tissue reveals alterations of free fatty acids, phosphatidylcholines, and ceramides. J Proteome Res. 2008;7(10):4266-77.
108. Koens LH, de Vries JJ, Vansenne F, de Koning TJ, Tijssen MAJ. How to detect late-onset inborn errors of metabolism in patients with movement disorders – A modern diagnostic approach. Parkinsonism & Related Disorders. 2021;85:124-32.
109. Mané-Damas M, Hoffmann C, Zong S, Tan A, Molenaar PC, Losen M, et al. Autoimmunity in psychotic disorders. Where we

stand, challenges and opportunities. Autoimmun Rev. 2019;18(9):102348.
110. Tomassoni-Ardori F, Hong Z, Fulgenzi G, Tessarollo L. Generation of Functional Mouse Hippocampal Neurons. Bio Protoc. 2020;10(15).
111. Cunquero M, Aguilar E, Loza-Alvarez P, Planaguma J. Hippocampal Neuronal Cultures to Detect and Study New Pathogenic Antibodies Involved in Autoimmune Encephalitis. J Vis Exp. 2022(184).

Part 1: Inborn Errors of Metabolism

Part 2: Autoantibodies

Part 3: Lipids





PART 1

Inborn Errors of Metabolism




CHAPTER 2

Psychiatric manifestations of inborn errors of metabolism: A systematic review

Nikita van de Burgt, Willem van Doesum, Mirjam Grevink, Stephanie van Niele, Tom de Koning, Nicole Leibold, Pilar Martinez-Martinez, Therese van Amelsvoort, Danielle Cath

Neuroscience & Biobehavioral reviews 2023; 144:125-12

ABSTRACT

Inborn errors of metabolism (IEMs) are characterized by deficits in metabolic enzymes due to an inherited disease, leading to the accumulation or decreased excretion of proteins, carbohydrates and lipids. Although IEMs are often diagnosed during childhood, adolescent and adult onset, variants may result in less somatic and more psychiatric manifestations, which often makes it difficult for psychiatrists to distinguish between a primary and organic psychiatric disorder. With this systematic review, we aimed to provide an overview of psychiatric manifestations in IEMs to help clinicians in the diagnostic process. Our literature search yielded 4380 records in total, of which 88 studies were included in the qualitative synthesis. Reported psychiatric disorders in adolescent and adult IEMs included depression, anxiety, psychosis, attention deficit hyperactivity disorder, autism spectrum disorder, bipolar disorder and obsessive-compulsive disorder as assessed by semi-structured diagnostic interviews and validated questionnaires. A diagnostic screener and joint IEM clinics are proposed to help clinicians during the diagnostic process, to prevent diagnostic delay and to raise awareness for psychiatric manifestations among IEMs.

Keywords: Psychiatry, psychiatric disorders, inborn errors of metabolism, inherited metabolic disorders, inherited mitochondrial disorders

ABBREVIATIONS

ADHD = attention deficit hyperactivity disorder; AIP = acute intermittent porphyria; ASD = autism spectrum disorder; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CASH = Comprehensive Assessment of Symptoms and History; CBCL = Child Behavior Checklist; cblC = cobalamin C disorder; CES-D = Center for Epidemiologic Studies Depression Scale; CTX = cerebrotendinous xanthomatos; DASS-21 = Depression, Anxiety and Stress scale; ESS = Epworth Sleepiness Scale; FD = Fabry disease, GAD = generalized anxiety disorder; GAF = Global Assessment of Functioning; GD = Gaucher disease; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Depression Rating Scale; IEM = inborn error of metabolism; NMDAS = Newcastle mitochondrial diseases adult scale; MINI = Mini-International Neuropsychiatric Interview; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MD = mitochondrial disorder; MDD = major depressive disorder; MLD = metachromatic leukodystrophy; MMPI-2 = Minnesota Multiphasic Personality Inventory; NBS = newborn screening; NGS = Next Generation Screening; NPC = Niemann-Pick disease type C; OCD = obsessive compulsive disorder; OTCD = ornithine transcarbamylase deficiency; PANSS = Positive and Negative Symptom Scale; PKU = phenylketonuria; PTPsd = 6-pyruvoyl-tetrahydropterin synthase deficiency; PTSD = post-traumatic stress disorder; SCID-I = Structured Clinical Interview for the DSM-IV axis-I disorders; SCID-II = Structured Clinical Interview for the DSM-IV axis-II disorders; SCL-90-R = Symptom Checklist-90-Revised; SF-36 = Short-Form 36 Health Survey; TSD = tay-sachs disease; WAIS = Wechsler Adult Intelligence Scale; WD = wilson's disease; WRAT3 = Wide Range Achievement Test Revision 3.

INTRODUCTION

Inborn errors of metabolism (IEMs) constitute a series of inherited diseases in which the normal level of metabolism (the process of converting food to energy on a cellular level) is disrupted (1). This disruption in metabolism is caused by a deficit in specific enzymes in the human cell, leading to an inability of the cell to perform critical biochemical actions (2). Consequently, a disruption in the processing of for example proteins, carbohydrates or lipids, leads to a deficit of important elements or excess of waste products (2).

Although IEMs are rare disorders individually, more than 1000 IEMs have been described and emerge in 1:800 to 1:1000 individuals cumulatively (1, 3-5). Often, IEMs present during (early) childhood and are diagnosed with newborn screening (NBS). However, the panels that are used with NBS differ greatly in their sensitivity to detect IEMs (6) and some IEMs manifest during adolescence or adulthood without preceding symptoms during childhood. These symptoms can emerge most commonly on a somatic level, in deterioration of cognitive functioning, but may also manifest as (predominantly) psychiatric symptoms (7). Consequently, a late-onset IEM may even emerge as isolated psychiatric symptoms before any somatic symptoms are present (8). Many psychiatric disorders often emerge during late adolescence and early adulthood and therefore, it may be difficult to distinguish between a primary psychiatric disorder and a psychiatric disorder as a result of an IEM. Furthermore, clinicians working in the field of adult psychiatry generally have little knowledge and awareness of the possible neuropsychiatric manifestations of IEMs in adolescents and adults. Thus, the difficulty to distinguish between primary and secondary manifestations of psychiatric disorders, may lead to insufficient recognition and diagnostic delay. Consequently, this may result in a group of patients with the combination of a psychiatric condition and an underlying metabolic disease, who remain unrecognized and untreated (2, 9).

This recognition, however, is crucial, because of several reasons. First, an IEM has consequences for the course of the psychiatric disease. Second, an underlying IEM sometimes entails a treatable disease, and thus recognition has consequences for the treatment of both the psychiatric disorder and the IEM. Third, the diagnosis of an IEM underlying a psychiatric condition, when untreatable, is still meaningful and potentially de-stigmatizing for both patients and their families with respect to suffering from a psychiatric condition. Fourth, IEMs are inherited disorders and, as a consequence, information and education of family members on prognosis and potential consequences of being carrier of an IEM significantly differs from the information given on primary psychiatric disorders. Family members might want to be examined on being carrier of the IEM. In sum, for patients

with a psychiatric disorder, the psychological meaning of having an IEM associated psychiatric disorder is crucially distinct (10).

There is a large variation in clinical presentation between the different IEMs. Until now, research only focused on individual classes of IEMs. However, a general overview, which combines various psychiatric presentations and their possible link with underlying IEMs, is lacking. Therefore, the purpose of this article is two-fold. First, it aims to create an overview of the reported psychiatric presentations of IEMs across the various IEM classes. Second, it aims to investigate whether there are 'red flags' in psychiatric symptoms in patients with a psychiatric disorder that can indicate the presence of an IEM, and presents a proposal for a screener that can be used in general psychiatric practice. Thereby, this review aims to help psychiatrists or any other clinician in this difficult diagnostic process.

METHODS

Literature search methodology

A systematic literature search was performed following Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (11). The review protocol was registered in the PROSPERO database (CRD42020161948). An academic librarian supervised the literature search.

Identification

Relevant literature was collected using Medline (PubMed) and Embase databases. The literature search was completed on September 1st and September 28th 2021, and for Embase and PubMed respectively. Additionally, studies were identified by searching reference lists of selected articles and review articles. The search was limited to humans and English-language publications. The search terms were selected by the use of the PICO approach (12). The search included search terms concerning inborn errors of metabolism, specific psychiatric symptoms, neurodevelopmental disorders, behavioral disorders, cognitive disorders and search terms concerning diagnosis, sensitivity and specificity. The specific search terms are described in S1 and S2.

Screening

An overview of the screening procedure can be found in Figure 1. In short, abstracts with relevant titles were evaluated by NvdB, WvD, MG, SvN and DC. Screening focused on psychiatric disorders and manifestations in original studies, reviews and case reports. Articles were excluded from full text analysis according to the exclusion criteria as described in section 2.4.

Eligibility

First, duplicates were removed using EndNote X9 (Thomson Reuters). Subsequently, eligible studies were identified on the basis of their full text following the same procedure as before (see 2.3). When full texts couldn't be retrieved by the researchers and the academic librarian, corresponding authors were contacted directly. In case authors did not respond to requests to share the manuscripts within a timeframe of two weeks, the studies were excluded. Full texts were excluded when the full text was not available in English as well.

Inclusion

Full text articles were screened on the quality of the psychiatric evaluation. Full text articles were included when some form of standardized diagnostic or psychiatric symptom severity questionnaires and/or interview procedures were used and specified. Additionally, full text

articles were included when the study included patients of 12 years and older. In case an article included two or more case reports with an onset of psychiatric manifestations of 12 years and older, the record was included.

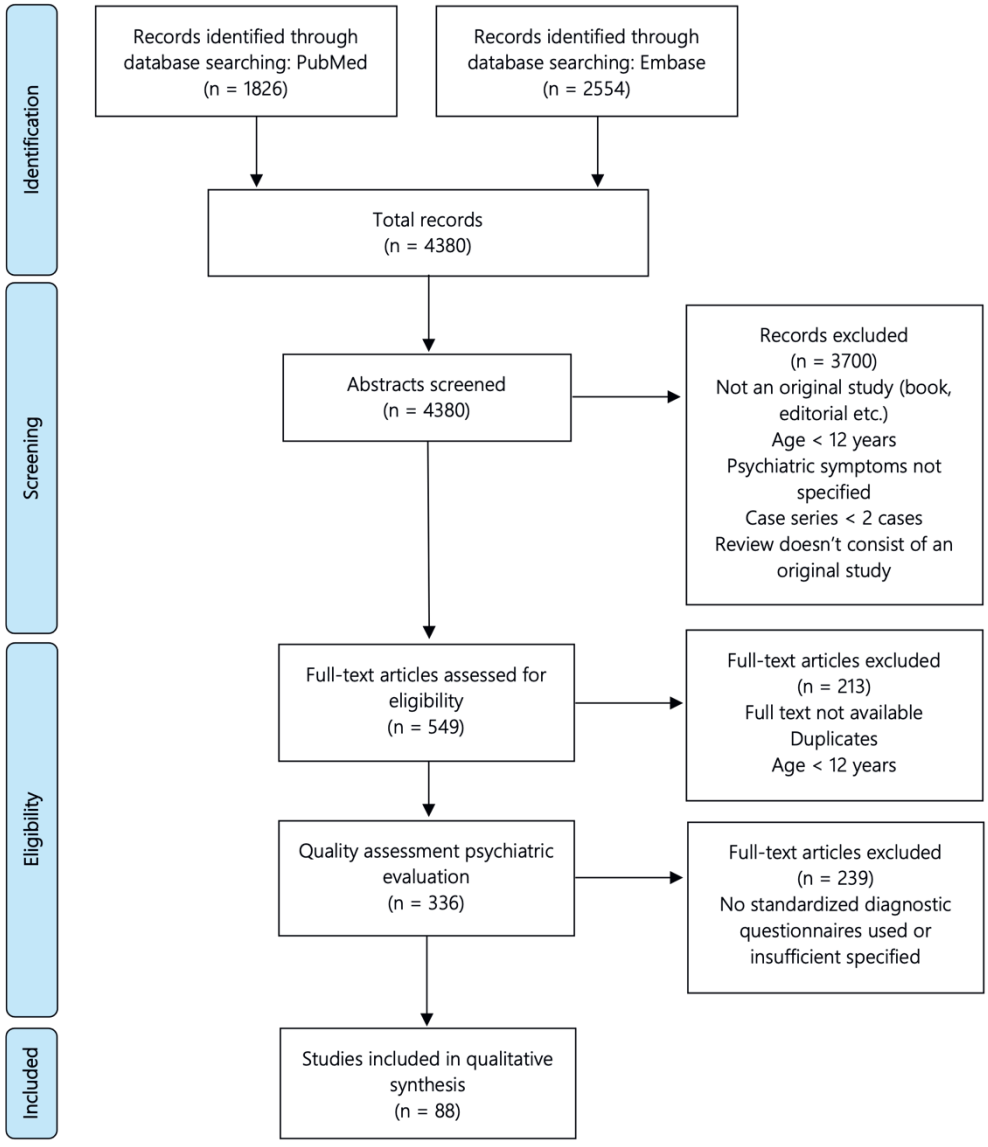


Figure 1 Flow-chart of this systematic review.

In total, 4380 records were identified through searching databases. Of these 4380 records, 549 papers met the initial inclusion criteria. Of these papers, 88 studies qualified to be included in the qualitative synthesis. Results are summarized in Table 3 and Figure 2. Included studies were classified according to general type of metabolism involved.

Disorders of carbohydrate metabolism

Disorders of carbohydrate metabolism constitute autosomal recessive IEMs characterized by the accumulation of sugars due to a lack of enzymes that break down carbohydrates such as glucose, fructose and galactose. Consequently, these sugars may accumulate inside the body and result in moderate to severe clinical manifestations. Galactosemia entailed the only disorder in this class of IEM with available literature on these psychiatric symptoms.

Galactosemia

Classic galactosemia (OMIM #230400) is an autosomal recessive disorder due to a galactose-1-phosphate uridyltransferase (GALT) deficiency. As a result of galactose food ingestion, galactose-1-phosphate and its metabolites accumulates in several bodily tissues. This results in a multitude of complications, including multi-organ failure, starting with liver failure, when not treated properly. Treatment consists of a galactose and lactose restricted diet. Most patients are diagnosed at an early age. However, most likely there are still patients without a diagnosis at adult age.

Psychiatric manifestations

Galactosemia primarily presents itself with neurological symptoms like movement disorders: ataxia, tremor and dystonia, impaired cognition and speech deficits (13, 14). Next to these neurological symptoms, psychiatric diagnoses are common in these patients. Only one research paper described these psychiatric symptoms (13). Kuiper et al. (2019) studied 37 patients with galactosemia and found that 21.6% of these patients had at least one psychiatric diagnosis. Among these diagnoses were autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), depression and generalized anxiety disorder (GAD). In 47.2% of patients' behavioral problems, mostly internalizing/depression like symptoms were found (13).

Disorders of mitochondrial energy metabolism

Mitochondrial disorders (MDs) are a group of inherited disorders characterized by mitochondrial dysfunction as a result of mutations in the nuclear DNA (nDNA) or mitochondrial DNA (mtDNA). Most mutations are associated with a clinical manifestation

as described in mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS, OMIM #540000), Myoclonic Epilepsy with Ragged Red Fibers (MERRF, OMIM #545000), and Neuropathy, Ataxia and Retinitis Pigmentosa (NARP, OMIM #551500). Because psychiatric manifestations are mainly described in MELAS, MERRF, NARP and clinical syndromes that result of mutations in the *POLG* gene, this review will focus on these MDs.

Psychiatric manifestations

Neuropsychiatric manifestations of MDs include psychosis, anxiety, depression and intellectual disability. In total, ten research papers described these psychiatric symptoms (15-24). First, Inczedy-Farkas et al. (2012) compared 19 patients with primary mutations of the mtDNA (MT) with 10 patients diagnosed with hereditary sensorimotor neuropathy (HMSN). HMSN are group of disorders that are characterized by an inherited, progressive form of neuropathy in which psychiatric symptoms are not part of the clinical manifestation (25). In the patients with MT, most identified mutations in the mtDNA were associated with a clinical syndrome including MELAS, MERFF and NARP. A Structured Clinical Interview for the DSM-IV axis-I (SCID-I) and axis-II disorders (SCID-II) was conducted to assess the presence of a psychiatric disorder. Psychiatric disorders ranged between types of major depressive disorder (MDD), bipolar I disorder, bipolar II disorder, dysthymia, postpartum depression and post-traumatic stress disorder (PTSS). Further, patients with MT scored significantly higher on severity of obsessive-compulsive behavior, depression, anxiety, paranoia, phobic anxiety and psychoticism compared to patients with HMSN as assessed by the Symptom Checklist-90-Revised (SCL-90-R). Additionally, patients with MT scored significantly higher on depressive symptoms as assessed by the Beck Depression Inventory-Short form (BDI-SF) and the Hamilton Depression Rating Scale (HAM-D). Interestingly, Inczedy-Farkas et al. (2012) found no correlation between somatic and psychiatric symptoms in either MT and HMSN patients, which led to the conclusion that the observed psychiatric symptoms may be part of the mitochondrial disorder and not secondary to the somatic disease itself (15). A similar conclusion was drawn by Mancusco et al. (2013), after conducting a study in 24 adult patients with a mitochondrial disorder who did not receive a psychiatric diagnosis earlier in life. Of these patients, 58.3% met the criteria of MDD, 29.2% met criteria for agoraphobia and/or panic disorder, 29.2% met the criteria for GAD and 12.5% met criteria for social anxiety disorder as assessed by the Mini-International Neuropsychiatric Interview (MINI, (26)). Additionally, four patients experienced psychosis, two patients experienced suicidal ideation and one patient received a diagnosis of PTSS. Interestingly, scores on the Newcastle mitochondrial diseases adult scale (NMDAS) showed that there was no correlation between psychiatric symptoms and the severity of the disorder, which led the authors to conclude that the observed psychiatric symptoms do not seem to

be related to the severity or progression of the mitochondrial disorder (16). Consequently, both studies suggest that psychiatric manifestations may be intrinsic to the manifestation of the mitochondrial disorder and not the result of living with the disorder or a lower quality of life.

Another study that used the MINI to determine the presence of psychiatric disorders within MDs, is the study of Fattal et al. (2007). This study included a total of 36 patients with a MD, including MELAS (n = 3), Kearns-Sayre syndrome (KSS, n = 1), complex I and complex IV deficiency (n = 6 and n = 5 respectively), mitochondrial cytopathy not otherwise specified (n = 7) and other MDs due to mtDNA mutations (n = 14), met the criteria of a life-time diagnosis of a psychiatric disorder. These patients did experience somatic symptoms as well, including chronic fatigue, muscle weakness, muscle pain, muscle spasms, headaches and visual problems. Of the patients who had both a MD and a life-time diagnosis of a psychiatric disorder, received psychiatric diagnosis included MDD, bipolar disorder, psychotic disorder, ADHD and panic disorder. Of these patients, 67% met the criteria of a current psychiatric disorder as well. Diagnoses included (recurrent) MDD (36%), dysthymia (11%), GAD (11%), social phobia (6%) and obsessive-compulsive disorder (OCD, 3%). Interestingly, patients with a MD and a psychiatric disorder experienced a significantly lower quality of life, more comorbid medial conditions and more hospital admissions, as assessed by the Short-Form 36 Health Survey (SF-36), compared to patients with a MD only (17). These findings contrast with a study by Kaufmann et al. (2009), which described 45 patients with MELAS who did not experience more psychiatric hospitalization, nor an increase in suicide attempts when compared with 78 carrier relatives and 30 controls. However, based on the psychiatric history, patients with MELAS did experience statistically significant more hallucinations, delusions and depression (18).

Mancuso et al. (2008) described 12 MD individuals from an Italian family without neurological symptoms or motor deficits who were diagnosed with a psychiatric disorder. Of these family members, 3 individuals were diagnosed with MDD and 3 with Bipolar Disorder as assessed by the SCID-I. The remaining family members received a diagnosis of schizophrenia, experienced nervous breakdowns and/or received psychiatric treatment. Overall, most family members had several depressive episodes throughout their lives and experienced insomnia, anhedonia, poor concentration, low energy levels and suicidal ideation. No abnormalities were shown on MRI, EEG, ECG, EMG and routine blood and urine assays. Interestingly, two family members experienced mild exercise intolerance and resting blood lactate levels were mildly increased as well. Genetic analysis revealed that no classified mutation could be identified as a causative factor of the MD in case of the proband. However, a reduction up to 40% in mitochondrial respiratory chain complexes I, III, and IV

activity was observed in this patient, as described in MDs (19). This study suggests that MDs may result in isolated psychiatric symptoms and that a differential diagnosis of MD should be considered in patients with the combination of a psychiatric disorder and mild exercise intolerance.

Koene et al. (2009) conducted a study with 35 adolescents with a MD due to a nDNA or mtDNA mutation. Of these 35 patients, 5 female patients met the criteria for a diagnosis of MDD according to DSM-IV criteria or HAM-D scores. The age of diagnosis of MDD varied between 12 and 16 years, followed by a diagnosis of a mitochondrial disorder 1 to 4 years later. In 2 out of 5 patients, there was a family history for depression. Additionally, 2 out of 5 patients showed intellectual disability and one of those individuals experienced a psychotic depression. The same patient suffered from chronic fatigue and ataxia as well. A low IQ (a score of 50 and 69 respectively) was observed in additional 2 out of 5 patients. The lowest IQ was observed in the patient with psychosis, chronic fatigue and ataxia (21). In addition, Parikh et al. (2019) described severe fatigue in all 48 patients with a MD, as well as depression, anxiety and sleepiness, as assessed by the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Epworth Sleepiness Scale (ESS). Interestingly, the severity of the MD was correlated with the level of depression, anxiety and sleepiness (20), which is in contrast with the findings of Inczedy-Farkas et al. (2012) and Mancusco et al. (2013), as they concluded that the psychiatric symptoms were not correlated to the severity of the MD.

Anglin et al. (2012e) described 12 late adolescent and adult patients with a history of psychiatric symptoms who were diagnosed with a mitochondrial disorder later in life. The age of diagnosis of the psychiatric disorder(s) varied between 15 and 53 years of age, followed by a diagnosis of a mitochondrial disorder 1 to 29 years later. Among these mitochondrial disorders were MELAS, MERRF, chronic progressive external ophthalmoplegia (CPEO) and mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE). Additionally, another 2 patients showed novel mtDNA mutations. All patients met the criteria of MDD and 2 patients met the criteria for bipolar disorder. Additionally, 7 patients met the criteria for an anxiety disorder as well and 4 other patients experienced psychosis. Importantly, 11 out of these 12 patients met the criteria of treatment resistant psychiatric illness and 3 out of 12 patients experienced an increase in symptoms while taking a psychotropic drug (23, 24).

Finally, Morava et al. (2010) showed that in early and late adolescent patients with a primary oxidative phosphorylation disorder (OXPHOS), depressive behavior was more frequently observed. More specifically, affective disorders and withdrawn and depressive behavior, as

assessed by the child behavior checklist (CBCL), was significantly increased in patients with OXPHOS. In contrast, anxious depressive behavior did not differ between patients with OXPHOS and controls. These patients often experienced muscle weakness and motor developmental delay as well (22). A wide array of biochemical analysis showed a significant decreased activity of one or more of the oxidative phosphorylation enzyme complexes in 9 out of the 18 included patients. Among them where mitochondrial complex I, II, III and IV. In one patient, additionally to a decreased activity of complex I and II, a significant decrease of the pyruvate dehydrogenase complex (1c) was observed.

Taken together, the described studies suggest that psychiatric and MDs co-occur and that somatic symptoms such as chronic fatigue, muscle weakness and exercise intolerance are often part of the clinical manifestation of a MD. Regarding the psychiatric symptoms, especially depressive disorders were frequently described in patients with mutations in nDNA or mtDNA.

Disorders of amino acid metabolism

Disorders of amino acid metabolism constitute autosomal recessive IEMs characterized by the inability to break down or transport certain amino acids into cells. Consequently, these amino acids and/or their byproducts accumulate in the body, which leads to toxicity in several organs, such as the brain. This group of disorders includes disorders such as phenylketonuria, hyperphenylalaninemia and homocystinuria.

Phenylketonuria

Phenylketonuria (PKU, OMIM #261600) is an autosomal-recessive disorder of phenylalanine metabolism characterized by a deficiency of phenylalanine-4-hydroxylase, an enzyme that is involved in the conversion of phenylalanine into tyrosine (27). The alterations in amino acids are thought to contribute to a disruption in the neurotransmitters, protein synthesis and cholesterol metabolism, oxidative stress, myelination and ultimately brain damage (28).

Psychiatric manifestations

Most patients who show neuropsychiatric symptoms in adulthood, already showed intellectual delay or seizures during childhood. Additionally, increased anxiety, depression, psychosis and attention deficits have been described in patients with PKU. In total, six research papers described these psychiatric symptoms in patients with PKU who either got diagnosed during childhood and discontinued a diet low in phenylalanine (Phe) that is used to treat PKU or who were diagnosed later in life (29-34). First, Steiner et al. (2003) described 84 patients with a diagnosis of autism spectrum disorder (ASD) according to the DSM-IV. The study used a structured clinical interviews, physical and neurological examination and

biochemical analysis to screen for IEMs. Of these 84 patients, two patients were diagnosed with untreated PKU.

Interestingly, neuropsychiatric symptoms have also been described in patients diagnosed with PKU who after neonatal screening did follow a diet low in Phe for several years. Daelman et al. (2014) described five patients with PKU, of whom four patients were diagnosed with PKU during infancy. The remaining patient was not diagnosed during infancy, as NBS was likely not executed, but in adulthood because of late onset of neuropsychiatric symptoms. Three out of the four in infancy diagnosed patients experienced psychiatric symptoms, including psychosis with auditory hallucinations, attention deficits, irritability, depression and anxiety. Two out of these four patients showed intellectual disability and all patients experienced either a delay in speech, a delay in walking or both during infancy. Of the four patients diagnosed after neonatal screening, a diet low in Phe resulted in improvement of the described symptoms, however, after the diet was discontinued after 11 years on average, a worsening of symptoms occurred after 1-23 years. After re-introducing a diet low in Phe, most patients experienced improvement or even complete disappearance of neuropsychiatric symptoms (30). A similar observation was done by Fisch et al. (1995), Koch et al. (2002), Pietz et al. (1997) and Ris et al. (1997). Fisch et al. (1995) described 19 patients who followed a diet low in Phe for 6.5 years on average and discontinued the diet after 12 years or more. Of these 19 patients, 5 patients were diagnosed with a psychiatric disorder by a psychiatrist or psychologist. Diagnoses included depression, impulse control disorder, phobia and dysthymia. No significant difference in IQ (as assessed by WAIS-R) was observed after discontinuing the diet low in Phe. However, psychiatric disorders were more frequently observed in patients with lower IQ or lower educational level and when the psychiatric disorder was taken into account, the patients with PKU and a psychiatric disorder scored significantly lower in IQ, with a mean difference of 23.3 points compared to the PKU patients without a psychiatric disorder (31). Koch et al. (2002) also observed that individuals with PKU, diagnosed after neonatal screening who discontinued the diet low in Phe after 6 years, reported more mental disorders, headache, hyperactivity and hypoactivity 4-6 years later compared to individuals who continued their diet low in Phe. Additionally, these early discontinuing patients scored lower in IQ and academic achievement as assessed by the WAIS-R and the Wide Range Achievement Test Revision 3 (WRAT3) (32).

Ris et al. (1997) investigated in 25 adult patients with early-treated PKU and 15 unaffected siblings on psychosocial and neuropsychological outcomes. Of all patients, 10 patients still followed a diet low in Phe at the time of inclusion, while the remaining 15 patients discontinued their diet during childhood or adolescence. Analysis revealed no significant

difference in psychosocial outcome between patients with PKU and controls, however, the scores of the SCL-90-R showed that patients with PKU reported more severe psychiatric symptoms than their unaffected siblings, with higher scores on the obsessive compulsive, psychoticism and interpersonal sensitivity domains. Additionally, psychiatric symptoms were strongly correlated with intellectual and neuropsychological functioning, especially executive functioning. Finally, similar to other studies, patients with PKU scored significantly lower on IQ compared to controls, as assessed by the WAIS-R (34). A similar observation was done by Pietz et al. (1997) in 35 adult patients with PKU and 181 controls. Interestingly, patients with PKU experienced more internalizing disorders, as assessed by a structured interview and the ICD-10, while more externalizing disorders were observed in controls. Patients experienced significantly more depression, phobia, generalized anxiety and hypochondriac worries, compared to controls. Most frequently observed diagnoses included depressive, anxiety and personality disorder. The presence of a psychiatric disorder was not associated with a lower IQ, as measured by the WAIS-R, however, a lower IQ was significantly associated with higher levels of Phe in plasma (33).

6-Pyruvoyl-tetrahydropterin synthase deficiency

6-Pyruvoyl-tetrahydropterin synthase deficiency (PTPSd, OMIM #261640) is an autosomal-recessive disorder of phenylalanine metabolism characterized by a deficiency in tetrahydrobiopterin. Consequently, this deficiency leads to increased levels of phenylalanine in the blood, a disruption in the neurotransmitters and the occurrence of neurodevelopmental disorders (35).

Psychiatric manifestations

Neuropsychiatric manifestations of PTPSd include anxiety, depression and intellectual disability, as described by only one recent research paper (36). More specifically, Manti et al. (2020) described 3 patients with PTPSd who received a diagnosis at the age of 28, 32 and 31 respectively, even though in all patients hyperphenylalaninemia was detected via NBS. All three patients were diagnosed with an anxiety disorder according to DSM-V criteria. Additionally, two patients experienced sleep problems, one patient was diagnosed with a depressive disorder and one patient was diagnosed with ADHD and OCD. Two out of three patients experienced mild intellectual disability, as measured by WAIS-R and WAIS-IV. Finally, one patient was diagnosed with a movement disorder and one patient had seizures. In contrast with patients who received a diagnosis during early childhood, the clinical manifestation of these patients suggests that the adult onset variant of PTPSd is non-progressive and not deteriorating (36).

Histidinemia

Histidinemia (OMIM #235800) is an autosomal-recessive disorder characterized by a deficiency of the enzyme histidase, involved in the breakdown of the amino acid histidine (37). A deficiency in this enzyme results in the accumulation of histidine in the blood and elevated levels of histidine in urine. Although histidinemia is currently considered to be a benign disorder, specific events in the neonatal period such as hypoxia, combined with elevated levels of histidine, may result in neuropsychiatric symptoms.

Psychiatric manifestations

Neuropsychiatric manifestations of histidinemia include hallucinations and delusions as described in one paper in 24 adult patients with schizophrenia, as established using DSM-III criteria, compared to 14 adult controls without a psychiatric disorder (38). Of all schizophrenic patients, 6 patients were identified as being heterozygous for histidinemia. Although these heterozygous patients were not affected by an IEM, these patients did show higher and more prolonged histidine excretion in both plasma and urine samples compared to non-heterozygous patients with schizophrenia and controls. This study suggests that there might be an association between schizophrenia and heterozygosity for histidinemia, although there was no statistically significant correlation between clinical variables and heterozygosity (38).

Homocystinuria

Homocystinuria (OMIM #236200) is an autosomal-recessive disorder of methionine metabolism characterized by a deficiency of cystathionine beta-synthase, an enzyme involved in the conversion of homocysteine into cystathionine. An increased level of homocysteine in the blood may result in an increased risk of vascular, muscular or skeletal abnormalities, disturbances of the central nervous system and psychiatric symptoms.

Psychiatric manifestations

Psychiatric manifestations of homocystinuria include depression, behavioral abnormalities including aggression, and personality changes as described in one paper only (39). Abbott et al. (1987) investigated 63 patients with a diagnosis of homocystinuria. After a structured psychiatric interview, 51% of these patients received a psychiatric diagnosis based on DSM-IV criteria at an average age of 19 years. The most common diagnoses included MDD, behavioral and personality disorder and OCD (39). Of all patients with homocystinuria, 48 patients (76%) had lower IQ of 83 according to the WAIS. Behavioral and obsessive-compulsive disorders were more frequently observed in patients with a low IQ (IQ <80), while depressive disorders were more frequently observed in patients with higher IQ (IQ > 80). Personality disorder was observed equally in both patients with a low or high IQ score.

Abbott et al. (1987) studied the effect of oral supplementation with vitamin B6 and folic acid to determine the effect of these two on homocystinuria patients. Interestingly, behavioral and obsessive-compulsive disorders were more frequently observed in patients who did not respond to supplementation of vitamin B6 and folic acid, and there was a statistically significant difference in IQ score between patients who did and did not respond to supplementation (average IQ of 89 versus 62). Additionally, there was a statistically significant difference in psychiatric disorders between responders and non-responders with a high IQ. Consequently, the authors concluded that the observed differences in psychiatric disorders and intelligence between patients who respond to treatment with vitamin B6 and non-responders support the hypothesis that there may be two types of homocystinuria, caused by different mutations (39).

Vitamin metabolism disorders

Vitamin metabolism disorders result from a mutation in vitamin cofactors or transporters. Among these vitamin metabolism disorders, are the inherited disorders of vitamin B12 (cobalamin). In these disorders, the gut is either not able to absorb vitamin B12 and transport it to the appropriate tissues, or target cells are unable to take up vitamin B12 within the cell, both leading to a deficiency of vitamin B12 in the target cells (40).

Cobalamin C disorder

Cobalamin C (cblC) disorder (OMIM #277400) entails an autosomal recessive disorder of inborn error of cobalamin (vitamin B12) metabolism. CblC disorder is characterized by a mutation in the *MMACHC* gene, which is necessary for the conversion of cobalamin into methylcobalamin and adenosylcobalamin, the active forms of vitamin B12. As a consequence of this mutation, these active forms of vitamin B12 cannot be processed in the cytosol, which results in an intracellular deficiency of vitamin B12 (41). Consequently, this disorder is characterized by methylmalonic acidemia with homocystinuria. Most (±90%) reported patients are diagnosed during infancy, due to feeding difficulties, lethargy, developmental delay, intellectual deficits and anemia. However, in case of late-onset forms, symptoms are usually restricted to neuropsychiatric manifestations, without hematological symptoms (42).

Psychiatric manifestations

Psychiatric manifestations of late onset forms of cobalamin C disorder include psychosis and anxiety as described in two papers (43, 44). Roze et al. (2003) described cobalamin C deficiency in two patients of 16 and 24 years of age, presenting with a wide range of neurological symptoms, cognitive impairment and psychosis-like symptoms with visual and auditive hallucinations (43). Wang et al. (2018) found cognitive impairment in 3 out of 8

patients with a cobalamin C deficiency. Additionally, 4 out of those 8 patients experienced psychiatric disturbances, although not further specified (44).

Urea cycle disorders

Urea cycle disorders (UCDs) are a group of IEMs as the result of a dysfunction of any of the six enzymes or two transport proteins involved in the urea biosynthesis or the transporters of the urea cycle pathway. Consequently, a dysfunction or defect in one of these enzymes results in the accumulation of ammonia. High concentrations of ammonia may result in changes in cerebral blood flow and metabolism, disturbances of neurotransmission, free radical damage and toxicity to the brain (45). Cognitive, attention and executive function deficits, learning disabilities, sleep disorders and psychosis have been described in patients with a urea cycle disorder (46).

Ornithine transcarbamylase deficiency

Ornithine transcarbamylase deficiency (OTCD, OMIM #311250) is an X-linked genetic disorder characterized by a complete or partial deficiency of the enzyme ornithine transcarbamylase. Consequently, ammonia accumulates in the blood. While a complete deletion often results in a severe, neonatal-onset form, a mutation leading to a partial deficiency of the enzyme often results in late-onset OTCD (47). Because psychiatric symptoms are mainly present in the late-onset form, this review will focus on this subtype of OTCD.

Psychiatric manifestations

Psychiatric manifestations of OTCD may include hallucinations, confusion and irritability as described in one case report of 5 patients (47). Cavicchi et al. (2014) described 5 adult patients with late-onset OTCD (LO-OTCD) that first manifested at respectively 21, 34, 44, 45 and 66 years. Reported symptoms of the first acute episode included confusion, irritability, drowsiness, hallucinations, headache, vomiting and slurred speech. Three out of five patients experienced seizures as well. All patients lost consciousness several days after the onset of the acute episode. Interestingly, at the onset of the acute episodes, misdiagnosis was common (e.g. depression, infectious disease, poisoning). Initially, these patients were diagnosed with fatal hyperammonemic encephalopathy. Hyperammonemia treatment was started in 4 out of 5 patients, which normalized ammonia levels in 3 out of 5 patients, without affecting the clinical manifestation of OCTD; all patients remained unconscious and eventually died. *OTC* sequence analysis of post-mortem material confirmed two novel and three previously reported mutations associated with OTCD (47).

Lysosomal storage disorders

Lysosomal storage disorders are often caused by mutations in genes that encode for a lysosomal enzyme, resulting in the reduction or absence of these lysosomal enzymes and accumulation of nondegraded material in endosomal and lysosomal compartments (48). This may result in a wide variation of symptoms.

Niemann-Pick disease type C

Niemann-Pick disease type C (NPC, OMIM #257220) is an autosomal-recessive lysosomal storage disorder characterized by a mutation in the *NPC1* or *NPC2* gene. A mutation in one of these two genes results in the accumulation of unesterified cholesterol and GM2 and GM3 gangliosides in the liver, spleen and brain (49, 50). Psychiatric symptoms are mainly present in late-onset patients (50). As psychiatric symptoms are mainly present in the late-onset form, this review will focus on this subtype of NPC.

Psychiatric manifestations

Psychiatric manifestations of late onset NPC often include psychosis, mania, aggression and sexual disinhibition. Additionally, cognitive impairment is commonly observed in patients with NPC. In total, 6 papers including a total of 38 patients have described psychosis including hallucinations, depression, anxiety, mood- and autistic related manifestations, impaired impulse control and cognitive impairment in patients with NPC (51-56). Josephs et al. (2003) described two patients with the late-onset form of NPC. One patient experienced depression and hypersomnolence at the age of 46 years, followed by mood liability, delusions and hypervigilance at the age of 49. At the age of 50 years, she developed a gait disorder, followed by auditory hallucinations, paranoia and obsessive-like behavior. A diagnosis of schizoaffective, bipolar or organic affective disorder was considered. Between the age of 55 and 61, her conditions worsened, and her symptoms were followed by dysarthria, bradykinesia and memory deficits. Finally, this patient received a diagnosis of NPC, 15 years after the onset of the manifestation of the disorder. The second patient experienced paranoid delusions at the age of 27 years. Although the psychotic episode initially stabilized after treatment with haloperidol, she developed a tardive syndrome. Subsequently, she experienced a second psychotic episode and neurological consultation revealed neurological symptoms and MRI abnormalities. At the age of 32, she was diagnosed with NPC (51). Walterfang et al. (2006) described 2 patients with late-onset NPC, experiencing psychotic symptoms, and behavioral disturbances at onset. Both patients initially received a diagnosis of schizophrenia. As the disease progressed, both patients showed cognitive decline and an ataxic gait. After 8-year history of a psychotic disorder, both patients were diagnosed with NPC after analysis of skin fibroblasts (54). In line with experiences, Maubert et al. (2015) described two siblings, brother and sister of 27 and 22

years of age, who were hospitalized because of disorganized behavior, mood instability, wandering and hallucinations, acute delirium and suicidal ideation. Both patients improved after receiving antipsychotics, however, in both cases psychiatric symptoms returned. The 27-year-old male developed pyramidal symptoms and involuntary movements. However, these were interpreted as side effects of the prescribed medication. After three and seven years respectively, both patients experienced gait symptoms and involuntary movements and in the male sibling, neurological and visceral symptoms were observed and subsequently, he was diagnosed (55).

Bauer et al. (2013) conducted a genetic screening study in 256 patients diagnosed with a psychotic disorder. Of these patients, 3 were diagnosed with NPC and all 3 patients experienced psychosis, attention deficits and memory impairment as assessed by the Mini-Mental State Examination (MMSE). Additionally, all patients experienced neurological symptoms as described in NPC (52). A similar observation was done by Koens et al. (2016), who described 7 patients diagnosed with the late-onset form of NPC. Of these patients, 2 patients presented with a psychotic presentation and were diagnosed with a psychotic disorder. Additionally, all patients showed deficits in working memory, attention, verbal fluency and learning of verbal information, based on the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (53). Maubert et al. (2016) additionally described 22 patients with NPC in which 19 out of those 22 patients, psychiatric symptoms and behavioral problems were described in the patient files. Among them were auditory and visual hallucinations, delusions, agitation, aggression, impulsiveness, sleep problems, apathy and psychomotor impairment. However, only in 11 of these 22 patients (50%) a psychiatric disorder was established. Psychiatric diagnosis included schizophrenia and depression in most cases (50% and 33% respectively). In 45% of the patients, the neurological symptoms manifested before the psychiatric symptoms. In another 27% of the patients, the neurological symptoms manifested after the isolated psychiatric symptoms. Furthermore, in 9% of the patients, the psychiatric and neurological symptoms manifested at the same time. In the remaining number of patients, the chronological order of the psychiatric and neurological symptoms was not described. The authors speculated that the absence of a psychiatric disorder in some patients may be due to the fact that these symptoms were considered to be part of the clinical manifestation of NPC rather than the result of a primary psychiatric disorder (56).

Tay-Sachs disease

Tay–Sachs disease (TSD, OMIM #272800) is an autosomal-recessive lysosomal storage disorder characterized by a deficiency of hexosaminidase A, an enzyme involved in the breakdown of GM2 gangliosides. Gangliosides are glycosphingolipids that are highly abundant in the central nervous system (57). A deficiency in this enzyme results in an

accumulation of GM2 gangliosides in the brain and nerve cells.

Psychiatric manifestations

Psychiatric manifestations of TSD include hallucinations, paranoid delusions, recurrent depression and agitation. Only one research paper described hallucinations, depression and anxiety in 4 patients with a late-onset form of TSD (58). Three of these patients were siblings and belonged to the same family. Two out of four patients experienced psychosis, hallucinations and anxiety. One patient mainly experienced depressive symptoms and committed suicide at the age of 24 years. All four patients showed speech disarticulations during childhood and two out of four patients showed unsteady gait as well. After having been misdiagnosed for over 10 years, a clinical evaluation by a neurologist, together with reduced plasma hexosaminidase A activity and molecular analysis in three out of four patients, led to a diagnosis of TSD. The fourth patient received a suspected diagnosis of TSD after both parents were identified as carriers of the *G269S* and *InsTATC1278* genes (58).

Mucopolysaccharidoses

Mucopolysaccharidoses (MPSs, OMIM #252700) consists of several recessive lysosomal storage disorders characterized by a deficiency or malfunction of enzymes that are involved in the degradation of glycosaminoglycans. Consequently, a deficiency or malfunction in these enzymes leads to the accumulation of mucopolysaccharides or glycosaminoglycans in several parts of the body, including the eyes, ears, skin, teeth, joints, bones and/or the arteries. Three of the MPSs are known for their psychiatric manifestations, namely Hurler-Scheie syndrome (MPS type IH/S, OMIM #607015), Hunter syndrome (MPS type II, OMIM #309900) and Sanfilippo syndrome (MPS type III, OMIM #252900, #252920, #252930, #252940).

Psychiatric manifestations

Only one case report described developmental delay, restlessness, aggressive and destructive behavior in patients with MPSs (59) that encompassed Sanfilippo syndrome. A total of 49 patients showed behavioral problems such as restlessness, aggressive and destructive behavior, including temper tantrums and emotional outbursts during childhood. Additionally, 33 patients (63%) experienced sleep disturbances. Most of these patients already showed developmental delay during childhood, but strikingly the age of diagnosis differed between early childhood and late adulthood (59).

Fabry disease

Fabry disease (FD, OMIM #301500) is an X-linked recessive lysosomal storage disorder that is characterized by a deficiency of alpha-galactosidase A, an enzyme involved in the

degradation of the alpha1-4 Gal-Gal part of glycolipids and glycoproteins. The deficiency results in the accumulation of globotriosylceramide (Gb3 or GL3) within most cell types in the body. However, how this accumulation exactly results in cellular and tissue damage is not yet fully understood.

Psychiatric manifestations

Psychiatric manifestations of FD include depression, anxiety and self-injurious behavior in both males and females, as described in 3 papers (60-62). First, Sigmundsdottir et al. (2014) described significantly increased anxiety and depression in adult male and female patients with FD who did not experience psychiatric manifestations during childhood and received the diagnosis of FD in adulthood (61, 62). When compared to control individuals, depression and anxiety symptoms were more pronounced in men than in women, according to the Depression, Anxiety and Stress scale (DASS-21). Further, males with FD scored statistically significant lower in processing speed, verbal fluency and problem-solving domains (based on the WAIS-IV) compared to control individuals (61). Similarly, Körver et al. (2019) also observed significantly lower processing speed in adult males with FD, compared to adult females with FD. Additionally, 31 out of a total of 81 included patients (38.3%) scored significantly higher on depression as assessed by the Center for Epidemiologic Studies Depression Scale (CES-D). However, there was no significant difference in mental and physical quality of life between men and women with FD, based on the SF-36 (60). Additionally, a study by Sadek et al. (2004) described 4 cases of adult female carriers of Fabry disease who experienced severe depressive symptoms and had suicidal ideation. All carriers scored higher than 26 points on the HAM-D, representing severe depressive symptoms and received a diagnosis of MDD according to DSM-IV. Additionally, 2 out of 4 carriers completed the SF-36, which showed that carriers experienced a low quality of life (62).

Gaucher disease

Gaucher disease (GD, OMIM #230800, #230900, #231000) is an autosomal-recessive lysosomal storage disorder characterized by a deficiency in the lysosomal enzyme ß-glucocerebrosidase. A deficiency in this enzyme results in the accumulation of undegraded glucosylceramide in macrophages. Consequently, "Gaucher cells" are formed: Enlarged cells with a striated cytoplasm. These cells are mainly found in the liver, spleen and bone marrow (63).

Psychiatric manifestations

Psychiatric manifestations of GD include depression, schizophrenia-like behavior and cognitive impairment. In total, three research papers described both psychiatric

manifestation in adult patients with GD (64-66). Packman et al. (2006) showed that patients with GD scored significantly higher on depression, schizophrenia and hysteria according to the Minnesota Multiphasic Personality Inventory (MMPI-2). Of these patients, 39% patients received a diagnosis of GD between the age of 21 and 50 years and only 3.6% patients reported somatic manifestations as described in GD, e.g. enlarged spleen or liver, enlarged abdomen, anemia or fatigue (64). In line with this, Beavan et al. (2015) showed that patients with GD (n = 30) scored significantly higher on depression according to the BDI compared to heterozygous carriers (n = 28, *GBA* mutation) and control individuals (n = 26) (65). A similar observation was done by Wilke et al. (2019), as 5 out of 23 patients diagnosed with GD in adulthood scored 16 or higher on the BDI, indicating moderate to severe depression. Among these 5 women, 4 women experienced signs of cognitive impairment (as assessed by the Montreal Cognitive assessment (MoCa)) as well. More cognitive impairment was associated with more severe GD manifestations and a higher age at diagnosis. One of those women suffered from increased daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS) (66).

Metachromatic leukodystrophy

Metachromatic leukodystrophy (MLD, OMIM #250100) is an autosomal recessive lysosomal storage disorder characterized by a deficiency of sulfatide sulfatase arylsulfatase A. A deficiency in this enzyme results in the accumulation of galactosylceramide-3-O-sulfate in the central and peripheral nervous system and severe demyelination (67).

Three subtypes of MLD are described: the late-infantile, juvenile and adult form. Each form is characterized by a different variety of symptoms, age of onset and severity of the disease. The adult form is characterized by psychiatric manifestations and progressive mental deterioration. Since these psychiatric symptoms mostly occur in the adult form, this review will focus on this type MLD.

Psychiatric manifestations

Psychiatric manifestations of adult onset MLD includes schizophrenia-like behavior, depression, behavioral abnormalities and intellectual disability. In total, three research articles described these psychiatric manifestations (68). Baumann et al. (2002) presented 12 cases with the adult form of MLD, of whom 6 patients experienced mainly psychiatric symptoms, including hallucinations and disorganized behavior without any neurological signs or motor deficits. In one of these 6 patients, auditory hallucinations were followed by disinhibition, memory disfunction and compulsive lying. In six other patients, disinhibition, memory disfunction and compulsive lying was observed as well. Consequently, a diagnosis of schizophrenia was considered after psychiatric examination in all of these patients (68-

70). A similar observation was done by Müller et al. (1969), who described two patients with the adult form of MLD that experienced mainly psychiatric symptoms, e.g. delusions and bizarre behavior. Additionally, both patients experienced progressive memory deficits, disorientation, lack of concentration and critical thinking, similar to the findings of Baumann et al. (2002) (69). In contrast, Kumperscak et al. (2005) described two siblings with late-onset MLD, who did not show cognitive impairment, other than poor attention, at the onset of the disease. However, in case of the first patient, several neuropsychological tests (e.g. WAIS, Stroop Color and Word Test, Rivermead Behavioural Memory Test and the Controlled Oral Word Association Test) revealed impairments in attention, executive functions, processing speed when her condition progressed. These patients were diagnosed with disorganized schizophrenia and postpartum depression according to the DSM-IV respectively (70). Additionally, one of the patients received a diagnosis of severe intellectual disability 10 months after the onset of psychotic symptoms as well.

Alpha-mannosidosis

Alpha-mannosidosis (OMIM #248500) is an autosomal recessive lysosomal storage disorder characterized by a deficiency in α-mannosidase, an enzyme that plays an important role in the breakdown of oligosaccharides (71). Consequently, oligosaccharides accumulate in lysosomes which may result in mild to severe clinical manifestations (72).

Psychiatric manifestations

Psychiatric manifestations of alpha-mannosidosis include psychosis, depression, behavioral problems and intellectual disability as described in two papers (73, 74). Malm et al. (2005) described 11 out of 45 patients with alpha-mannosidosis that experienced episodes of depression, psychosis, anxiety and disturbed sleeping patterns. For most patients, the onset of the psychiatric symptoms started during adolescence, although for one patient, the psychiatric symptoms started at the age of 32 years (73). Additionally, Malm et al. (2014) observed intellectual disability in 109 out of 114 patients and psychosis and other behavioral problems, such as confusion, depression and anxiety, in 26 out of 57 patients. Both studies observed intellectual disability present during childhood in most cases, however, for some patients the intellectual disability was not observed until adolescence or adulthood. For the behavioral problems and psychosis, onset typically occurred during adolescence, although around 20% of these patients experienced symptoms during childhood already (74).

Bile acid synthesis defects

Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis (CTX, OMIM #213700) is an autosomal-recessive lysosomal storage disorder characterized by a deficiency in the mitochondrial enzyme sterol

27-hydroxylase that plays a role in the conversion of cholesterol into chenodeoxycholic acid (CDCA). Consequently, a deficiency in this enzyme results in the accumulation of cholesterol in the membranes of (nerve) cells.

Psychiatric manifestations

Psychiatric manifestations of CTX includes ASD and cognitive impairment as described in two papers (75, 76). Stelten et al. (2018) described 77 patients with CTX of which 9 children and one adult that were diagnosed with ASD by a psychiatrist based on the version of the DSM used at the time of diagnosis. However, not all of these patients underwent a psychiatric interview. In 9 out of these 10 patients, the diagnosis of ASD proceeded the diagnosis of CTX. Additionally, the remaining patient experienced symptoms related to ASD as well before receiving the diagnosis of CTX retrospectively. None of these patients experienced neurological symptoms at the time of diagnosis of ASD. However, intellectual disability, and moreover diarrhea was described in the medical files of all patients. Therefore, Stelten et al. (2018) proposed that ASD could be an early indicator of CTX and that genetic screening in patients with ADS could be considered when this is accompanied by cognitive impairment, diarrhea and/or juvenile cataract (75). When ASD would be considered as one of the symptoms of CTX, diagnosis could be established earlier in life in case of 7 out of these 10 patients. Interestingly, the psychiatric manifestations as observed in the patient that was diagnosed during adulthood worsened after treatment with CDCA, while improvement was seen in the patients that we diagnosed during childhood instead (77). Similar findings were published by Yunisova et al. (2019) who studied 7 patients with CTX in Turkish hospitals and also found depression and ASD to be one of the first manifestations of this disease (76). This makes CTX one of the few IEMs in which isolated psychiatric symptoms are seen in its initial presentation in the absence of any other somatic or neurological symptom.

Porphyrias

Porphyria consists of a group of autosomal recessive disorders characterized by a disruption of the heme biosynthesis. Since the disease has been associated with anxiety and psychotic symptoms, it has been subject of numerous case reports but also dozens of cohort studies and prospective studies have been published. Additionally, since psychiatric symptoms mostly occur in a subgroup of AP, e.g. acute intermittent porphyria (AIP, OMIM #176000), this review will focus on this type of porphyria.

Psychiatric manifestations

When patients with porphyria are seen by a psychiatrist, they are often diagnosed with a primary anxiety disorder, psychosis, drug induced psychosis, schizophrenia, bipolar disorder,

depression or conversion disorder (78, 79). Doctors' delays of six years or more, often until neurological signs of AIP appear, are not unusual (80). A strong association has been found between porphyria and psychiatric disorders, suggesting common biological pathways.

Cederlöf et al. (2015), in a large-scale study in 717 patients diagnosed with AIP and their first-degree relatives, found a strong association between AIP and schizophrenia and bipolar disorder. Patients with AIP had a fourfold increased risk of schizophrenia and bipolar disorder compared to the healthy population. Interestingly, their relatives appeared to have a twofold increased risk of these psychiatric disorders, although none of them was diagnosed with AIP. A similar observation was done by Patience et al. (1994), who also found an increased risk of psychiatric disease in first-degree relatives carrying latent AIP mutations (81). This suggests commonalities (pleiotropy) with respect to genetic pathways involved in the pathophysiology of AIP, schizophrenia and bipolar disorder (82). Possibly latent AIP mutations are responsible for the psychiatric symptoms in first-degree relatives. Cederlöf et al. (2015) suggest that in AIP, tryptophan 2,3-dioxygenase (TDO2) and indoleamine 2,3-dioxygenase (IDO) levels, enzymes involved in the first and rate-limiting enzymatic step in kynurenine generation, are decreased. The kynurenine synthesis pathway is linked to schizophrenia and might together with the pleiotropic effects of the PBG deaminase gene that is responsible for conversion PBG to hydroxymethylbilane in the heme formation pathway, at least partially explain the association between AIP and psychotic symptoms (82).

Patience et al. (1994), in 344 patients with AIP, did only find a correlation between patients with AIP and occurrence of anxiety disorders, but not with features of schizophrenia and bipolar disorder, which differs from the findings of Cederlöf et al. (2015). However, Millward et al. (2001) also observed a higher score on anxiety and depression, as measured by the BAI, the BDI and the Hospital Anxiety and Depression Scale (HADS), in patients with AIP compared to controls (80). Furthermore, anxiety scores and levels of porphyrin metabolites in urine correlated, supporting an association between the two parameters (81). However, in a review of Elder et al. (1997) it is stated that `there is little evidence that porphyria produces chronic psychiatric illness, apart from generalized anxiety' (83). Consequently, generalized anxiety and depression seem to be the most common psychiatric symptoms concordant with AIP, while symptoms of schizophrenia and bipolar disorder might occur as well.

Mineral and metal metabolism disorders

Mineral and metal metabolism disorders can be distinguished in copper, iron and manganese disorders, and are caused by mutations in genes that encode for transporters

or enzymes, resulting in the accumulation of specific minerals or metals in the blood. This may result in a wide variation of symptoms. Since psychiatric symptoms are most commonly described in patients with Wilson's Disease, this review focusses on this type of metal metabolism disorder.

Wilson's disease

Wilson's disease (WD, OMIM #277900) is an autosomal-recessively inherited metal storage disorder characterized by a deficiency of the ATP7B copper transporter, a transporter that is involved in the excretion of copper into the bile (84). Consequently, a deficiency in this transporter results in an accumulation of unbound copper in serum. These deposits of copper in organs such as the liver and the brain ultimately lead to a wide range of symptoms as seen in WD, such as brain lesions and psychiatric symptoms (84, 85). Clinicians distinguish hepatic and neurological WD, which indicates the disease progression. In hepatic WD depositions are confined to the liver whereas in the neurological form, depositions are found in several organs, including the brain. Consequently, hepatic WD is characterized by mainly hepatic metabolic symptomatology, while in neurological WD neuropsychiatric symptoms are present as well.

Psychiatric manifestations

Psychiatric manifestations of WD include changes in behavior, irritability, disinhibition, obsession, aggressive behavior and deterioration in school or work. In total, 19 papers have described these psychiatric manifestations (84-87). Neurological symptoms include dystonic postures, postural and action tremor. These tremors have high amplitudes and a low frequency. Also, Parkinsonian symptoms with rigidity, akinesia and whispering dysphonia are observed (84, 88).

Depression-like affective symptoms are more common than psychosis or schizophrenia-like observations in WD (85, 86, 89, 90). Based on an association between WD and the incidence of comorbid bipolar disorder and MDD (Carta et al. 2012), it was hypothesized that in some instances the etiology of these psychiatric disorders might involve metal metabolism including copper and zinc metabolism. According to this hypothesis of Carta et al. (2012) WD mimics parts of the etiology of bipolar disorder and MDD as seen in the common population (91). However, depression-like and psychosis resembling symptoms may be an overestimation, due to the fact that many reports were made by non-psychiatrists, which resulted in absent standardized diagnostic criteria and variable terminology (85).

Interestingly, a difference between men and women in prevalence of hepatic and neurological WD has been found. Although in both genders the neuropsychiatric variant of

WD is the most predominant, the hepatic variant occurs more frequently in women compared to men. Also, development from hepatic to neuropsychiatric WD is delayed in women by an average of 2 years compared to men. Moreover, male patients display more cerebellar atrophy and cortical brain atrophy, while lesions in the globus pallidus are more extensive in women (92). Consequently, the researchers hypothesize differences in estrogen and metal metabolism between women and men as a possible cause (93). However, the precise mechanism remains to be elucidated.

In general, psychiatric manifestations like depression, psychotic symptoms and personality changes are more often seen in patients who present themselves with neurological symptoms rather than in patients with solely hepatic pathology, indicating a multiphase disease progression from the liver (without psychiatric symptoms) spreading to other organs like the brain (with psychiatric involvement) (86, 89, 94). Biochemical markers in serum like copper (Cu) and ceruloplasmin (Cp) levels are comparable in hepatic WD and neurological WD (95). However, the presence of Kayser Fleischer rings, which are golden to greenish-brown rings that encircle the iris of the eye, are often only observed in patients with psychotic symptoms and personality changes. Consequently, the presence of Kayser Fleischer rings suggest that these copper deposits spread throughout the body and reflects the neurological form of WD. Due to the fact that patients often initially present with psychiatric symptoms and due to the lack of experience with WD by psychiatrists a delay in diagnosis of WD ranging from 1 to 5 years often is seen (85, 96). Between 14% and 20% of patients is initially seen by a psychiatrist before diagnosis of WD (95).

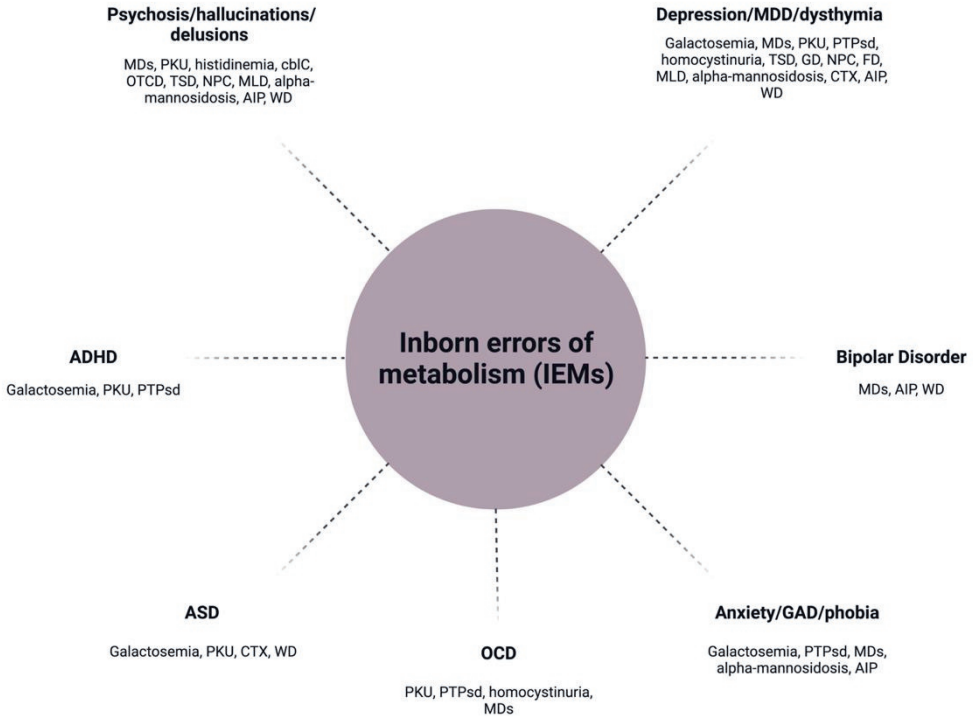


Figure 2 Overview of psychiatric manifestations of inborn errors of metabolism. MDs = mitochondrial disorders, PKU = phenylketonuria, cblC = cobalamin C disorder, OTCD = ornithine transcarbamylase deficiency, PTPsd = 6-pyruvoyl-tetrahydropterin synthase deficiecy, TSD = tay-sachs disease, GD = Gaucher disease, NPC = Niemann-Pick disease type C, FD = Fabry disease, MLD = metachromatic leukodystrophy, CTX = cerebrotendinous xanthomatosis, AIP = acute intermittent porphyria, WD = wilson's disease, MDD = major depressive disorder, GAD = generalized anxiety disorder, OCD = obsessive compulsive disorder, ASD = autism spectrum disorder, ADHD = attention deficit hyperactivity disorder.

Table 1 Included articles of this systematic review.

Author	Year	Type of study	IEM	Classification of IEM	Psychiatric manifestations	Red flags
Kuiper et al.	2019	Original study	Galactosemia	Disorders of carbohydrate metabolism	ASS, ADHD, depression, anxiety	n.a.
Inczedy-Farkas et al.	2012	Original study	Primary mutations of the mtDNA, including MELAS, MERFF and NARP	Mitochondrial disorders	MDD, bipolar disorder, dysthymia, postpartum depression, PTSS	n.a.
Mancusco et al.	2013	Original study	Mitochondrial myopathy, mitochondrial encephalomyopathy	Mitochondrial disorders	MDD, agoraphobia, panic disorder, anxiety disorder, psychosis, suicidal ideation, PTSS	n.a.
Fattal et al.	2007	Original study	MELAS, KSS, complex I and complex IV deficiency and mitochondrial cytopathy NOS and other MDs due to mtDNA mutations	Mitochondrial disorders	MDD, dysthymia, GAD, social phobia, OCD	Chronic fatigue, muscle weakness, muscle pain, muscle spasms
Kaufmann et al.	2009	Original study	MELAS	Mitochondrial disorders	Hallucinations, delusions, depression	Motor developmental delay, learning difficulties and memory deficits, exercise intolerance, loss of hearing, night blindness, gastrointestinal symptoms, growth failure, ptosis, hirsutism, limb weakness, loss of sensation, difficulty with balance, clumsiness, myoclonus, diabetes
Mancuso et al.	2008	Case series	No classified mutation	Mitochondrial disorders	Bipolar disorder, schizophrenia, nervous breakdowns, depression, insomnia, anhedonia, poor concentration, suicidal ideation	Low energy levels, mild exercise intolerance
Parikh et al.	2019	Original study	Mitochondrial myopathy, MELAS, CPEO, MERRF, KSS, LHON and other MDs due to nDNA mutations	Mitochondrial disorders	Depression, anxiety	Severe fatigue, sleepiness

Table 1 Continued

Koene et al.	2009	Original study	nDNA or mtDNA mutation	Mitochondrial disorders	MDD, psychotic depression	Chronic fatigue, ataxia, low IQ, intellectual disability
Morava et al.	2010	Original study	OXPHOS	Mitochondrial disorders	Depression, withdrawal	Muscle weakness, motor developmental delay
Anglin et al.	2012	Original study	MELAS, MERRF, CPEO, MNGIE, novel mtDNA mutations	Mitochondrial disorders	MDD, bipolar disorder, anxiety disorder, psychosis	Treatment resistance, adverse side effects
Steiner et al.	2003	Original study	Phenylketonuria	Disorders of protein metabolism	ASD	
Daelman et al.	2014	Case series	Phenylketonuria	Disorders of protein metabolism	Psychosis, auditory hallucinations, attention deficits, irritability, depression, anxiety	Intellectual disability, delay in speech, delay in walking
Fisch et al.	1995	Original study	Phenylketonuria	Disorders of protein metabolism	Depression, impulse control disorder, phobia, dysthymia	Low IQ
Koch et al.	2002	Original study	Phenylketonuria	Disorders of protein metabolism	Depression, impulse control disorder, phobia, dysthymia, hyperactivity, hypoactivity	Low IQ
Pietz et al.	1997	Original study	Phenylketonuria	Disorders of protein metabolism	Depression, phobia, generalized anxiety, hypochondriac worries	n.a.
Ris et al.	1997	Original study	Phenylketonuria	Disorders of protein metabolism	Obsessive compulsive behavior, psychoticism	Low IQ
Manti et al.	2020	Original study	6-Pyruvoyl-tetrahydropterin synthase deficiency	Disorders of protein metabolism	Anxiety disorder, sleep problems, depression, ADHD, OCD	Mild intellectual disability, movement disorder, seizures
Lucca et al.	1990	Original study	Histidinemia (heterozygous)	Disorders of protein metabolism	Schizophrenia	n.a.
Abbott et al.	1987	Original study	Homocystinuria	Disorders of protein metabolism	MDD, behavioral disorder, personality disorder, OCD	Low IQ

Table 1 Continued

Roze et al.	2003	Case series	Cobalamin C disorder	Vitamin metabolism disorders	Psychosis, visual hallucinations, auditory hallucinations	Cognitive impairment, neurological symptoms
Wang et al.	2018	Original study	Cobalamin C disorder	Vitamin metabolism disorders	Psychiatric disturbances	Cognitive impairment
Cavicchi et al.	2014	Original study	Ornithine transcarbamylase deficiency	Urea cycle disorders	Confusion, irritability, drowsiness, hallucinations, slurred speech	Vomiting
Josephs et al.	2003	Case series	Niemann-Pick disease type C	Lysosomal storage disorders	Depression, hypersomnolence, mood liability, delusions, hypervigilance, auditory hallucinations, paranoia, obsessive-like behavior, psychosis	Gait disorder, dysarthria, bradykinesia, memory deficits, tardive syndrome
Bauer et al.	2013	Original study	Niemann-Pick disease type C	Lysosomal storage disorders	Psychosis	Memory impairment, attention deficits, neurological symptoms
Koens et al.	2016	Original study	Niemann-Pick disease type C	Lysosomal storage disorders	Psychosis	Deficits in working memory, attention, verbal fluency and learning of verbal information
Walterfang et al.	2006	Case series	Niemann-Pick disease type C	Lysosomal storage disorders	Psychosis, behavioral disturbances	Cognitive decline, ataxic gat
Maubert et al.	2015	Case series	Niemann-Pick disease type C	Lysosomal storage disorders	Disorganized behavior, mood instability, wandering, hallucinations, acute delirium, suicidal ideation	Pyramidal symptoms, involuntary movements, gait symptoms
Maubert et al.	2016	Original study	Niemann-Pick disease type C	Lysosomal storage disorders	Psychosis, schizophrenia, depression, hallucinations, delusions, agitation, aggression, sleep problems, impulsiveness, apathy and psychomotor impairment	Neurological symptoms (not specified)

Table 1 Continued

Rozenberg et al.	2006	Original study	Tay-Sachs disease	Lysosomal storage disorders	Psychosis, hallucinations, anxiety, depression	Speech disarticulations during childhood, unsteady gait
Valstar et al.	2010	Original study	Mucopolysaccharidoses	Lysosomal storage disorders	Restlessness, aggressive and destructive behavior, sleep disturbances	Developmental delay, temper tantrums and emotional outbursts during childhood
Sigmundsdottir et al.	2014	Original study	Fabry disease	Lysosomal storage disorders	Depression, anxiety	Lower processing speed, decreased verbal fluency and problem-solving
Körver et al.	2019	Original study	Fabry disease	Lysosomal storage disorders	Depression	Lower processing speed
Sadek et al.	2004		Fabry disease	Lysosomal storage disorders	Depression, suicidal ideation	
Packman et al.	2006	Original study	Gaucher disease	Lysosomal storage disorders	Depression, schizophrenia, hysteria	Hepatosplenomegaly, enlarged abdomen, anemia and fatigue in only 3.6% patients
Beavan et al.	2015	Original study	Gaucher disease	Lysosomal storage disorders	Depression	
Wilke et al.	2019	Original study	Gaucher disease	Lysosomal storage disorders	Depression	Cognitive impairment, increased sleepiness
Baumann et al.	2002	Original study	Metachromatic leukodystrophy	Lysosomal storage disorders	Hallucinations, disorganized behavior, disinhibition, compulsive lying	Memory disfunction
Müller et al.	1969	Case series	Metachromatic leukodystrophy	Lysosomal storage disorders	Delusions, bizarre behavior	Memory deficits, disorientation, lack of concentration and critical thinking
Kumperscak et al.	2005	Case series	Metachromatic leukodystrophy	Lysosomal storage disorders	Disorganized schizophrenia postpartum, depression	Impairments in attention, executive functions, processing speed and intellectual disability
Malm et al.	2005	Original study	Alpha-mannosidosis	Lysosomal storage disorders	Depression, psychosis, anxiety, disturbed sleeping patterns	n.a.
Malm et al.	2014	Original study	Alpha-mannosidosis	Lysosomal storage disorders	Psychosis, confusion, depression, anxiety	Intellectual disability
Stelten et al.	2018	Original study	Cerebrotendinous xanthomatosis	Bile acid synthesis defects	ASD	Intellectual disability, diarrhea

Table 1 Continued

Yunisova et al.	2019	Original study	Cerebrotendinous xanthomatosis	Bile acid synthesis defects	Depression, ASD	n.a.
Cederlöf et al.	2015	Original study	Acute intermittent porphyria	Porphyrias	Schizophrenia, bipolar disorder	n.a.
Patience et al.	1994	Original study	Acute intermittent porphyria	Porphyrias	Anxiety disorders	Generalized anxiety
Elder et al.	1997	Review	Acute intermittent porphyria	Porphyrias	Anxiety, depression	Acute onset abdominal symptoms, onset symptoms after physical exercise
Akil et al.	1995	Case series	Wilson's disease	Mineral and metal metabolism disorders	Depression	Organic dementia, neurosis, psychosis, impulsivity, catatonia, sexual preoccupation
Akil et al.	1991	Case series	Wilson's disease	Mineral and metal metabolism disorders	Depression	Personality changes, catatonia
Bem et al.	2011	Case series	Wilson's disease	Mineral and metal metabolism disorders	Neuropsychiatric symptoms (unspecified)	Cerebellar syndrome, Kaiser Fleischer rings, tremor, dysarthria, dystonia, jaundice, portal hypertension, high digestive hemorrhage, skin hyperpigmentation
Demily et al.	2017	Original study	Wilson's disease	Mineral and metal metabolism disorders	Schizophrenia, bipolar disorder, alcohol abuse, depression, anxiety disorder, behavioral disorder, personality disorder, autism spectrum disorder, anorexia nervosa, cannabis addiction	Intellectual disability, miscellaneous neurological disorder, extrapyramidal syndrome, MRI abnormalities in basal ganglia
Parker et al.	1985	Case series	Wilson's disease	Mineral and metal metabolism disorders	Psychosis	Intellectual impairment, whispering dysphonia
Dening et al.	1989	Case series	Wilson's disease	Mineral and metal metabolism disorders	Depression	Personality change, cognitive impairment, dystonic disorders
Srinivas et al.	2008	Case series	Wilson's disease	Mineral and metal metabolism disorders	Depression	Family history of WD, jaundice, Kaiser Fleischer rings,

Table 1 Continued

Carta et al.	2012	Original study	Wilson's disease	Mineral and metal metabolism disorders	Bipolar disorder, depression	Mania/hyperactivity as initial manifestation, tremors of upper limbs, loss of sexual inhibition, catatonia, Kaiser Fleischer rings
Litwin et al.	2012	Original study (case control)	Wilson's disease	Mineral and metal metabolism disorders	Mood disorders, anxiety	Tremors, rigidity, dystonia
Shanmugiah et al.	2008	Original study	Wilson's disease	Mineral and metal metabolism disorders	Bipolar disorder, depression	Excessive talkativeness aggressive behavior, dystonia, tremors, Kaiser Fleischer rings, speech disturbances, drooling
Litwin et al.	2013	Original study	Wilson's disease	Mineral and metal metabolism disorders	Anxiety, mood disorders	Cognitive impairment, seizures, involuntary movements, writing and gait disturbances, salivation, adynamia
Soltanzadeh et al.	2007	Original study	Wilson's disease	Mineral and metal metabolism disorders	Depression, psychosis	Dysarthria, salivation, movement disorders, Kaiser Fleischer rings

MDD = major depressive disorder, GAD = generalized anxiety disorder, OCD = obsessive compulsive disorder, ASD = autism spectrum disorder, AHDH = attention deficit hyperactivity disorder.

DISCUSSION

In this review we have aimed at systematically exploring the relationship between IEMs and psychopathological symptoms and psychiatric diagnoses. The results of our review indicate that a wide range of psychiatric symptoms and disorders occur in patients with an IEM, which represent the spectrum of psychiatric disorders in general (see Figure 2). Depression and anxiety were the most commonly described symptoms in patients with both a psychiatric disorder and an underlying IEM. Depression was observed in case of galactosemia, mitochondrial disorders, PKU, PTPsd, homocystinuria, TSD, GD, NPC, FD, MLD, alpha-mannosidosis, CTX, AIP and WD. In addition to depression, hallucinations, delusions or psychosis were described as part of the psychiatric manifestation in case of mitochondrial disorders, PKU, TSD, NPC, MLD, alpha-mannosidosis, AIP and WD as well. In some IEMs, only depression and anxiety were observed. Additionally, psychotic symptoms including hallucinations and delusions without the occurrence of depression and anxiety were observed in some cases of cblC and OTCD. Generally, it is assumed that visual hallucinations, olfactory, gustatory and somatosensory hallucinations, more than auditory hallucinations, are prominent in organic disease (98-100). Unfortunately, we were unable to investigate this assumption in the current review, because the included studies of this review often did not specify subtypes of hallucination. This review also demonstrates the overall paucity of research on psychiatric manifestations associated with IEMs and the need for future studies.

Moreover, the cross-sectional design of most reports in this qualitative review did mostly not allow to determine whether the clinical manifestation was intrinsic or secondary to the IEM, as these patients usually experience a lower quality of life and daily functioning may be affected negatively. Patients often experience job loss, divorce or a limitation of family size due to their disease. However, there are several exceptions suggesting that causal inferences can only be made to a certain extent. In MDs the severity or progression of the MD was not correlated with the psychiatric symptoms, which led to the suggestion that psychiatric manifestations may actually be intrinsic to the manifestation of the IEM (16). A similar suggestion in AIP was done by Millward et al. (2005), who concluded that the anxiety symptoms found in patients with AIP were a 'relative stable personality trait' rather than a 'transitory emotional state', indicating that this anxiety is more likely the result of the pathologic processes of AIP than reactive to living with the disease (80). To provide more insight into this matter, future research should possibly focus on including longitudinal prospective cohorts such as the Maastricht study or Lifelines (101, 102). By executing genetic screening for IEMs such as Next Generation Sequencing (NGS) and implementing standardized scales and descriptions in such a large population, one might be able to

compare the incidence of psychiatric symptoms in healthy individuals (without an IEM and/or psychiatric manifestations), with the incidence of psychiatric symptoms in patients with an IEM that are not yet aware of their underlying disorder and the incidence of psychiatric symptoms in patients with a diagnosis of an IEM over time.

Unfortunately, although we have included only reports that used some form of standardized scales and descriptions, the clinical psychiatric descriptions were still imprecise and psychiatric assessments were often not specified. This is likely due to the fact that psychiatric assessment was generally not part of routine clinical diagnostics in most studies. As a consequence of not using standard interviews to assess the whole range of psychiatric conditions, a reporting bias with respect to psychiatric diagnoses might have occurred. Consequently, only the most commonly occurring or the most disturbing diagnoses might have been recognized, but others might have been overlooked.

One of the aims of this review was to identify "red flags" that might alert clinicians of the potential presence of an IEM underlying the psychiatric condition of their patients. We assigned the label "red flag" to those symptoms and/or conditions present in most IEM reports. A so-called "red flag", as supported by the described literature in this review, includes a state of confusion and a deterioration in cognitive functioning. Although -to a lesser degree- cognitive deficits are described in patients with a non-organic psychotic disorder as well (103, 104), progressive memory impairment and attention deficits that deteriorate strongly, should alert to a suspicion of an IEM (105). These deficits are sometimes only noticed later in life due to deteriorating performance within academia or at work and are often mistaken as a symptom of depression rather than a symptom of an IEM. A second "red flag" entails developmental delay or intellectual disability, especially in combination with an onset of behavioral problems during childhood. Sometimes, interrogating retrospectively on biographical aspects of IEM patients, developmental delay was indeed often observed during childhood. Often, in case of an IEM, children start out with a normal developmental course with respect to acquired milestones, followed by a loss of developmental milestones while growing up. Especially when developmental delay is associated with onset of irritability, impulsivity, hyperactivity and aggression, screening for an IEM should be part of diagnostics. The typical combination of this development delay and the occurrence of behavioral problems during childhood is often described in mucopolysaccharidoses and other lysosomal storage disorders, PKU and galactosemia (106). The current review confirms this observation for MPS (60), in which patients retrospectively indeed showed both developmental delay and behavioral problems during childhood. Behavioral problems included restlessness, aggressive and destructive behavior, temper tantrums and emotional outbursts (60). A high incidence of developmental delay

and intellectual disability in combination with an onset of psychiatric symptoms was also found in other IEMs including PKU, PTPSd, alpha-mannosidosis and to a lesser extent in case of MDs in which psychiatric symptoms manifested during adolescence or adulthood (21, 29-34, 36, 75). In case of PKU, development delay and intellectual disability during childhood was often followed by increased anxiety, depression, psychosis and attention deficits later in life (29-34). A similar observation was done in case of alpha-mannosidosis (75). Unfortunately, some reports regarding cognitive deficits, developmental delay and intellectual disability of the current review are inconclusive, because they might not have been recognized during childhood and were first diagnosed at the onset of the psychiatric manifestations (71, 75).

Another potential "red flag" that has not been the subject of this review, entails the occurrence of motor symptoms and movement disorders in IEMs within the scope of neurological abnormalities. Although tremor, involuntary muscle contractions and psychomotor slowing are examples of motor symptoms that can also be observed in patients with a psychiatric disorder, mostly as a consequence of psychopharmaca use (107-109), they can be prominent in patients with an IEM (2, 110). For example, these motor symptoms have been described in galactosemia, NPC and WD (13, 87, 92, 111). Especially when no psychopharmaca have been prescribed, these symptoms can be considered as red flags.

Further, although not a primary aim of our review, in MDs we found a clear association between psychiatric manifestations such as psychosis, depression and anxiety, and the occurrence of mild exercise intolerance (19). Although severe chronic fatigue, sleepiness and muscle weakness were described in patients with a MD as well (17, 21), mild exercise intolerance can be considered as a "red flag", but may be missed when not specifically investigated during psychiatric assessment. Another IEM that is associated with acute psychiatric symptoms in combination with physical activity, is acute intermittent porphyria (112). However, in contrast with MDs, a porphyria attack is triggered by physical strain or intense physical exercise. Therefore, when psychiatric symptoms are present during or after (intense) physical activity, this should also raise the suspicion of psychiatric manifestations due to an IEM.

A final "red flag", although, again, not the primary aim of this review, encompasses the onset or occurrence of gastro-intestinal symptoms such as diarrhea, vomiting, abdominal pain or exercise intolerance in addition to psychiatric manifestations of IEMs. Gastrointestinal symptoms such as abdominal pain, nausea and vomiting may be present alongside psychiatric symptoms. This is especially the case for porphyria, and has been described

extensively in the literature (113-116). What is more, our results showed that vomiting has also been described in patients with late-onset OTCD (113), a urea cycle disorder. This is in line with previous research, which showed that nausea and vomiting are often observed in patients with urea cycle disorders (113, 117). Therefore, the combination of atypical psychiatric symptomology with gastro-intestinal symptoms may be the key to recognize and differentiate a psychiatric disorder that is the result of an underlying IEM from primary psychiatric disorders (see Table 3). An additional help to suspect an IEM may be the failure to establish a gastro-intestinal diagnosis after ultrasound, CT, endoscopies and blood analysis in patients with gastrointestinal and abdominal symptoms. Often, in these patients an incorrect diagnosis of a functional disorder, a personality disorder, bipolar disorder or syndrome of Münchausen is established (2).

Screening tool for psychiatrists

Recognizing IEMs in patients with a psychiatric disorder may be complex, especially when they display isolated psychiatric symptoms or show no somatic symptomology. However, when (atypical) psychiatric symptoms occur especially when no clear environmental stressors have preceded the onset of psychiatric symptoms, combined with neurological symptoms and a developmental delay or cognitive deficits after initial normal development, an IEM should be considered. To give insight in and help to establish the appropriate diagnostic procedure and follow-up, we have developed a diagnostic screener based on the results of this study (see Figure 3). This screener may help psychiatrists to systematically assess the different clinical manifestations that raise the suspicion of an IEM and to help psychiatrists or any other clinician in this difficult diagnostic process.

Clinical relevance

When red flags are present it is important to test for an IEM because some IEMs can be treated by a diet or supplementation of specific vitamins and therefore, reduce the risk of serious complications and further deterioration of the patient. For example, in PKU and homocystinuria patients, a diet low in phenylalanine and supplementation of vitamin B6, B9 and B12 respectively, or a diet low in methionine (if patients do not respond to supplementation with vitamin B6, B9 and B12) are part of the treatment possibilities (118, 119). In case of AIP, treatment consists of alteration in lifestyle and stress reduction, as several lifestyle factors such as alcohol and drug use and carbohydrate intake/fasting, alongside physical or psychological stress, can significantly increase the risk of provoking an attack (81). Additionally, treatment is most effective when IEMs are diagnosed early in disease development (120). In case the IEM is not treatable, it is still important to diagnose patients as soon as possible, because it aids patients and family members in relieving guilt and shame of having a psychiatric disorder, it helps in decision making with respect to future

family planning in relation to genetic IEM-related issues, and finally patients and their family members could benefit from psychiatric or psychological help in dealing with the IEM and/or the psychiatric manifestations that are caused by the IEM. Additionally, by diagnosing patients with an IEM, treatable or untreatable, family members may want to know whether they are a carrier and how this IEM may affect their (future) lives as well.

Strengths and limitations

A strength of the current research is its extensive search within multiple databases and the inclusions of several types of IEMs. Additionally, we tried to strengthen the validity of our findings by only including report that have used some form of systematic testing (by using standard self-reports or assessment interviews) of the psychopathology. Further, a broad range of psychiatric manifestations was included, as this review was not limited to one type of IEM or a specific psychiatric manifestation. However, we also note that this review comes with some limitations. A risk of publication bias cannot be ruled out, as this review only included published, peer-reviewed studies retrieved from different databases, and as a limited number of databases was used to search for literature (e.g. Pubmed and Embase). However, we included the references of reviews to check whether literature was missing, trying to limit the risk of publication bias. Moreover, only studies in English were included, which may increase the chance of reporting bias. Finally, the quality of the included studies overall was variable, with a number of studies being cross-sectional only, with limited structured assessment of psychopathology, and often missing a control group.

Future research and recommendations

Considering the high prevalence of psychiatric symptoms and disorders that onset in adolescence and adulthood across the whole range of IEMs, in our opinion psychiatric assessments and clinical scales should be standardly incorporated in the diagnostic procedures of potential IEM patients. This would in the future enable appropriate comparisons across all available research. Furthermore, future research should focus on investigating the proposed screener (see Figure 3) with respect to its reliability and usability. Moreover, another suggestion for raising more awareness for psychiatric manifestations as a result of IEMs would be to include this topic within psychiatric training. Ideally this would take place as part of the specialized psychiatric training, by incorporating the psychiatric manifestations of IEMs within lectures, seminars and case-based learning. Additionally, we propose joint specialized IEM clinics between departments of psychiatry, neurology, pediatrics and internal medicine to enable assessment of the whole clinical phenotype if IEMs. So for example, psychiatrists sit in clinics with internal medicine specialists to screen for psychopathology, and vice versa, somatic specialists advise psychiatrists on suspected cases of IEMs. Dietitians specialized in IEMs may be part of this joint clinic, to help patients

with adaptations in their diet and maintain a healthy lifestyle and prevent deficiencies in patients with an IEM. Finally, occupational therapy may be another field that could be beneficial within these joint clinics, to help patients with an IEM maintaining their work and daily occupations as much as possible. In this way, patients can be referred by general practitioners and other clinicians for both diagnosis and treatment. These clinics could also act as a consultation center for clinicians who see patients with the described red flags and are unsure what the next step would be, regarding both diagnosis and treatment. Additionally, these joint clinics may act as an educational center for psychiatrists in training. If a mandatory internship as part of the psychiatric training could be established, future psychiatrists may be more aware about the diversity of the psychiatric manifestations of IEMs and what is necessary in order to efficiently diagnose patients and provide the appropriate treatment. Taken together, this will help closing the current knowledge-practice gap by raising awareness for psychiatric manifestations of IEMs, prevent diagnostic delay and improve the possibility for appropriate treatment for patients suffering from IEMs.

With respect to the question on common etiologies between psychiatric manifestations and IEMs, future genetic studies might focus on commonalities between the two. Therefore, a final recommendation for the future, besides the use of the proposed screener, would be to implement genetic screening, including NGS panels, within routine clinical diagnostics. Although NGS is still mostly used within research (121-123) and the high costs are still a limitation for implementing this technique within routine clinical diagnostics, the possibility to test for IEMs in screen-positive cases with only one blood sample in combination with thorough psychiatric assessment and standardized clinical scales could further help clinicians to establish the appropriate diagnosis in a much faster and less invasive manner.

Table 2 Red flags for an underlying IEM within the psychiatric field.

Red flags	Examples
Atypical psychotic symptoms	Visual hallucinations, confusion, acute onset, treatment resistance, unusual or severe side effects of a psychotropic drug
Atypical depression with psychotic symptoms	Visual hallucinations, confusion, acute onset, treatment resistance, unusual or severe side effects of a psychotropic drug
Strong and/or progressive cognitive decline	
Motor symptoms	Tremor, involuntary movements, involuntary muscle contractions or spasms
Intellectual disability	
Gastrointestinal and abdominal symptoms	Vomiting, diarrhea, (acute) abdominal pain
Exercise intolerance	Unusual or severe muscle cramps, fatigue and/or tenderness, nausea and/or vomiting after exercise and rapid loss of breath and/or insufficient heart rate during exercise

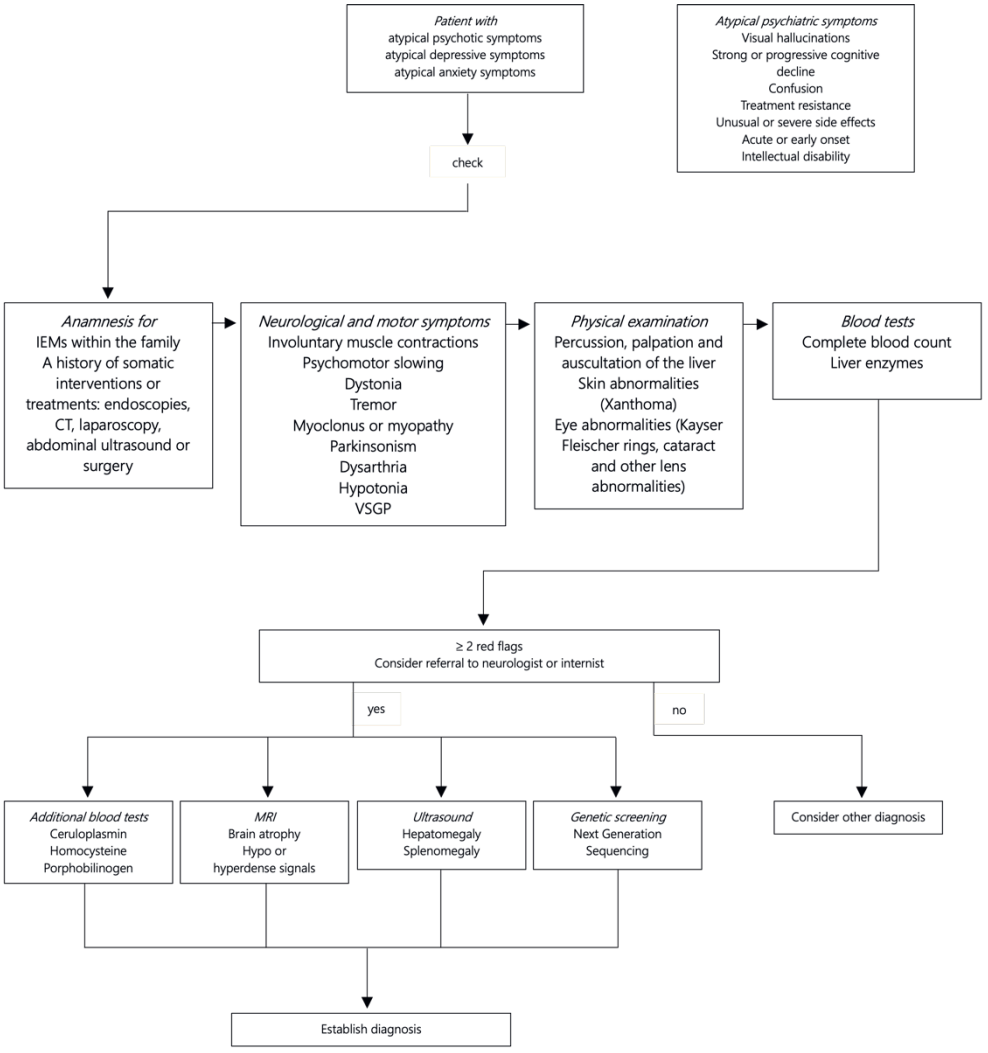


Figure 2 Diagnostic screener for psychiatrists.

CONCLUSION

Psychiatric symptoms are an important component of many IEMs, however, standardized clinical scales and psychiatric assessments are still largely lacking in recently published literature. Clinicians within the psychiatric field should be aware of the possibility that (atypical) psychiatric manifestations and treatment resistance might reflect underlying IEMs. We aimed to give an overview of the psychiatric manifestations of IEMs and to propose a screening tool for clinicians (see Figure 3). This screening tool may help to ask the right questions during anamnesis, look for specific symptoms during a physical examination and/or to refer to the appropriate field to confirm diagnosis and appropriate treatment. Additionally, multidisciplinary IEM clinics are recommended.

REFERENCES

1. Saudubray JM, Garcia-Cazorla A. Inborn Errors of Metabolism Overview: Pathophysiology, Manifestations, Evaluation, and Management. Pediatr Clin North Am. 2018;65(2):179-208.
2. Walterfang M, Bonnot O, Mocellin R, Velakoulis D. The neuropsychiatry of inborn errors of metabolism. J Inherit Metab Dis. 2013;36(4):687-702.
3. Pampols T. Inherited metabolic rare disease. Adv Exp Med Biol. 2010;686:397-431.
4. Ahrens-Nicklas RC, Slap G, Ficicioglu C. Adolescent presentations of inborn errors of metabolism. J Adolesc Health. 2015;56(5):477-82.
5. Gambello MJ, Li H. Current strategies for the treatment of inborn errors of metabolism. J Genet Genomics. 2018;45(2):61-70.
6. Mak CM, Lee HC, Chan AY, Lam CW. Inborn errors of metabolism and expanded newborn screening: review and update. Crit Rev Clin Lab Sci. 2013;50(6):142-62.
7. Nia S. Psychiatric signs and symptoms in treatable inborn errors of metabolism. Journal of Neurology. 2014;261(SUPPL. 2):559-68.
8. Sedel F, Baumann N, Turpin JC, Lyon-Caen O, Saudubray JM, Cohen D. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J Inherit Metab Dis. 2007;30(5):631-41.
9. Bonnot O, Klunemann HH, Sedel F, Tordjman S, Cohen D, Walterfang M. Diagnostic and treatment implications of psychosis secondary to treatable metabolic disorders in adults: a systematic review. Orphanet journal of rare diseases. 2014;9:65.
10. Mak CM, Law EC, Lee HH, Siu WK, Chow KM, Au Yeung SK, et al. The first pilot study of expanded newborn screening for inborn errors of metabolism and survey of related knowledge and opinions of health care professionals in Hong Kong. Hong Kong medical journal = Xianggang yi xue za zhi. 2018;24(3):226-37.
11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PloS Med. 2009;6(7).
12. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak. 2007;7:16.
13. Kuiper A, Grunewald S, Murphy E, Coenen MA, Eggink H, Zutt R, et al. Movement disorders and nonmotor neuropsychological symptoms in children and adults with classical galactosemia. J Inherit Metab Dis. 2019;42(3):451-8.
14. Waisbren SE, Potter NL, Gordon CM, Green RC, Greenstein P, Gubbels CS, et al. The adult galactosemic phenotype. Journal of inherited metabolic disease. 2012;35(2):279-86.
15. Inczedy-Farkas G, Remenyi V, Gal A, Varga Z, Balla P, Udvardy-Meszaros A, et al. Psychiatric symptoms of patients with primary mitochondrial DNA disorders. Behavioral and brain functions : BBF. 2012;8:9.
16. Mancuso M, Orsucci D, Ienco EC, Pini E, Choub A, Siciliano G. Psychiatric involvement in adult patients with mitochondrial disease. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2013;34(1):71-4.
17. Fattal O, Link J, Quinn K, Cohen BH, Franco K. Psychiatric comorbidity in 36 adults with mitochondrial cytopathies. CNS Spectr. 2007;12(6):429-38.
18. Kaufmann P, Engelstad K, Wei Y, Kulikova R, Oskoui M, Battista V, et al. Protean phenotypic features of the A3243G mitochondrial DNA mutation. Arch Neurol. 2009;66(1):85-91.
19. Mancuso M, Ricci G, Choub A, Filosto M, DiMauro S, Davidzon G, et al. Autosomal

dominant psychiatric disorders and mitochondrial DNA multiple deletions: report of a family. Journal of affective disorders. 2008;106(1-2):173-7.
20. Parikh S, Galioto R, Lapin B, Haas R, Hirano M, Koenig MK, et al. Fatigue in primary genetic mitochondrial disease: No rest for the weary. Neuromuscular Disorders. 2019;29(11):895-902.
21. Koene S, Kozicz TL, Rodenburg RJT, Verhaak CM, de Vries MC, Wortmann S, et al. Major depression in adolescent children consecutively diagnosed with mitochondrial disorder. Journal of affective disorders. 2009;114(1-3):327-32.
22. Morava E, Gardeitchik T, Kozicz T, de Boer L, Koene S, de Vries MC, et al. Depressive behaviour in children diagnosed with a mitochondrial disorder. Mitochondrion. 2010;10(5):528-33.
23. Rosebush PI, Anglin RE, Rasmussen S, Mazurek MF. Mental illness in patients with inherited mitochondrial disorders. Schizophr Res. 2017;187:33-7.
24. Anglin RE, Tarnopolsky MA, Mazurek MF, Rosebush PI. The psychiatric presentation of mitochondrial disorders in adults. The Journal of neuropsychiatry and clinical neurosciences. 2012;24(4):394-409.
25. Azevedo H, Pupe C, Pereira R, Nascimento OJM. Pain in Charcot-Marie-Tooth disease: an update. Arq Neuropsiquiatr. 2018;76(4):273-6.
26. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 4-57.
27. Williams RA, Mamotte CD, Burnett JR. Phenylketonuria: an inborn error of phenylalanine metabolism. Clin Biochem Rev. 2008;29(1):31-41.
28. Surtees R, Blau N. The neurochemistry of phenylketonuria. Eur J Pediatr. 2000;159 Suppl 2:S109-13.
29. Steiner CE, Guerreiro MM, Marques-de-Faria AP. Genetic and neurological evaluation in a sample of individuals with pervasive developmental disorders. Arquivos de neuro-psiquiatria. 2003;61(2a):176-80.
30. Daelman L, Sedel F, Tourbah A. Progressive neuropsychiatric manifestations of phenylketonuria in adulthood. Revue neurologique. 2014;170(4):280-7.
31. Fisch RO, Chang PN, Weisberg S, Guldberg P, Guttler F, Tsai MY. Phenylketonuric patients decades after diet. Journal of inherited metabolic disease. 1995;18(3):347-53.
32. Koch R, Burton B, Hoganson G, Peterson R, Rhead W, Rouse B, et al. Phenylketonuria in adulthood: A collaborative study. Journal of inherited metabolic disease. 2002;25(5):333-46.
33. Pietz J, Fatkenheuer B, Burgard P, Armbruster M, Esser G, Schmidt H. Psychiatric disorders in adult patients with early-treated phenylketonuria. Pediatrics. 1997;99(3):345-50.
34. Ris MD, Weber AM, Hunt MM, Berry HK, Williams SE, Leslie N. Adult psychosocial outcome in early-treated phenylketonuria. Journal of Inherited Metabolic Disease : Official Journal of the Society for the Study of Inborn Errors of Metabolism. 1997;20(4):499-508.
35. Opladen T, Hoffmann GF, Blau N. An international survey of patients with tetrahydrobiopterin deficiencies presenting with hyperphenylalaninaemia. J Inherit Metab Dis. 2012;35(6):963-73.
36. Manti F, Nardecchia F, Banderali G, Burlina A, Carducci C, Donati MA, et al. Long-term clinical outcome of 6-pyruvoyl-tetrahydropterin synthase-deficient patients. Molecular Genetics and Metabolism. 2020;131(1-2):155-62.
37. La Du BN, Howell RR, Jacoby GA, Seegmiller JE, Zannoni VG. The enzymatic defect in histidinemia. Biochem Biophys Res Commun. 1962;7:398-402.

38. Lucca A, Catalano M, Valsasina R, Fara C, Smeraldi E. Biochemical investigation of histidinemia in schizophrenic patients. Biological psychiatry. 1990;27(1):69-75.
39. Abbott MH, Folstein SE, Abbey H, Pyeritz RE. Psychiatric manifestations of homocystinuria due to cystathionine beta-synthase deficiency: prevalence, natural history, and relationship to neurologic impairment and vitamin B6-responsiveness. American journal of medical genetics. 1987;26(4):959-69.
40. Rosenblatt DS, Cooper BA. Inherited disorders of vitamin B12 metabolism. Blood Rev. 1987;1(3):177-82.
41. Huemer M, Scholl-Burgi S, Hadaya K, Kern I, Beer R, Seppi K, et al. Three new cases of late-onset cblC defect and review of the literature illustrating when to consider inborn errors of metabolism beyond infancy. Orphanet J Rare Dis. 2014;9:161.
42. Rosenblatt DS, Aspler AL, Shevell MI, Pletcher BA, Fenton WA, Seashore MR. Clinical heterogeneity and prognosis in combined methylmalonic aciduria and homocystinuria (cblC). J Inherit Metab Dis. 1997;20(4):528-38.
43. Roze E, Gervais D, Demeret S, Ogier de Baulny H, Zittoun J, Benoist JF, et al. Neuropsychiatric disturbances in presumed late-onset cobalamin C disease. Archives of neurology. 2003;60(10):1457-62.
44. Wang SJ, Yan CZ, Liu YM, Zhao YY. Late-onset cobalamin C deficiency Chinese sibling patients with neuropsychiatric presentations. Metab Brain Dis. 2018;33(3):829-35.
45. Walker V. Ammonia metabolism and hyperammonemic disorders. Adv Clin Chem. 2014;67:73-150.
46. Gyato K, Wray J, Huang ZJ, Yudkoff M, Batshaw ML. Metabolic and neuropsychological phenotype in women heterozygous for ornithine transcarbamylase deficiency. Annals of neurology. 2004;55(1):80-6.
47. Feighner JP, Robins E, Guze SB, Woodruff RAJ, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry. 1972;26(1):57-63.
48. Rajkumar V, Dumpa V. Lysosomal Storage Disease. StatPearls. Treasure Island (FL)2022.
49. Vanier MT. Lipid changes in Niemann-Pick disease type C brain: personal experience and review of the literature. Neurochem Res. 1999;24(4):481-9.
50. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010;5:16.
51. Josephs KA, Van Gerpen MW, Van Gerpen JA. Adult onset Niemann-Pick disease type C presenting with psychosis. Journal of neurology, neurosurgery, and psychiatry. 2003;74(4):528-9.
52. Bauer P, Balding DJ, Klunemann HH, Linden DE, Ory DS, Pineda M, et al. Genetic screening for Niemann-Pick disease type C in adults with neurological and psychiatric symptoms: findings from the ZOOM study. Human molecular genetics. 2013;22(21):4349-56.
53. Koens LH, Kuiper A, Coenen MA, Elting JW, de Vries JJ, Engelen M, et al. Ataxia, dystonia and myoclonus in adult patients with Niemann-Pick type C. Orphanet journal of rare diseases. 2016;11(1):121.
54. Walterfang M, Fietz M, Fahey M, Sullivan D, Leane P, Lubman DI, et al. The neuropsychiatry of Niemann-Pick type C disease in adulthood. The Journal of neuropsychiatry and clinical neurosciences. 2006;18(2):158-70.
55. Maubert A, Hanon C, Metton JP. [Niemann-Pick type C disease and psychosis: Two siblings]. Encephale. 2015;41(3):238-43.
56. Maubert A, Hanon C, Sedel F. [Psychiatric disorders in adult form of Niemann-Pick disease type C]. Encephale. 2016;42(3):208-13.
57. Sipione S, Monyror J, Galleguillos D, Steinberg N, Kadam V. Gangliosides in the Brain: Physiology, Pathophysiology and Therapeutic Applications. Front Neurosci. 2020;14:572965.
58. Rozenberg R, Kok F, Burin MG, Sa Miranda MC, Vasques C, Henriques-Souza AM, et al. Diagnosis and molecular characterization of

non-classic forms of Tay-Sachs disease in Brazil. Journal of child neurology. 2006;21(6):540-4.
59. Valstar MJ, Bruggenwirth HT, Olmer R, Wevers RA, Verheijen FW, Poorthuis BJ, et al. Mucopolysaccharidosis type IIIB may predominantly present with an attenuated clinical phenotype. Journal of inherited metabolic disease. 2010;33(6):759-67.
60. Korver S, Geurtsen GJ, Hollak CEM, van Schaik IN, Longo MGF, Lima MR, et al. Predictors of objective cognitive impairment and subjective cognitive complaints in patients with Fabry disease. Sci Rep. 2019;9(1):188.
61. Sigmundsdottir L, Tchan MC, Knopman AA, Menzies GC, Batchelor J, Sillence DO. Cognitive and psychological functioning in Fabry disease. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists. 2014;29(7):642-50.
62. Sadek J, Shellhaas R, Camfield CS, Camfield PR, Burley J. Psychiatric findings in four female carriers of Fabry disease. Psychiatric genetics. 2004;14(4):199-201.
63. Guggenbuhl P, Grosbois B, Chales G. Gaucher disease. Joint Bone Spine. 2008;75(2):116-24.
64. Packman W, Crosbie TW, Riesner A, Fairley C, Packman S. Psychological complications of patients with Gaucher disease. Journal of inherited metabolic disease. 2006;29(1):99-105.
65. Beavan M, McNeill A, Proukakis C, Hughes DA, Mehta A, Schapira AH. Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. JAMA neurology. 2015;72(2):201-8.
66. Wilke M, Dornelles AD, Schuh AS, Vairo FP, Basgalupp SP, Siebert M, et al. Evaluation of the frequency of non-motor symptoms of Parkinson's disease in adult patients with Gaucher disease type 1. Orphanet J Rare Dis. 2019;14(1):103.
67. Gieselmann V, Krageloh-Mann I. Metachromatic leukodystrophy--an update. Neuropediatrics. 2010;41(1):1-6.
68. Baumann N, Turpin JC, Lefevre M, Colsch B. Motor and psycho-cognitive clinical types in adult metachromatic leukodystrophy: genotype/phenotype relationships? Journal of physiology, Paris. 2002;96(3-4):301-6.
69. Müller D, Pilz H, ter Meulen V. Studies on adult metachromatic leukodystrophy. 1. Clinical, morphological and histochemical observations in two cases. Journal of the neurological sciences. 1969;9(3):567-84.
70. Kumperscak HG, Paschke E, Gradisnik P, Vidmar J, Bradac SU. Adult metachromatic leukodystrophy: disorganized schizophrenia-like symptoms and postpartum depression in 2 sisters. Journal of psychiatry & neuroscience : JPN. 2005;30(1):33-6.
71. Desnick RJ, Sharp HL, Grabowski GA, Brunning RD, Quie PG, Sung JH, et al. Mannosidosis: clinical, morphologic, immunologic, and biochemical studies. Pediatr Res. 1976;10(12):985-96.
72. Malm D, Nilssen O. Alpha-mannosidosis. Orphanet journal of rare diseases. 2008;3:21.
73. Malm D, Pantel J, Linaker OM. Psychiatric symptoms in alpha-mannosidosis. Journal of intellectual disability research : JIDR. 2005;49(Pt 11):865-71.
74. Malm D, Riise Stensland HM, Edvardsen O, Nilssen O. The natural course and complications of alpha-mannosidosis--a retrospective and descriptive study. Journal of inherited metabolic disease. 2014;37(1):79-82.
75. Stelten BML, Bonnot O, Huidekoper HH, van Spronsen FJ, van Hasselt PM, Kluijtmans LAJ, et al. Autism spectrum disorder: an early and frequent feature in cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2018;41(4):641-6.
76. Yunisova G, Tufekcioglu Z, Dogu O, Bilgic B, Kaleagasi H, Akca Kalem S, et al. Patients with Lately Diagnosed Cerebrotendinous Xanthomatosis. Neurodegener Dis. 2019;19(5-6):218-24.
77. Stelten BML, Bonnot O, Huidekoper HH, van Spronsen FJ, van Hasselt PM, Kluijtmans

LAJ, et al. Autism spectrum disorder: an early and frequent feature in cerebrotendinous xanthomatosis. Journal of inherited metabolic disease. 2018;41(4):641-6.
78. Cross TN. Porphyria; a deceptive syndrome. The American journal of psychiatry. 1956;112(12):1010-4.
79. Millward LM, Kelly P, King A, Peters TJ. Anxiety and depression in the acute porphyrias. Journal of inherited metabolic disease. 2005;28(6):1099-107.
80. Millward LM, Kelly P, Deacon A, Senior V, Peters TJ. Self-rated psychosocial consequences and quality of life in the acute porphyrias. Journal of inherited metabolic disease. 2001;24(7):733-47.
81. Patience DA, Blackwood DH, McColl KE, Moore MR. Acute intermittent porphyria and mental illness--a family study. Acta psychiatrica Scandinavica. 1994;89(4):262-7.
82. Cederlof M, Bergen SE, Larsson H, Landen M, Lichtenstein P. Acute intermittent porphyria: comorbidity and shared familial risks with schizophrenia and bipolar disorder in Sweden. The British journal of psychiatry : the journal of mental science. 2015;207(6):556-7.
83. Elder GH, Hift RJ, Meissner PN. The acute porphyrias. Lancet. 1997;349(9065):1613-7.
84. Bem RS, Muzzillo DA, Deguti MM, Barbosa ER, Werneck LC, Teive HA. Wilson's disease in southern Brazil: a 40-year follow-up study. Clinics (Sao Paulo, Brazil). 2011;66(3):411-6.
85. Akil M, Brewer GJ. Psychiatric and behavioral abnormalities in Wilson's disease. Advances in neurology. 1995;65:171-8.
86. Akil M, Schwartz JA, Dutchak D, Yuzbasiyan-Gurkan V, Brewer GJ. The psychiatric presentations of Wilson's disease. The Journal of neuropsychiatry and clinical neurosciences. 1991;3(4):377-82.
87. Demily C, Parant F, Cheillan D, Broussolle E, Pavec A, Guillaud O, et al. Screening of Wilson's disease in a psychiatric population: difficulties and pitfalls. A preliminary study. Ann Gen Psychiatry. 2017;16:19.
88. Parker N. Hereditary whispering dysphonia. Journal of neurology, neurosurgery, and psychiatry. 1985;48(3):218-24.
89. Dening TR, Berrios GE. Wilson's disease: a prospective study of psychopathology in 31 cases. The British journal of psychiatry : the journal of mental science. 1989;155:206-13.
90. Srinivas K, Sinha S, Taly AB, Prashanth LK, Arunodaya GR, Janardhana Reddy YC, et al. Dominant psychiatric manifestations in Wilson's disease: a diagnostic and therapeutic challenge! Journal of the neurological sciences. 2008;266(1-2):104-8.
91. Carta MG, Sorbello O, Moro MF, Bhat KM, Demelia E, Serra A, et al. Bipolar disorders and Wilson's disease. BMC psychiatry. 2012;12:52.
92. Litwin T, Gromadzka G, Czlonkowska A, Golebiowski M, Poniatowska R. The effect of gender on brain MRI pathology in Wilson's disease. Metabolic brain disease. 2013;28(1):69-75.
93. Litwin T, Gromadzka G, Czlonkowska A. Gender differences in Wilson's disease. Journal of the neurological sciences. 2012;312(1-2):31-5.
94. Shanmugiah A, Sinha S, Taly AB, Prashanth LK, Tomar M, Arunodaya GR, et al. Psychiatric manifestations in Wilson's disease: a cross-sectional analysis. The Journal of neuropsychiatry and clinical neurosciences. 2008;20(1):81-5.
95. Dening TR, Berrios GE. Wilson's disease. Psychiatric symptoms in 195 cases. Archives of general psychiatry. 1989;46(12):1126-34.
96. Soltanzadeh A, Soltanzadeh P, Nafissi S, Ghorbani A, Sikaroodi H, Lotfi J. Wilson's disease: a great masquerader. European neurology. 2007;57(2):80-5.
97. Lautenschlager NT, Forstl H. Organic psychosis: Insight into the biology of psychosis. Curr Psychiatry Rep. 2001;3(4):319-25.
98. Waters F, Collerton D, Ffytche DH, Jardri R, Pins D, Dudley R, et al. Visual hallucinations in the psychosis spectrum and comparative information from

neurodegenerative disorders and eye disease. Schizophr Bull. 2014;40 Suppl 4:S233-45.
99. Lewandowski KE, DePaola J, Camsari GB, Cohen BM, Ongur D. Tactile, olfactory, and gustatory hallucinations in psychotic disorders: a descriptive study. Ann Acad Med Singap. 2009;38(5):383-5.
100. Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol. 2015;44(4):1172-80.
101. Schram MT, Sep SJ, van der Kallen CJ, Dagnelie PC, Koster A, Schaper N, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. Eur J Epidemiol. 2014;29(6):439-51.
102. Sheffield JM, Karcher NR, Barch DM. Cognitive Deficits in Psychotic Disorders: A Lifespan Perspective. Neuropsychol Rev. 2018;28(4):509-33.
103. McCleery A, Nuechterlein KH. Cognitive impairment in psychotic illness: prevalence, profile of impairment, developmental course, and treatment considerations. Dialogues Clin Neurosci. 2019;21(3):239-48.
104. Olkinuora M. Organic brain syndromes from a psychiatric point of view: diagnostic and nosological aspects. Acta Neurol Scand Suppl. 1982;92:47-57.
105. Eun SH, Hahn SH. Metabolic evaluation of children with global developmental delay. Korean J Pediatr. 2015;58(4):117-22.
106. Sanders RD, Gillig PM. Extrapyramidal examinations in psychiatry. Innov Clin Neurosci. 2012;9(7-8):10-6.
107. Dhir A, Schilling T, Abler V, Potluri R, Carroll B. ESTIMATION OF EPIDEMIOLOGY OF TARDIVE DYSKINESIA IN THE UNITED STATES (P2.018). Neurology. 2017;88(16 Supplement):P2.018.
108. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf. 2000;22(1):73-81.
109. Pan L, Vockley J. Neuropsychiatric Symptoms in Inborn Errors of Metabolism: Incorporation of Genomic and Metabolomic Analysis into Therapeutics and Prevention. Curr Genet Med Rep. 2013;1(1):65-70.
110. Eggink H, Kuiper A, Peall KJ, Contarino MF, Bosch AM, Post B, et al. Rare inborn errors of metabolism with movement disorders: a case study to evaluate the impact upon quality of life and adaptive functioning. Orphanet J Rare Dis. 2014;9:177.
111. Storjord E, Dahl JA, Landsem A, Ludviksen JK, Karlsen MB, Karlsen BO, et al. Lifestyle factors including diet and biochemical biomarkers in acute intermittent porphyria: Results from a case-control study in northern Norway. Mol Genet Metab. 2019;128(3):254-70.
112. Benque A, Bommelaer G, Rozental G, Cales P, Cathelineau L, Pham Dinh D, et al. Chronic vomiting in a case of citrullinaemia detected after treatment by total parenteral nutrition. Gut. 1984;25(5):531-3.
113. Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. Br J Haematol. 2017;176(4):527-38.
114. Brodie MJ, Thompson GG, Moore MR, Beattie AD, Goldberg A. Hereditary coproporphyria. Demonstration of the abnormalities in haem biosynthesis in peripheral blood. Quarterly Journal of Medicine. 1977;46(182):229-41.
115. Forbes D. Differential diagnosis of cyclic vomiting syndrome. J Pediatr Gastroenterol Nutr. 1995;21:Suppl 1:S11-4.
116. Hasbaoui BE, Boujrad S, Abilkacem R, Agadr A. [Vomiting associated with weight stagnation and convulsions: urea cycle disorder should be suspected]. Pan Afr Med J. 2018;31:103.
117. MacDonald A, van Wegberg AMJ, Ahring K, Beblo S, Belanger-Quintana A, Burlina A, et al. PKU dietary handbook to accompany PKU guidelines. Orphanet J Rare Dis. 2020;15(1):171.
118. Kumar T, Sharma GS, Singh LR. Homocystinuria: Therapeutic approach. Clin Chim Acta. 2016;458:55-62.

119. Trakadis YJ, Fulginiti V, Walterfang M. Inborn errors of metabolism associated with psychosis: literature review and case-control study using exome data from 5090 adult individuals. J Inherit Metab Dis. 2018;41(4):613-21.
120. van de Burgt N, van Koningsbruggen S, Behrens L, Leibold N, Martinez-Martinez P, Mannens M, et al. Screening for inborn errors of metabolism in psychotic patients using Next Generation Sequencing. J Psychiatr Res. 2021;138:125-9.
121. Malaga DR, Brusius-Facchin AC, Siebert M, Pasqualim G, Saraiva-Pereira ML, Souza CFM, et al. Sensitivity, advantages, limitations, and clinical utility of targeted next-generation sequencing panels for the diagnosis of selected lysosomal storage disorders. Genet Mol Biol. 2019;42(1 suppl 1):197-206.
122. Komlosi K, Sólyom A, Beck M. The Role of Next-Generation Sequencing in the Diagnosis of Lysosomal Storage Disorders. Journal of Inborn Errors of Metabolism and Screening. 2016;4:2326409816669376.

CHAPTER 3

Screening for inborn errors of metabolism in psychotic patients using Next Generation Sequencing

Nikita van de Burgt, Silvana van Koningsbruggen, Leonie Behrens, Nicole Leibold, Pilar Martinez-Martinez, Marcel Mannens, Therese van Amelsvoort

Journal of Psychiatric Research 2021; 138:125-129

ABSTRACT

Inborn errors of metabolism (IEMs) are a group of rare genetic disorders which, when emerging later in life, are often characterized by neuropsychiatric manifestations including psychosis. This study aimed to determine whether it would be useful to screen patients presenting with a psychotic disorder for IEMs by a single blood sample using Next Generation Sequencing (NGS), in order to detect rare, treatable causes of psychotic disorders. Blood was drawn from 60 patients with a psychotic disorder, with a duration of illness of less than 5 years. Blood samples were screened for 67 genes using NGS (Illumina® MiSeq sequencing technique). The results were compared to the human reference genome (GoNL, n=498). The identified variants were classified according to the ACMG classification. For the psychotic patients, 6 variants of a likely pathogenic (class 4, n=2) or pathogenic (class 5, n=4) origin were found. As all variants were heterozygous, no patients were considered to be affected by an IEM. For the GoNL control group, 73 variants of a likely pathogenic (class 4, n=31) or pathogenic (class 5, n=42) origin were found. All of these found variants were heterozygous. Therefore, these individuals from the control group were considered to be a carrier only. Thus, no patients were identified to have an IEM as an underlying disease using this approach. However, NGS may be useful to detect variants of genes associated with IEMs in an enriched subgroup of psychotic patients.

Keywords: gene variants, genetic disorders, inborn errors of metabolism, next generation sequencing, psychosis.

ABBREVIATIONS

CASH = Comprehensive Assessment of Symptoms and History; GAF = Global Assessment of Functioning; IEM = inborn error of metabolism; NGS = Next Generation Sequencing; PANSS = Positive and Negative Symptom Scale; WAIS-III = Wechsler Adult Intelligence Scale.

INTRODUCTION

Inborn errors of metabolism (IEMs) are a group of rare genetic disorders, characterized by a defect in specific metabolic enzymes or transport proteins. Consequently, the body is not able to turn food into energy properly (1). IEMs may result in a wide variety of symptoms and may affect any organ at any age. However, from all the 750 IEMs that have been described so far, some IEMs may result in isolated neuropsychiatric symptoms before any somatic symptoms are present (2). Furthermore, it is known that when IEMs manifest later in life, neuropsychiatric manifestations including psychosis are more prominent (3). IEMs that are associated with neuropsychiatric symptoms include diseases of homocysteine metabolism, urea cycle disorders, porphyria, Wilson disease, cerebrotendinous xanthomatosis and Niemann-Pick disease type C (2). In a cohort of 34 patients with Wilson's disease, 50% of these patients reported psychiatric symptoms and in some of these cases, psychosis was the only clinical manifestation for several months before any organic symptoms were reported (4). Additionally, neuropsychiatric symptoms are observed in 24-70% of the patients with acute porphyria (5, 6). The emergence of neuropsychiatric symptoms may be due to the accumulation of substrates (and therefore, direct toxicity to neurons), a deficiency of products and/or the result of toxicity due to alternative metabolite production (7). Neurons are easily affected by disturbances in metabolic pathways, leading to neuronal damage and therefore, neuropsychiatric symptoms (8).

However, due to the rarity of the individual IEMs, only few psychiatrists are aware of psychotic symptoms due to underlying diseases as IEMs. Therefore, patients with psychotic symptoms due to IEMs may be misdiagnosed and miss the opportunity to receive appropriate treatment (8-10). For most IEMs treatment options, e.g. adjustment of diet or taking supplements, are available nowadays. Early treatment is of great importance because a delayed or no treatment can result in irreversible neurological damage and cognitive decline. Furthermore, treatment is most efficient when IEMs are detected early in disease development (9). Therefore, it is important to raise awareness for IEMs and its relationship with neuropsychiatric manifestations.

Standard diagnostic procedures for individual IEMs often involve several separate tests including multiple blood samples, a urine sample and sometimes cerebrospinal fluid draw and MRI scans as well. This makes the diagnosis for most IEMs invasive, time consuming and expensive, resulting in diagnostic delays. Next Generation Sequencing (NGS) however, can be used to screen for a large panel of genes by using only a single blood sample. For example, NGS can be used as a non-invasive method to screen for genes that are associated with treatable IEMs that may affect brain function and result in psychotic symptoms. IEMs

that are associated with these genes include adrenoleukodystrophy, citrullinemia, coenzyme Q10 deficiency, coproporphyria, GLUT1 deficiency syndrome, Hartnup disease, homocystinuria, hyperphenylalaninemia, mannosidosis, maple syrup urine disease, methylmalonic acidemia, methylmalonic aciduria, molybdenum cofactor deficiency, mucopolysaccharidosis (Sanfilippo syndrome), Niemann-Pick Disease type C1, purine nucleoside phosphorylase deficiency, Tay-Sachs disease and Wilson's disease. The Amsterdam University Medical Centre developed a NGS panel that allows detection of 67 genes that are associated with 56 treatable IEMs that are present with neuropsychiatric symptoms. NGS is not used in routine clinical psychiatric practice yet because of its relatively high costs, and unknown diagnostic yield. However, compared to current routine diagnostics NGS might prove valuable to detect genetic hetero- or homozygous variants of genes related to IEMs. Therefore, this study aimed to determine whether it would be useful to screen patients with a recent onset psychotic disorder for IEMs with a novel NGS panel, in order to detect rare, treatable causes of psychotic disorders. Additionally, this study aimed to determine whether there would be a possible statistical difference between patients with a psychotic disorder and controls for being a carrier of a gene associated with an IEM.

METHODS

A total of 60 patients with a psychotic disorder, with a duration of illness of less than 5 years and a minimum age of 16, were recruited through various psychiatric facilities in the Netherlands or patients were referred for clinical diagnostic testing by their psychiatrist. Patients with severe brain injury or trauma were excluded from the study. After receiving full information on the study, participants or their legal guardians gave written consent to participate in the study. The study was approved by the Medical Ethical Committee of Maastricht University and Amsterdam University Medical Centre. All procedures followed were in accordance with the ethical standards of the responsible committee and with the Helsinki Declaration of 1975. The Comprehensive Assessment of Symptoms and History (CASH, (11)) was used to validate the diagnosis of a psychotic disorder. The Positive and Negative Syndrome Scale (PANSS, (12)) was conducted to measure psychotic symptoms severity. IQ was determined using a shortened version of the Wechsler Adult Intelligence Scale (WAIS III, (13)).

After blood draw, DNA was isolated from at least 7ml of blood by using robot Gentra® AUTOPURE LS 98 or by isolating the DNA manually. NGS was used to determine the genotype of the patients of the following 67 metabolic genes: *ABCD1, ADCK3, ABCD2, ADCK4, ABCD3, ADCK5, ARG1, ARSA, ASL, ASS1, ATP7B, BCK- DHA, BCKDHB, CBS, COQ2, COQ9, CPOX, CPS1, CYP27A1, DBT, DDC, DLD, GAMT, GCDH, GCH1, GNS, HEXA, HGSNAT, HLCS, HPRT1, IDS, IDUA, IVD, LMBRD1, MAN2B1, MLYCD, MMAA, MMAB, MMACHC, MMADHC, MOCS1, MOCS2, MTHFR, MTR, MTRR, MUT, NAGLU, NAGS, NPC1, NPC2, OTC, PCBD1, PCCA, PCCB, PDSS1, PDSS2, PNP, PNPO, PPOX, PTS, QDPR, SGSH, SLC2A1, SLC6A19* and *SPR*.

NGS was executed according to the Illumina® MiSeq sequencing technique. The results of this technique were compared to the DNA sequences of 498 Dutch individuals. These DNA sequences were obtained via the Genome of the Netherlands (GoNL), which consists of DNA sequences from 498 representative Dutch individuals, derived from 4 different biobanks in the Netherlands. The DNA sequences of all 498 individuals were included in the study. For the purposes of the study, the DNA sequences of these 498 individuals were reduced to the coding regions of the 67 metabolic genes.

The identified variants of the patients and control group were classified according to their predicted pathogenicity and were given a score between 1 to 5, based on the American College of Medical Genetics and Genomics (ACMG) classification and in silico predictions (14, 15). The classification was as followed: 1 as benign; 2 as likely benign; 3 as a variant of

uncertain significance (VOUS); 4 as likely pathogenic and 5 as a pathogenic variant (14). Statistical analysis was performed using SPSS (version 25). For the statistical analysis, Fisher's exact tests were executed to determine whether there was a statistically significant difference between the psychotic patients and control group for being a carrier of a gene of interest. Statistical significance was defined as a p-value <0.05.

RESULTS

In total, blood samples from 60 patients with a diagnosis of a psychotic disorder were collected and screened for 67 genes (Table 1). In these patients, 6 variants of class 4 and 5 were found (Table 2). These variants were classified as likely pathogenic (class 4, n=2) and pathogenic (class 5, n=4). All variants were heterozygous. Therefore, no patients were considered to be affected by an IEM, but as carrier of a (likely) pathogenic mutation. For the control group, 73 variants of class 4 and 5 were found (Table 2). These variants were classified likely pathogenic (class 4, n=31) and pathogenic (class 5, n=42). Of these variants, 35 variants were missense mutations and 2 variants were single base changes in the intronic region. Furthermore, one stoploss, one stopgain and one frame-shift deletion were found as well. All of these variants were heterozygous. Therefore, individuals from the control group were considered to be a carrier only and not affected by an IEM. There was no statistically significant difference in prevalence for the found variants between the psychotic patients and the control group ($p > 0.0592$).

Table 1 Demographic data, clinical information and diagnosis of included psychotic patients.

		Psychotic patients	
	n	Mean	SD
Demographics			
Male | Female (n)	60	28 | 32	
Age (years)	60	29.18	8.06
IQ	60	98.45	13.47
Clinical information			
Number of episodes (n)	60	2.39	4.17
Duration of illness (years)	60	5.18	4.98
Diagnosis	n	%	
Psychotic Disorder NOS	21	35.0	
Schizophrenia, Paranoid Type	15	25.0	
Schizoaffective Disorder	13	21.7	
Schizophreniform Disorder	4	6.7	
Brief Psychotic Disorder	4	6.7	
Schizophrenia, Undifferentiated Type	2	3.3	
Schizophrenia, Disorganized Type	1	1.7	

Table 2 Class 4 and 5 variants in psychotic patients and controls.

Psychotic patients (n=60)							
Patient number	Gene	Variant	RefSeq ID	Frequency	Homo- or heterozygous	Class	Described as
17	*PDSS1*	del	n/a	1	n/a	4	Likely pathogenic
29	*SLC6A19*	c.517G>A	NM_001003841.3	1	Heterozygous	5	Pathogenic
31	*PCCB*	c.932G>A	NM_001178014.1	1	Heterozygous	4	Likely pathogenic
49	*MMACHC*	c.276G>T	NM_015506.2	1	Heterozygous	5	Pathogenic
69	*CBS*	c.833T>C	NM_000071.3	1	Heterozygous	5	Pathogenic
70	*CBS*	c.833T>C	NM_000071.3	1	Heterozygous	5	Pathogenic
Control (n=498)							
Mutation number	Gene	Variant	RefSeq ID	Frequency	Homo- or heterozygous	Class	Described as
1	*MMACHC*	c.276G>T	NM_015506.2	1	Heterozygous	5	Pathogenic
2	*MMACHC*	c.440G>C	NM_015506.3	1	Heterozygous	4	Likely pathogenic
3	*MMACHC*	c.482G>A	NM_015506.2	1	Heterozygous	5	Pathogenic
6	*CYP27A1*	c.1016C>T	Not described	1	Heterozygous	4	Likely pathogenic
7	*IDUA*	c.208C>T	NM_000203.5	4	Heterozygous	5	Pathogenic
10	*SLC6A19*	c.517G>A	NM_001003841.3	9	Heterozygous	4	Likely pathogenic
11	*ALDH7A1*	c.1279G>C	NM_001182.5	1	Heterozygous	5	Pathogenic
14	*MUT*	c.1106G>A	NM_000255.3	1	Heterozygous	4	Likely pathogenic
15	*MUT*	c.655A>T	NM_000255.3	1	Heterozygous	5	Pathogenic
16	*BCKDHB*	c.832G>A	NM_183050.3	1	Heterozygous	5	Pathogenic
18	*ASL*	c.35G>A	NM_000048.4	3	Heterozygous	5	Pathogenic
19	*ASL*	c.446+1G>A	NM_000048.4	1	Heterozygous	5	Pathogenic
21	*ATP7B*	c.4135C>T	NM_000053.4	1	Heterozygous	4	Likely pathogenic
22	*ATP7B*	c.3207C>A	NM_000053.4	2	Heterozygous	5	Pathogenic
26	*NPC2*	c.441+1G>A	NM_006432.4	5	Heterozygous	5	Pathogenic
27	*IVD*	c.941C>T	NM_002225.3	5	Heterozygous	5	Pathogenic
28	*HEXA*	c.805G>A	NM_000520.5	1	Heterozygous	5	Pathogenic
30	*NAGLU*	c.2021G>A	NM_000263.3	2	Heterozygous	5	Pathogenic
31	*SGSH*	c.734G>A	NM_000199.5	5	Heterozygous	5	Pathogenic
32	*SGSH*	c.220C>T	NM_000199.5	1	Heterozygous	5	Pathogenic
34	*CBS*	c.833T>C	NM_000071.3	18	Heterozygous	4	Likely pathogenic
36	*CBS*	c.146C>T	NM_000071.2	1	Heterozygous	5	Pathogenic
37	*ADSL*	c.1277G>A	NM_000026.4	4	Heterozygous	5	Pathogenic
39	*ARSA*	c.1283C>T	NM_000487.6	3	Heterozygous	5	Pathogenic

PDSS1 = Decaprenyl-diphosphate Synthase Subunit 1, *SLC6A19* = Solute Carrier Family 6 Member 19, *PCCB* = Propionyl-CoA Carboxylase Subunit Beta, *MMACHC* = Metabolism Of Cobalamin Associated C, *BCKDHB* = Branched Chain Keto Acid Dehydrogenase E1 Subunit Beta, *CBS* = Cystathionine Beta-Synthase, *CYP27A1* = Cytochrome P450 Family 27 Subfamily A member 1, *IDUA* = Alpha-L-iduronidase, *ALDH7A1* = Aldehyde Dehydrogenase 7 Family Member A1, *MUT* = Methylmalonyl Coenzyme A Mutase, *ASL* = Argininosuccinate Lyase, *ATP7B* = copper-transporting ATPase 2, *NPC2* = Niemann-Pick Disease Type C2, *IVD* = isovaleryl-CoA Dehydrogenase, *HEXA* = Beta-hexosaminidase A, *NAGLU* = Alpha-N-acetylglucosaminidase, *SGSH* = N-Sulfoglucosamine Sulfohydrolase, *ARSA* = Arylsulfatase A.

DISCUSSION

In this study, we detected 6 heterozygous variants described as (likely) pathogenic in 6 patients with a recent onset of psychotic disorder. Furthermore, 73 heterozygous variants described as (likely) pathogenic were detected in 498 control individuals. Among these heterozygous mutations, a deletion of the *PDSS1* gene was found in a patient with a psychotic disorder and not in one of the control individuals. A homozygous mutation in the *PDSS1* gene is associated with coenzyme Q10 deficiency, which is observed in patients with schizophrenia (16). Furthermore, a heterozygous variant of the *CBS* gene, associated with homocystinuria, was detected in several patients with a psychotic disorder and the control individuals. Additionally, 3 control individuals were considered to be a carrier for the *ATP7B* gene. A homozygous mutation in the *ATP7B* gene is associated with Wilson's disease (17). However, as the found variants are all heterozygous variants, it is not likely that these variants could result in an IEM although it may be possible that heterozygous variants result in mild symptoms or other neuropsychiatric disorders (10, 18). In some cases, low ceruloplasmin and serum copper levels, which are associated with Wilson's Disease, have been observed in psychiatric patients with a heterozygous variant of *ATP7B* gene (19). Furthermore, psychiatric symptoms and Parkinsonians tremors were described in case reports of patients with a heterozygous variant of the *ATP7B* gene (20, 21). Heterozygous variants of the *NPC* gene were observed in patients with delirium or paranoid schizophrenia as well (22). Additionally, it may be possible that these heterozygous variants result in increased vulnerability for psychotic and/or neurological disorders. Consequently, further research is necessary to study the effect of these heterozygous variants on neuropsychiatric manifestations.

As for limitations, the small number of included patients may contribute to the absence of affected patients. Previous research showed that an IEM may result in neuropsychiatric symptoms and that several variants are significantly associated with schizophrenia (9). However, this study used a large sample of whole exome data of adults with psychotic disorder and unrelated controls, which increases the likelihood of detecting these rare genetic disorders. Additionally, it may be possible that the occurrence of a psychotic disorder in case of an underlying disease such as an IEM also depends on the degree to which the metabolic process is disrupted and to the presence of other biological or genetic factors (9). Screening in a large 'enriched, high risk' sample of patients only would be a next step for future research. These 'enriched, high risk' patients may present atypical psychotic symptoms, neurological symptoms, catatonia, cognitive decline, movement abnormalities, an intellectual disability or do not respond to treatment as expected (2, 9, 23, 24). The presence of an underlying disease such as IEMs is probably higher in such patients and

therefore, screening and clinical evaluation should be prioritized in these patients.

However, as screening for IEMs still requires invasive and time-consuming methods, this study showed that a NGS approach is a good, relatively cheap, alternative to using multiple blood samples, urine samples, cerebrospinal fluid and MRI scans to detect hetero- or homozygous variants of genes related to IEMs. Consequently, the detection of IEMs may be limited to the use of only one blood sample in the future.

Taken together, future research should focus on screening for genetic variants associated with IEMs in 'enriched, high risk' patients with the use of NGS.

REFERENCES

1. Saudubray JM, Garcia-Cazorla A. Inborn Errors of Metabolism Overview: Pathophysiology, Manifestations, Evaluation, and Management. Pediatr Clin North Am. 2018;65(2):179-208.
2. Sedel F, Baumann N, Turpin JC, Lyon-Caen O, Saudubray JM, Cohen D. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J Inherit Metab Dis. 2007;30(5):631-41.
3. Klunemann HH, Santosh PJ, Sedel F. Treatable metabolic psychoses that go undetected: what Niemann-Pick type C can teach us. International journal of psychiatry in clinical practice. 2012;16(3):162-9.
4. Rathbun JK. Neuropsychological aspects of Wilson's disease. Int J Neurosci. 1996;85(3-4):221-9.
5. Stein JA, Tschudy DP. Acute intermittent porphyria. A clinical and biochemical study of 46 patients. Medicine. 1970;49(1):1-16.
6. Goldberg A. Acute intermittent porphyria: a study of 50 cases. The Quarterly journal of medicine. 1959;28(110):183-209.
7. Fekete K, Decsi T. Long-chain polyunsaturated fatty acids in inborn errors of metabolism. Nutrients. 2010;2(9):965-74.
8. Walterfang M, Bonnot O, Mocellin R, Velakoulis D. The neuropsychiatry of inborn errors of metabolism. J Inherit Metab Dis. 2013;36(4):687-702.
9. Trakadis YJ, Fulginiti V, Walterfang M. Inborn errors of metabolism associated with psychosis: literature review and case-control study using exome data from 5090 adult individuals. J Inherit Metab Dis. 2018;41(4):613-21.
10. Bonnot O, Klunemann HH, Sedel F, Tordjman S, Cohen D, Walterfang M. Diagnostic and treatment implications of psychosis secondary to treatable metabolic disorders in adults: a systematic review. Orphanet J Rare Dis. 2014;9:65.
11. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Archives of general psychiatry. 1992;49(8):615-23.
12. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.
13. Velthorst E, Levine SZ, Henquet C, de Haan L, van Os J, Myin-Germeys I, et al. To cut a short test even shorter: reliability and validity of a brief assessment of intellectual ability in schizophrenia--a control-case family study. Cogn Neuropsychiatry. 2013;18(6):574-93.
14. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine : official journal of the American College of Medical Genetics. 2015;17(5):405-24.
15. Ellard S, Baple LB, Owens M, Eccles DM, Turnbull C, Abbs S, et al. ACGS Best Practice Guidelines for Variants Classification 2018. 2018.
16. Maguire A, Hargreaves A, Gill M. The Impact of Coenzyme Q10 on the Cognitive Deficits and Symptoms of Schizophrenia: Protocol and Baseline Data of a Randomised, Placebo-Controlled Study. Schizophrenia Bulletin. 2018;44:S357-S.
17. Chang IJ, Hahn SH. The genetics of Wilson disease. Handbook of clinical neurology. 2017;142:19-34.
18. Klunemann HH, Santosh PJ, Sedel F. Treatable metabolic psychoses that go undetected: what Niemann-Pick type C can teach us. Int J Psychiatry Clin Pract. 2012;16(3):162-9.
19. Demily C, Parant F, Cheillan D, Broussolle E, Pavec A, Guillaud O, et al. Screening of Wilson's disease in a psychiatric population:

difficulties and pitfalls. A preliminary study. Ann Gen Psychiatry. 2017;16:19.
20. Sechi G, Antonio Cocco G, Errigo A, Deiana L, Rosati G, Agnetti V, et al. Three sisters with very-late-onset major depression and parkinsonism. Parkinsonism & related disorders. 2007;13(2):122-5.
21. Gromadzka G, Chabik G, Mendel T, Wierzchowska A, Rudnicka M, Czlonkowska A. Middle-aged heterozygous carriers of Wilson's disease do not present with significant phenotypic deviations related to copper metabolism. J Genet. 2010;89(4):463-7.
22. Maubert A, Hanon C, Metton JP. [Niemann-Pick type C disease and psychosis: Two siblings]. Encephale. 2015;41(3):238-43.
23. Bonnot O, Herrera PM, Tordjman S, Walterfang M. Secondary psychosis induced by metabolic disorders. Front Neurosci. 2015;9:177.
24. Lauterbach MD, Stanislawski-Zygaj AL, Benjamin S. The differential diagnosis of childhood- and young adult-onset disorders that include psychosis. The Journal of neuropsychiatry and clinical neurosciences. 2008;20(4):409-18.





PART 2

Autoantibodies




CHAPTER 4

Prevalence of neuronal surface antibodies in a cohort of recent-onset psychosis: The PSYANTIB study – an update

Nikita de Buck, Nicole Leibold, Therese van Amelsvoort, Pilar Martinez-Martinez et al.

In preparation

CHAPTER 5

Autoantibodies against myelin oligodendrocyte glycoprotein in psychiatric disorders

Nikita van de Burgt, [illegible] Kulsvehagen, Marina Mane-Damas, Luc Lutz, Clara Monserrat, Anita Vinke, Cem İsmail Küçükali, Chenghua Zong, Carolin Hoffmann, Nicole Leibold, Mario Losen, Erdem Tüzün, [illegible] van Beveren, Anna Mané-Santacana, Rob Rouhl, For GROUP, Therese van Amelsvoort, Anne-Katrin Pröbstel, Pilar Martinez-Martinez

Submitted





PART 3

Lipids




CHAPTER 6

Altered levels of phospholipids and sphingolipids in cerebrospinal fluid of patients with psychotic symptoms

Nikita van der Burgt, Jaan van Kruining, Therese van Amelsvoort, Mar Martinez-Martinez, Nicole Leibold

In preparation

CHAPTER 7

General discussion

PURPOSE OF THIS THESIS

This thesis builds upon the available research on psychosis due to an underlying somatic cause, such as inborn errors of metabolism (IEMs) or the presence of autoantibodies that target receptors, proteins and channels in the brain and spinal cord. Although significant advances have been made in the understanding and diagnosis of these rare, treatable forms of psychosis, many questions remain to be answered. The present thesis aimed to increase the current knowledge on these rare forms, by investigating possible ways to identify and classify patients with such an underlying somatic cause of their psychotic episodes. The results of the studies included in this thesis and their impact on future research and psychiatric care are discussed in this chapter.

MAIN FINDINGS

Inborn errors of metabolism and psychotic symptoms

IEMs are rare inherited metabolic disorders that can be screened for during the neonatal period by the use of newborn screening (NBS). However, the panels used differ greatly and only a small number of IEMs are currently being detected via this screening method (1, 2). Additionally, when tested too early after birth, the result of NBS may be falsely negative, as the toxic metabolites did not reach the detection threshold yet (3). When manifested during infancy and childhood, these metabolic disorders often result in severe and deteriorating symptoms. However, most of these disorders are also known for a less severe and often treatable variant, which often manifests during adolescence or even adulthood (4, 5). These disorders may also manifest with neuropsychiatric symptoms, which are often more prominent in the late-onset variants. These neuropsychiatric symptoms can even be isolated for years before any other somatic sign becomes part of the clinical manifestation (5, 6). Previously, it was thought that psychotic symptoms, such as hallucinations and delusions, were most commonly observed in patients with neuropsychiatric symptoms due to an IEM. However, when taking into account more recent research, the clinical manifestation among IEMs actually consists of a much broader spectrum of neuropsychiatric symptoms, as shown in **chapter 2**. Based on semi-structured diagnostic interviews and validated questionnaires, not only psychotic disorders but also depressive disorders, anxiety disorders, attention deficit hyperactivity disorder (ADHD), autism and obsessive compulsive disorder (OCD) are part of the psychiatric diagnoses that patients with an IEM receive (7). More specifically, depression and anxiety were the most commonly described co-diagnoses in our literature review, which is in contrast with the earlier idea that mainly psychotic disorders co-occur with IEM. This previous belief could be the result of a reporting bias, as only the most disturbing symptoms might have been recognized by clinicians and other, more subtle

symptoms, might have been overlooked. Furthermore, for some IEMs the clinical manifestation also differs between males and females. For example, in the case of the IEM Fabry disease, anxiety, depression and cognitive deficits are more pronounced in males, compared to females (8). Finally, psychotic symptoms are most commonly observed in IEMs that are relatively well studied, for example, Niemann-Pick disease type C, Wilson's disease and acute intermittent porphyria (4, 7, 9), while more than 1000 IEMs have been described in total (10).

Additionally, our results in **chapter 2** showed that psychiatric comorbidity is high, independent of the class of IEM. Often psychotic disorders are accompanied by depression and depressive disorders are often accompanied by anxiety disorders (7). Our results are in line with previous research (11, 12, 13, 14) that showed high comorbidity, and particularly a combination of a psychotic, depressive, behavioral and/or anxiety disorder is common. However, when taking into account the medical history of these patients retrospectively, other possible signs of an underlying IEM were often present. For example, developmental milestones were not reached in time or a loss of previously reached developmental milestones was described. Additionally, our literature review revealed that (a mild form of) intellectual disability was common but often not recognized during childhood. Intellectual disability or developmental delay is generally considered to be a "red flag" for clinicians, a sign that is considered an indication that some underlying disease may be present. However, for an underlying somatic cause such as IEMs no such "red flags" are yet routinely implemented in clinical psychiatry. Therefore, recently, we and others have tried to identify "red flags" in order to help clinicians distinguish primary psychiatric disorders from psychiatric manifestations due to an underlying cause, such as an IEM (7, 15, 16). **Chapter 2** of this thesis shows that developmental delay or intellectual disability should indeed be considered to be such a "red flag". Especially in combination with other childhood behavioral problems, such as restlessness, irritability, agitation, temper tantrums, emotional outbursts and aggressive behavior, developmental delay or intellectual disability should raise suspicion of an underlying IEM. Other "red flags" of IEMs that we (and others) propose are visual hallucinations, confusion, an acute onset, unusual or severe side effects of psychotropic drugs, treatment resistance and a combination of psychiatric symptoms and strong cognitive decline, motor symptoms, gastrointestinal and abdominal symptoms and exercise intolerance (7). The clinical use of such "red flags" can improve the recognition and, therefore, the diagnostic process and adequate treatment of these rare disorders.

With regard to diagnosing an IEM, a wide array of techniques, such as a thorough physical examination, multiple blood tests, urine tests, an ultrasound, a neurological examination and an MRI are often executed. Hence, the current diagnostic process is in part invasive and

time-consuming with sometimes delays of several years. However, next generation sequencing (NGS) may be used as an alternative to screen for both hetero- and homozygous variants of genes that are associated with IEMs, as seen in **chapter 3**. Although the current NGS panels do not allow the detection of variants of genes that are associated with all IEMs, one blood sample is sufficient to detect at least 56 treatable IEMs that may manifest with neuropsychiatric symptoms. Especially in the case of patients within psychiatric care that present with "red flags", NGS could be easily used to detect currently detectable IEMs and applied within routine diagnostics similar to the use of NGS within the field of cardiology or oncology, with significant improvements in patient care in those clinical fields (17, 18, 19).

Autoantibodies and psychotic symptoms

Not only IEMs, also autoantibodies against neural receptors, proteins and ion channels are considered to be a rare underlying cause of neuropsychiatric symptoms. Previously, psychotic symptoms were mostly associated with autoantibodies against the NMDAR and considered part of the prodromal phase of the development of autoimmune encephalitis. Additionally, it was thought that these autoantibodies symptoms occurred in young women only, as a consequence of a teratoma (20, 21, 22). However, nowadays, it is known that a teratoma is present in only 20-40% of young women with antibodies against the NMDAR (23, 24) and that the occurrence of autoimmune encephalitis is not limited to autoantibodies against the NMDAR and young women. Many more antigens that act as a target of these autoantibodies in the brain and spinal cord with different pathogenic effects have been identified since the discovery of NMDAR autoantibodies in 2007, of which a large proportion has been associated with neuropsychiatric symptoms. Among them are autoantibodies against neuronal receptors such as the AMPAR, $GABA_A$- and $GABA_B$R, CASPR2 and proteins such as GAD65 and, recently, MOG (**chapter 5**).

Nowadays, the prevalence of isolated psychiatric symptoms among patients with autoantibodies against the NMDAR is estimated between 1-5% of the cases (25, 26), with an even lower percentage of isolated psychotic symptoms (0.9%) (27). Psychotic symptoms specifically are also described in patients with autoantibodies against the AMPAR, $GABA_A$R, $GABA_B$R, D2DR, the glycine receptor and GAD65, although in a lower prevalence than against the NMDAR (28, 29, 30, 31, 32, 33, 34, 35, 36, 37). The previously observed prevalence of autoantibodies among patients with psychiatric disorders can be considered in line with our preliminary results in **chapter 4**, in which we observed the presence of autoantibodies by immunohistochemistry in 1 out of 45 (2.2%) patients with a psychotic or schizoaffective disorder, although the specific antigen to which these autoantibodies bind and whether this patient tests positive by other methods is yet to be confirmed. In this

study, we screened for autoantibodies by immunohistochemistry in patients that experienced at least one psychotic episode, with a manifestation less than 5 years ago. Previously, within research, psychiatric assessment often only included reported symptoms and no standardized clinical scales or validated assessments were described. However, including standardized clinical scales and validated assessments are important in order to get an accurate overview of the psychiatric, neuropsychological, neurological and cognitive symptoms that autoantibody positive patients may or may not experience. Hence, we included a variety of validated questionnaires and rating scales, among them were the Positive and Negative Syndrome Scale (PANSS) to measure the severity of the psychotic symptoms, the Beck Depression Inventory – Second Edition (BDI-II) to measure the severity of the depressive symptoms, the Cambridge Neuropsychological Test Automated Battery (CANTAB) to assess the cognitive functioning and several other questionnaires such as the Social Functioning Scale (SFS) to measure functioning in daily life. Recently other studies within the field of autoantibodies also started to include a variety of standardized assessments (38, 39), among them the PANNS, similar to our study (**chapter 4**), the Mini-Mental State Examination (MMSE) and the Brief Assessment of Cognition in Schizophrenia (BACS) to determine the level of cognitive functioning within these patients, and finally, the Neurological Evaluation Scale (NES) for the detection of neurological soft signs – a combination (of psychiatric, neuropsychological, cognitive and neurological assessments) that is proposed as part of **chapter 4**.

The presence of autoantibodies is determined in serum and/or CSF. Until recently it was thought that in the case of autoantibodies against the NMDAR, these autoantibodies should always be present in CSF in order to diagnose a patient with autoimmune encephalitis. However, recent research shows that a lack of autoantibodies in the CSF does not seem to exclude the possibility of autoimmune encephalitis and that the severity of the disease may be dependent on whether the autoantibodies are present in serum, CSF or both (37, 40, 41, 42, 43). Consequently, an autoimmune continuum is considered, in which the presence of these autoantibodies seems to be associated with the severity of the clinical manifestation. It is thought that the psychiatric or isolated psychotic symptoms are more frequently observed in patients that have these autoantibodies only in their serum (40, 42, 44), while the combination of psychiatric and (severe) neurological symptoms and abnormalities in the CSF, EEG and MRI are more frequently observed in patients with autoantibodies present in both serum and CSF or in CSF only. Consequently, testing both the serum and CSF of the same patient is of great importance. Hence, for our study (**chapter 4**), we asked patients whether they gave consent to draw CSF alongside serum. However, even though 56% of the patients consented to donate CSF for the study, it was only possible to successfully draw in 36% of the cases due to the use of an atraumatic needle. Using an atraumatic needle

reduces the risk of side effects such as discomfort or pain during the procedure but makes it challenging or even impossible to draw CSF in case of increased adipose tissue or the presence of scar tissue.

Antibodies that are usually only present in serum are autoantibodies against MOG (45). In contrast with the autoantibodies described above, MOG is not present at the surface or inside neurons, but present at the surface of myelin and oligodendrocytes instead. Consequently, autoantibodies against MOG were previously only associated with MOG-antibody-associated disease, or MOGAD, a demyelinating autoimmune disorder characterized by neurological symptoms such as visual disturbance, limb weakness, pain, headache, and seizures. However, recent case reports showed that MOG autoantibodies were also present in patients with isolated psychotic symptoms (46, 47, 48). It has to be noted that the psychiatric assessment of these patients only included reported symptoms and no standardized clinical rating scales or validated assessments. Hence, as part of **chapter 5**, we systematically screened for autoantibodies against MOG in patients with at least one psychotic episode by the use of several standardized clinical rating scales. Using this approach, we found that MOG autoantibodies could indeed play a role in the etiology of psychiatric disorders as well. Four patients and none of the controls tested positive for MOG autoantibodies, although the clinical significance of those autoantibodies is yet to be determined.

In addition to considering whether the presence of autoantibodies should be determined in serum, CSF or both, the used laboratory technique should also be critically evaluated. Generally, commercially available kits are used to determine the presence of autoantibodies in a patient. These kits often test only for the presence of a selected subset of autoantibodies against several antigens, including those against the NMDAR, AMPAR, $GABA_BR$, GAD65, LGI1, and CASPR2. Consequently, autoantibodies against many other antigens may be missed, leading to false negative results. To avoid this situation, a combination of several kits is advised (**chapter 4**). However, even with a combination of several kits false negative results may occur, especially in the case of low antibody titers (49). Therefore, ideally, also in vitro culture (of primary hippocampal neurons) should be included in the screening for autoantibodies to validate the findings of the commercially available kits and to confirm that these autoantibodies bind to antigens on the surface of neurons. However, including all methods during the diagnostic process may result in more extensive labor and increased costs. Hence, similar to the application of NGS, screening for the presence of autoantibodies in patients within clinical care may only be advised in case of atypical symptoms, i.e., a presentation with "red flags".

"Red flags", or atypical symptoms, in patients with autoantibodies that should not be overlooked include atypical psychotic symptoms such as visual hallucinations, confusion, acute onset and/or strong cognitive decline. Visual hallucinations are often associated with psychotic symptoms due to a medical condition (50, 51), an observation that is supported by our findings in **chapter 5**. Three out of the four patients that tested positive for the presence of autoantibodies against MOG experienced visual hallucinations, which is more commonly observed in patients with autoantibodies against the NMDAR and VGKC (52, 53, 54, 55).

Additionally, among the "red flags" in patients with autoantibodies is also mutism. Mutism has been described as a result of the presence of autoantibodies in several case reports (56, 57). The clinical manifestation often included depressive symptoms, confusion, agitation and/or aggression. Although the specific antigen and whether these autoantibodies bind to the surface of neuronal antigens is yet to be determined, the clinical manifestation of our suspected positive patient in **chapter 4** was mainly characterized by mutism, agitation, aggression and difficulties with cognitive functioning. Mutism has been described in patients with schizophrenia and patients with other neuropsychiatric symptoms, although the condition may improve after treatment with psychotropic drugs and electroconvulsive therapy (ECT) (58). No or an adverse response to psychotropic drugs should raise suspicion for the presence of autoantibodies as well and is hence considered a "red flag". In line with this, the suspected positive patient as described in **chapter 4** only showed minor improvement while being prescribed several psychotropic drugs and ECT.

Lipids and psychotic symptoms

Disruptions in classes of lipids and individual lipid species have been observed in neuropsychiatric disorders in the last decade (59, 60). These lipids, especially phospholipids and sphingolipids, have been found altered in patients with psychotic symptoms previously (61, 62, 63, 64, 65). Alongside the use of standardized assessments and scales and screening for red flags within psychiatry, including genetic, environmental and biological factors may further improve early diagnosis and enable more personalized treatment. Identifying biomarkers, among others, may contribute to this shift to "precision psychiatry" (66). Recently, lipids as possible biomarkers have raised interest within the medical field, including psychiatry, by the use of metabolomics (67, 68). For example, a combination of the six individual lipids with the highest AUC, among them two LPC species, one PC species, one PC-O species, one LPE species and one PE species, was used to create ROC curves to determine whether individual lipid species could be used as a possible biomarker to distinguish between patients with psychotic symptoms and controls by Wang et al. (2019) (65). However, previous research often included only a few classes of lipids overall or a

limited set of individual lipids species. For example, the study by Wang et al (2019) yielded 758 individual lipid species, of which 391 individual lipid species were included in the analysis, while more than a thousand individual lipids can be measured. Furthermore, it is known that lipid levels that are commonly measured in serum, plasma and the membranes of red blood cells (61, 62, 63, 64, 65) are affected by lifestyle factors such as BMI and smoking (69, 70, 71, 72). Hence, the measurement of lipid levels in CSF may yield a better reflection of sphingolipid levels in the central nervous system instead, as the central nervous system, due to the blood-brain barrier, is a more controlled environment and therefore, may be less affected by these lifestyle factors (73). Consequently, **chapter 6** focused on the measurement of a large number of lipids, belonging to 15 different lipid classes in patients with psychotic symptoms compared to controls. In total, 1432 individual lipids were detected, of which 41 individual lipid species, among them several phosphatidylcholine, phosphatidylethanolamine and sphingomyelin species, remained significant after correction for sex and age. Indeed, it was shown that especially age has a great effect on several lipid species, especially the LPEs. Hence, after correction for sex and age, these LPE species especially no longer remained significantly different between patients with psychotic symptoms and controls (**chapter 6**). Some of these species were increased in patients with psychotic symptoms, among them PC, PC-P and some PE species, while SM, DG, CE, HexCer, PE-P and other PE species were decreased in these patients compared to controls. Among the top 5 most significant individual lipid species consisted of three SM species, one PE-P and one PE-O species. These results are mostly contradicting with previously published research, although research measured these lipid levels in serum and plasma, rather than CSF. For example, previous studies also observed decreased levels of SM, similar to the findings of **chapter 6** (74, 75). However, increases in SM have been reported as well (64, 65). Interestingly, the differences in PC and PE species between patients with psychotic symptoms and controls have been speculated to be influenced by the type of psychotic disorder (e.g. a decrease in PC in the white matter and an increase in PC in grey matter was previously only observed in patients with schizophrenia, but not in patients with bipolar disorder with psychotic features). However, whether this is actually related to the type of psychotic disorder or whether this is associated the severity of cognitive symptoms is hypothesized but yet to be determined (76, 77). It has also been speculated that the content of polyunsaturated fatty acids in PE and PC species may play a role in the observed differences in these lipid species in some, but not all patients with psychotic symptoms (78, 79). Therefore, the altered levels of especially sphingolipids and phospholipids in CSF of patients with psychotic symptoms are considered preliminary results and although an important step in the right direction, whether these changes are unique for patients with psychotic symptoms and whether they are associated with other clinical characteristics is yet to be determined.

BIOMARKERS IN PSYCHOTIC SPECTRUM DISORDERS

Currently, psychotic spectrum disorders are diagnosed based on the medical and psychiatric history and current symptoms, and classified according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or the International Statistical Classification of Diseases and Related Health Problems, Eleventh Edition (ICD-11). However, in order to prevent diagnostic delay and provide better treatment outcomes in the feature, especially in case of patients with a rare forms of psychosis, the identification of biomarkers is of great importance. However, of all biomarkers (i.e. neuroimaging, genetic and epigenetic, neuroinflammatory and metabolic biomarkers) that have been identified so far, it is often uncertain whether their measurements may have a diagnostic, therapeutic or even possibly predictive value, as a correlation with disease does not necessarily entail causation. Nevertheless, based on the results of this thesis, measurements in blood and CSF may still have a beneficial value in regard to diagnosing patients with a rare form of psychosis. For example, NGS has been shown of great added value to detect a variety of treatable IEMs in patients with psychosis (**chapter 3**). Although genetic testing within routine diagnostics is sometimes executed, this is often limited to traditional sequencing methods and used as confirmation to already executed biochemical testing. However, one must keep in mind that each of the proposed tests, i.e. biomarkers, are specific for the corresponding underlying rare form. At first sight this specificity may be attractive to combine different tests to be able to perform a broad comprehensive screening, however, this will result in a large amount of work hindering practical implementation. In addition, more tests performed would not necessarily lead to a proportional increase in the meaningfulness of the outcomes obtained. For example, while NGS may have an added value in case of atypical psychiatric symptoms in combination with intellectual disability, exercise intolerance or gastrointestinal and abdominal symptoms (**chapter 2**), an immunological panel (i.e. a combination of immunohistochemistry, cell based assays and primary hippocampal neurons) would be more appropriate in case of atypical psychiatric symptoms in combination with mutism, headache and seizures or prodromal symptoms such as fever. Furthermore, executing more tests also entails increased costs, which may not be desired with the already rising healthcare costs over the past few years. However, when taking into account the costs of the combination of the currently used techniques within routine clinical care, additional costs for applying these tests in a subgroup of patients may be limited. Consequently, the combination of different symptoms should be critically evaluated and leading in the decision of the panel tests that are run. Hence, although these tests have been shown to be a possible alternative to current methods, the yield of performing these tests may increase in case these tests are only run in case of clinical suspicion. To further reduce additional costs and to ensure that tests are only run in case of clinical suspicion,

these tests should be performed at specialized centers or joint clinics (**chapter 2**), in which both experts within different clinical fields and specialized laboratory experts are situated.

STRENGTHS AND LIMITATIONS

One of the major strengths of the research in this thesis is the combination of standardized clinical rating scales with validated laboratory research techniques. For each study, we combined standardized and validated questionnaires such as the PANSS (80) to measure the severity of the positive and negative symptoms as described in psychotic disorders. Additionally, questionnaires such as the BDI-II (81) were used to measure depressive symptoms. Regarding laboratory techniques, the gold standard (cell based assays using commercially available kits and fluorescence activated cell sorting) was used to detect MOG autoantibodies in patients with a psychotic disorder as described in **chapter 5**, while **chapter 4** consisted of a combination of techniques, among them immunohistochemistry, cell based assays and primary hippocampal neurons. A combination of these techniques has been lacking in previous research and is necessary to prevent false positive results. Additionally, in **chapter 4**, a standardized neurological examination was used to determine whether (subtle) neurological symptoms were present in patients with a psychotic disorder. However, by combining all these examinations within a study, the burden on the patient increases as well. Hence, while we consider the combination a strength, it may be considered a limitation as well. Especially in the case of acutely ill patients, in which the first and foremost goal during their admission is their recovery, choices have to be made regarding what is feasible and tolerable for the patient. Hence, when conducting research within this patient group, a lot of flexibility and support is necessary. Therefore, data regarding psychiatric, neuropsychological and cognitive functioning may be missing for some patients. Consequently, research done within this population often only consists of basic demographic and clinical information, without the use of standardized rating scales. Sometimes a more detailed clinical description is provided, by tracing back notes in patient files and using retrospective data. However, this may lead to a large discrepancy between used questionnaires and tests, which makes comparison across studies difficult. Ideally, research should focus on ways to combine these scales without increasing the burden on the patient.

To decrease the burden on the patient and improve the diagnostic process, a critical assessment of used diagnostic procedures was conducted in **chapter 3** and **chapter 4**. As IEMs are currently diagnosed with a wide variety of techniques within routine clinical care, which are often considered invasive, we used NGS to detect both homozygous and heterozygous mutations that are associated with IEMs by the use of only one blood sample

(**chapter 3**). As this decreases the burden on the patient and associated costs massively, we consider this critical assessment as a strength of this thesis. Unfortunately, this technique is still quite expensive and it may not be feasible to implement this within routine clinical care. However, when taking into account the costs of the combination of the currently used techniques to diagnose these IEMs, the costs of NGS should no longer be considered to be a major limitation.

Another strength of the current thesis would be the collaborations across the different fields. Although positive changes have been proposed and implemented in some healthcare facilities, current research (**chapter 2**) still emphasizes the need to collaborate between different medical specialties as done in this thesis. Especially in the case of these rare underlying somatic causes, patients may not only be seen by a psychiatrist but by a neurologist or a specialist within the field of internal medicine or pediatrics as well. For the studies included in this thesis, a collaboration was formed between experts within different healthcare disciplines and between healthcare and laboratory experts. For example, in **chapter 2**, not only clinicians working within psychiatry were involved, but pediatrics as well. For the research conducted as described in **chapter 3**, a collaboration was established between psychiatrists and experts in the field of clinical genetics (both clinical and laboratory experts). For both **chapter 4** and **chapter 5**, clinical and research experts in the field of neurology (e.g. epilepsy, immunology and auto-immune encephalitis) and psychiatry were involved as well. Our research showed that this collaboration is not only necessary within research but an essential part of clinical care as well in order to prevent diagnostic delay and provide appropriate and timely treatment for patients. In order to implement this collaboration across different medical specialties, we proposed joint IEM clinics, in which experts of different specialties are located within one clinic and closely collaborate, in **chapter 2**. However, such clinics may be proposed for all sorts of somatic disorders or causes, for example, patients with (a suspected presence of) autoantibodies. These expertise centers may guide patients not only in the diagnostic process but also during the process of treatment and reintegration within society. Ideally, these centers should include in-house laboratories that carry out the suggested techniques.

These specialized centers may also help to deal with another limitation of the research conducted as part of this thesis. Recruitment and inclusion of patients with psychosis or psychiatric symptoms in general, is a challenge, which often leads to a small number of patients included in studies. Especially in the case of more acutely ill patients, recruitment and inclusion is a challenge. Not only because patients with a psychiatric disorder may not engage with mental health services consistently, fluctuating symptoms, i.e. acute episodes or symptom exacerbation, difficulties trusting clinical or research personnel and an

increased risk for missing appointments may increase the difficulty to identify and recruit patients that are eligible for research studies and reach the desired sample size. Research conducted within this patient group requires more time, empathy and flexibility than research conducted in (relatively) healthy adults. In order to increase the sample size to a large number of patients, a team of individuals helping with recruitment and inclusion, such as research assistants, is necessary. Hence, to tackle this limitation, future studies should include clinicians who pre-screen and refer patients for inclusion, as well as research assistants and trained personnel, to conduct the standardized clinical assessments, questionnaires and tests and laboratory personnel to execute the analysis in the laboratory.

FUTURE RESEARCH AND CLINICAL PRACTICE

As previously touched upon, several suggestions for future research and clinical practice have been proposed. Ideally, research on these rare forms of psychosis should focus on including standardized assessments and scales to provide an objective presentation of the observed psychiatric symptoms and to compare between patients and cohorts, combined with standardized protocols in the laboratory with a combination of different techniques. For future research in the field of IEMs, routine psychiatric care should determine whether patients present with atypical psychiatric manifestations that are considered "red flags" and use these standardized tools to characterize the symptoms. Additionally, NGS should be implemented within routine psychiatric care in case patients show these atypical symptoms. For future research in the field of autoantibodies, research should focus on combining the use of standardized scales with a combination of different laboratory techniques, among them immunohistochemistry, commercially available kits (cell based assays) and primary hippocampal neurons to comprehensively test for the presence of autoantibodies.

Other future recommendations would entail national and international collaborations and establishing joint clinics (**chapter 2**). National and international collaborations are already established in the case of other rare disorders, such as 22q11.2 deletion syndrome (82). These collaborations are important, not only because these disorders are rare and including a large number of patients may be difficult without these collaborations, but also because developing new methods may be easier in case of such collaborations. Additionally, sharing knowledge, equipment, laboratories and/or infrastructures among different collaborating partners may yield better research output and lead to better science (and subsequently, patient care) in the future. Future perspectives would also entail raising awareness among current and future clinicians. The joint clinics, as proposed in **chapter 2**, could help to raise awareness, however, in order to provide more knowledge among future clinicians, changes have to be made as part of education or clinical training. This could be done by touching

upon these causes in lectures, seminars and case-based learning. Similar to implementing more knowledge on nutrition and lifestyle within medical training. These joint clinics may also act as an education center for clinicians during specialization.

Finally, another important point for improvement would be to shift to a transdiagnostic approach instead of a disorder-specific one. Psychiatric comorbidity is reported in 40% of the patients within psychiatric care (83), indicating that many patients are diagnosed with more than one psychiatric disorder. Some epidemiological findings even suggest that single and uncomplicated clinical manifestations are rare and that comorbidity among psychiatric disorders is common (84). It is hypothesized that this high comorbidity is the result of a similar underlying basis between different psychiatric disorders rather than simply a co-occurrence of several disorders (85, 86, 87). Hence, this high comorbidity suggests that psychopathology has a dimensional nature and is not restricted to a specific disorder. By shifting to a transdiagnostic approach, which is a trend we currently see in psychiatric research, novel insights regarding our understanding of psychiatric disorders may arise (88, 89).

CONCLUDING REMARKS

The studies compiled in this thesis offer a deeper insight into the prevalence and clinical characteristics of rare forms of psychosis and the importance of screening for such disorders within psychiatric care. Although rare individually, collectively they are relatively common, and the effects of such a disorder can significantly impact the patient and their surroundings. Hence, early identification and diagnosis including using a combination of standardized clinical scales and validated assessments is necessary. Therefore, more awareness and education among clinicians is needed including the recognition of alarm signals or red flags. Once recognized, adequate treatment can be given and this may have a major impact on patients' lives.

REFERENCES

1. Mak CM, Lee HC, Chan AY, Lam CW. Inborn errors of metabolism and expanded newborn screening: review and update. Crit Rev Clin Lab Sci. 2013;50(6):142-62.
2. Wang T, Ma J, Zhang Q, Gao A, Wang Q, Li H, et al. Expanded Newborn Screening for Inborn Errors of Metabolism by Tandem Mass Spectrometry in Suzhou, China: Disease Spectrum, Prevalence, Genetic Characteristics in a Chinese Population. Front Genet. 2019;10:1052.
3. Jeanmonod R, Asuka E, Jeanmonod D. Inborn Errors Of Metabolism. 2022 July 18, 2022. In: StatPearls [Internet]. Treasure Island, Florida: StatPearls Publishing.
4. Demily C, Sedel F. Psychiatric manifestations of treatable hereditary metabolic disorders in adults. Ann Gen Psychiatry. 2014;13:27.
5. Sedel F, Baumann N, Turpin JC, Lyon-Caen O, Saudubray JM, Cohen D. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J Inherit Metab Dis. 2007;30(5):631-41.
6. Trakadis YJ, Fulginiti V, Walterfang M. Inborn errors of metabolism associated with psychosis: literature review and case-control study using exome data from 5090 adult individuals. J Inherit Metab Dis. 2018;41(4):613-21.
7. van de Burgt N, van Doesum W, Grevink M, van Niele S, de Koning T, Leibold N, et al. Psychiatric manifestations of inborn errors of metabolism: A systematic review. Neurosci Biobehav Rev. 2023;144:104970.
8. Sigmundsdottir L, Tchan MC, Knopman AA, Menzies GC, Batchelor J, Sillence DO. Cognitive and psychological functioning in Fabry disease. Arch Clin Neuropsychol. 2014;29(7):642-50.
9. Nia S. Psychiatric signs and symptoms in treatable inborn errors of metabolism. J Neurol. 2014;261 Suppl 2(Suppl 2):S559-68.
10. Jans JJM, Broeks MH, Verhoeven-Duif NM. Metabolomics in diagnostics of inborn metabolic disorders. Curr Opin Syst Biol. 2022;29.
11. Mura G, Zimbrean PC, Demelia L, Carta MG. Psychiatric comorbidity in Wilson's disease. Int Rev Psychiatr. 2017;29(5):445-62.
12. Shanmugiah A, Sinha S, Taly AB, Prashanth LK, Tomar M, Arunodaya GR, et al. Psychiatric manifestations in Wilson's disease: A cross-sectional analysis. Journal of Neuropsychiatry and Clinical Neurosciences. 2008;20(1):81-5.
13. Bilder DA, Kobori JA, Cohen-Pfeffer JL, Johnson EM, Jurecki ER, Grant ML. Neuropsychiatric comorbidities in adults with phenylketonuria: A retrospective cohort study. Mol Genet Metab. 2017;121(1):1-8.
14. Fattal O, Link J, Quinn K, Cohen BH, Franco K. Psychiatric comorbidity in 36 adults with mitochondrial cytopathies. CNS Spectr. 2007;12(6):429-38.
15. Koens LH, de Vries JJ, Vansenne F, de Koning TJ, Tijssen MAJ. How to detect late-onset inborn errors of metabolism in patients with movement disorders-A modern diagnostic approach*. Parkinsonism Relat D. 2021;85:124-32.
16. Ortigoza-Escobar JD. A Proposed Diagnostic Algorithm for Inborn Errors of Metabolism Presenting With Movements Disorders. Front Neurol. 2020;11.
17. Ware JS, Roberts AM, Cook SA. Next generation sequencing for clinical diagnostics and personalised medicine: implications for the next generation cardiologist. Heart. 2012;98(4):276-81.
18. Shen T, Pajaro-Van de Stadt SH, Yeat NC, Lin JC. Clinical applications of next generation sequencing in cancer: from panels, to exomes, to genomes. Front Genet. 2015;6:215.
19. Khorshidi S, Palangi A. Strategies and clinical applications of next generation sequencing. Multidisciplinary Cancer Investigation. 2018;2(4).
20. Yu M, Li S, Cheng J, Zhou L, Jiang Z, Di W. Ovarian teratoma-associated anti-NMDAR encephalitis: a single-institute series of six

patients from China. Arch Gynecol Obstet. 2021;303(5):1283-94.
21. Acien P, Acien M, Ruiz-Macia E, Martin-Estefania C. Ovarian teratoma-associated anti-NMDAR encephalitis: a systematic review of reported cases. Orphanet J Rare Dis. 2014;9:157.
22. Maat P, de Graaff E, van Beveren NM, Hulsenboom E, Verdijk RM, Koorengevel K, et al. Psychiatric phenomena as initial manifestation of encephalitis by anti-NMDAR antibodies. Acta Neuropsychiatr. 2013;25(3):128-36.
23. Dalmau J, Armangue T, Planaguma J, Radosevic M, Mannara F, Leypoldt F, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol. 2019;18(11):1045-57.
24. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157-65.
25. Al-Diwani A, Handel A, Townsend L, Pollak T, Leite MI, Harrison PJ, et al. The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data. Lancet Psychiatry. 2019;6(3):235-46.
26. Pollak TA, McCormack R, Peakman M, Nicholson TR, David AS. Prevalence of anti-N-methyl-D-aspartate (NMDA) receptor [corrected] antibodies in patients with schizophrenia and related psychoses: a systematic review and meta-analysis. Psychol Med. 2014;44(12):2475-87.
27. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-d-aspartate receptor encephalitis. JAMA Neurol. 2013;70(9):1133-9.
28. Dalmau J, Geis C, Graus F. Autoantibodies to Synaptic Receptors and Neuronal Cell Surface Proteins in Autoimmune Diseases of the Central Nervous System. Physiol Rev. 2017;97(2):839-87.
29. Grain R, Lally J, Stubbs B, Malik S, LeMince A, Nicholson TR, et al. Autoantibodies against voltage-gated potassium channel and glutamic acid decarboxylase in psychosis: A systematic review, meta-analysis, and case series. Psychiatry Clin Neurosci. 2017;71(10):678-89.
30. Luo Y, Li J, Jiang F, Tan A, Qin X, Xiao X, et al. Autoimmune Encephalitis With Psychotic Manifestations and Cognitive Impairment Presenting as Schizophrenia: Case Report and Literature Review. Front Psychiatry. 2022;13:827138.
31. Hansen N, Lipp M, Vogelgsang J, Vukovich R, Zindler T, Luedecke D, et al. Autoantibody-associated psychiatric symptoms and syndromes in adults: A narrative review and proposed diagnostic approach. Brain Behav Immun Health. 2020;9:100154.
32. Broadley J, Seneviratne U, Beech P, Buzzard K, Butzkueven H, O'Brien T, et al. Prognosticating autoimmune encephalitis: A systematic review. J Autoimmun. 2019;96:24-34.
33. Mayorova MA, Butoma BG, Churilov LP, Gilburd B, Petrova NN, Shoenfeld Y. Autoimmune Concept of Schizophrenia: Historical Roots and Current Facets. Psychiatr Danub. 2021;33(1):3-17.
34. Murashko AA, Pavlov KA, Pavlova OV, Gurina OI, Shmukler A. Antibodies against N-Methyl D-Aspartate Receptor in Psychotic Disorders: A Systematic Review. Neuropsychobiology. 2022;81(1):1-18.
35. Pathmanandavel K, Starling J, Merheb V, Ramanathan S, Sinmaz N, Dale RC, et al. Antibodies to surface dopamine-2 receptor and N-methyl-D-aspartate receptor in the first episode of acute psychosis in children. Biol Psychiatry. 2015;77(6):537-47.
36. Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain. 2012;135(Pt 11):3453-68.
37. Theorell J, Ramberger M, Harrison R, Mgbachi V, Jacobson L, Waters P, et al. Screening for pathogenic neuronal autoantibodies in serum and CSF of patients with first-episode psychosis.

Transl Psychiatry. 2021;11(1):566.
38. Jeppesen R, Nilsson AC, Sorensen NV, Orlovska-Waast S, Christensen RHB, Benros ME. Antineuronal antibodies in cerebrospinal fluid and serum of 104 patients with psychotic disorders compared to 104 individually matched healthy controls. Schizophr Res. 2023;252:39-45.
39. Wang J, Liu X, Lian J, Zheng H, Cai D, Cai H, et al. Autoimmune antibodies in first-episode psychosis with red flags: A hospital-based case-control study protocol. Front Psychiatry. 2022;13:976159.
40. Blackman G, Lim MF, Pollak T, Al-Diwani A, Symmonds M, Mazumder A, et al. The clinical relevance of serum versus CSF NMDAR autoantibodies associated exclusively with psychiatric features: a systematic review and meta-analysis of individual patient data. J Neurol. 2022;269(10):5302-11.
41. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol. 2014;13(2):167-77.
42. Guasp M, Modena Y, Armangue T, Dalmau J, Graus F. Clinical features of seronegative, but CSF antibody-positive, anti-NMDA receptor encephalitis. Neurol Neuroimmunol Neuroinflamm. 2020;7(2).
43. Pandey S, Balint B. Mind the Gap: Seronegative but Cerebrospinal Fluid Antibody-Positive Anti-N-Methyl-D-Aspartate Receptor Encephalitis. Mov Disord Clin Pract. 2020;7(5):500-1.
44. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurology. 2014;13(2):167-77.
45. Ramanathan S, Dale RC, Brilot F. Anti-MOG antibody: The history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun Rev. 2016;15(4):307-24.
46. Singh B, Cruz-Flores S, Chaudhry MR, Piriyawat P, Ponce CP. Psychiatric manifestations of anti-MOG antibody disease. Neuroimmunology Reports. 2022;2:100073.
47. Zhou J, Tan W, Tan SE, Hu J, Chen Z, Wang K. An unusual case of anti-MOG CNS demyelination with concomitant mild anti-NMDAR encephalitis. J Neuroimmunol. 2018;320:107-10.
48. von Zedtwitz K, Matteit I, Michel M, Feige B, Runge K, Denzel D, et al. Anti-MOG autoantibody-associated schizophreniform psychosis. Acta Neuropsychiatr. 2021:1-8.
49. 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.
50. Lautenschlager NT, Forstl H. Organic psychosis: Insight into the biology of psychosis. Curr Psychiatry Rep. 2001;3(4):319-25.
51. Waters F, Collerton D, Ffytche DH, Jardri R, Pins D, Dudley R, et al. Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye disease. Schizophr Bull. 2014;40 Suppl 4(Suppl 4):S233-45.
52. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10(1):63-74.
53. Thieben MJ, Lennon VA, Boeve BF, Aksamit AJ, Keegan M, Vernino S. Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. Neurology. 2004;62(7):1177-82.
54. Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain. 2004;127:701-12.
55. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and Characteristics of

Isolated Psychiatric Episodes in Anti-N-Methyl-D-Aspartate Receptor Encephalitis. Jama Neurology. 2013;70(9):1133-9.
56. Urgoiti GR, Sinnarajah A, Hussain S, Hao D. Paraneoplastic neuropsychiatric syndrome presenting as delirium. Bmj Support Palliat. 2017;7(2):218-20.
57. de Jaime Ruiz P, Garcia-Fogeda Romero JL, Gutierrez-Rojas L. Catatonia and Mutism: Neurotic, Psychotic, or Organic Disorder? Case Rep Psychiatry. 2021;2021:5936673.
58. Smith KP, Penzner JB. Mutism in non-catatonic schizophrenia: Psychotic symptom and adaptive behavioral strategy. Schizophr Res. 2015;168(1-2):569-70.
59. Narayan S, Thomas EA. Sphingolipid abnormalities in psychiatric disorders: a missing link in pathology? Front Biosci (Landmark Ed). 2011;16:1797-810.
60. van Kruining D, Luo Q, van Echten-Deckert G, Mielke MM, Bowman A, Ellis S, et al. Sphingolipids as prognostic biomarkers of neurodegeneration, neuroinflammation, and psychiatric diseases and their emerging role in lipidomic investigation methods. Adv Drug Deliv Rev. 2020;159:232-44.
61. Schwarz E, Prabakaran S, Whitfield P, Major H, Leweke FM, Koethe D, et al. High throughput lipidomic profiling of schizophrenia and bipolar disorder brain tissue reveals alterations of free fatty acids, phosphatidylcholines, and ceramides. J Proteome Res. 2008;7(10):4266-77.
62. Narayan S, Head SR, Gilmartin TJ, Dean B, Thomas EA. Evidence for disruption of sphingolipid metabolism in schizophrenia. J Neurosci Res. 2009;87(1):278-88.
63. Liu J, Xiu M, Liu H, Wang J, Li X. Plasma Lysophosphatidylcholine and Lysophosphatidylethanolamine Levels Were Associated With the Therapeutic Response to Olanzapine in Female Antipsychotics-naive First-episode Patients With Schizophrenia. Front Pharmacol. 2021;12:735196.
64. Keshavan MS, Mallinger AG, Pettegrew JW, Dippold C. Erythrocyte membrane phospholipids in psychotic patients. Psychiatry Res. 1993;49(1):89-95.
65. Wang DF, Cheng SL, Fei Q, Gu HW, Raftery D, Cao B, et al. Metabolic profiling identifies phospholipids as potential serum biomarkers for schizophrenia. Psychiat Res. 2019;272:18-29.
66. Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of 'precision psychiatry'. BMC Med. 2017;15(1):80.
67. Zhang A, Sun H, Yan G, Wang P, Wang X. Metabolomics for Biomarker Discovery: Moving to the Clinic. Biomed Res Int. 2015;2015:354671.
68. Matanes F, Twal WO, Hammad SM. Sphingolipids as Biomarkers of Disease. Adv Exp Med Biol. 2019;1159:109-38.
69. Sui J, He M, Wang Y, Zhao X, He Y, Shi B. Sphingolipid metabolism in type 2 diabetes and associated cardiovascular complications. Exp Ther Med. 2019;18(5):3603-14.
70. Jensen PN, Fretts AM, Hoofnagle AN, McKnight B, Howard BV, Umans JG, et al. Circulating ceramides and sphingomyelins and the risk of incident cardiovascular disease among people with diabetes: the strong heart study. Cardiovasc Diabetol. 2022;21(1).
71. Hu XM, Fan Y, Li HY, Zhou RL, Zhao XY, Sun YS, et al. Impacts of Cigarette Smoking Status on Metabolomic and Gut Microbiota Profile in Male Patients With Coronary Artery Disease: A Multi-Omics Study. Front Cardiovasc Med. 2021;8.
72. Fretts AM, Jensen PN, Hoofnagle AN, McKnight B, Howard BV, Umans J, et al. Plasma ceramides containing saturated fatty acids are associated with risk of type 2 diabetes. J Lipid Res. 2021;62.
73. Mielke MM, Lyketsos CG. Alterations of the sphingolipid pathway in Alzheimer's disease: new biomarkers and treatment targets? Neuromolecular Med. 2010;12(4):331-40.
74. Tessier C, Sweers K, Frajerman A, Bergaoui H, Ferreri F, Delva C, et al. Membrane lipidomics in schizophrenia patients: a

correlational study with clinical and cognitive manifestations. Transl Psychiat. 2016;6.

75. Schmitt A, Wilczek K, Blennow K, Maras A, Jatzko A, Petroianu G, et al. Altered thalamic membrane phospholipids in schizophrenia: A postmortem study. Biol Psychiat. 2004;56(1):41-5.

76. Whiley L, Sen A, Heaton J, Proitsi P, Garcia-Gomez D, Leung R, et al. Evidence of altered phosphatidylcholine metabolism in Alzheimer's disease. Neurobiol Aging. 2014;35(2):271-8.

77. Mapstone M, Cheema AK, Fiandaca MS, Zhong XG, Mhyre TR, MacArthur LH, et al. Plasma phospholipids identify antecedent memory impairment in older adults. Nat Med. 2014;20(4):415-+.

78. Bentsen H, Solberg DK, Refsum H, Gran JM, Bohmer T, Torjesen PA, et al. Bimodal distribution of polyunsaturated fatty acids in schizophrenia suggests two endophenotypes of the disorder. Biol Psychiatry. 2011;70(1):97-105.

79. Hoen WP, Lijmer JG, Duran M, Wanders RJA, van Beveren NJM, de Haan L. Red blood cell polyunsaturated fatty acids measured in red blood cells and schizophrenia: A meta-analysis. Psychiat Res. 2013;207(1-2):1-12.

80. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin. 1987;13(2):261-76.

81. Beck AT, Steer RA, Brown G. Beck depression inventory–II. Psychological assessment. 1996.

82. McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JAS, et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers. 2015;1.

83. Jacobi F, Hofler M, Siegert J, Mack S, Gerschler A, Scholl L, et al. Twelve-month prevalence, comorbidity and correlates of mental disorders in Germany: the Mental Health Module of the German Health Interview and Examination Survey for Adults (DEGS1-MH). Int J Methods Psychiatr Res. 2014;23(3):304-19.

84. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617-27.

85. Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, et al. The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? Clin Psychol Sci. 2014;2(2):119-37.

86. Lahey BB, Krueger RF, Rathouz PJ, Waldman ID, Zald DH. Validity and utility of the general factor of psychopathology. World Psychiatry. 2017;16(2):142-4.

87. Lahey BB, Krueger RF, Rathouz PJ, Waldman ID, Zald DH. A hierarchical causal taxonomy of psychopathology across the life span. Psychol Bull. 2017;143(2):142-86.

88. 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.

89. Van Amelsvoort TAMJ, Klaassen MC, Van den Heuvel OA. Transdiagnostische psychiatrie: concept in ontwikkeling. Tijdschrift voor psychiatrie. 2018;60.

APPENDICES

Summary

A diagnosis of a psychotic disorder consists of one or more psychotic episodes characterized by a variation of symptoms, among them hallucinations, delusions, a lack of motivation, and cognitive impairment. The cause of a psychotic disorder is often not precisely known, although several risk factors for developing psychotic symptoms have been described. In some cases, an underlying disease may cause the occurrence of psychotic symptoms. This thesis focused on a few of these rare underlying causes of psychosis, among them inborn errors of metabolism (IEMs) and the presence of antibodies against receptors, complexes, and proteins in the brain. Additionally, this thesis focused on the role of sphingolipids in psychotic symptoms. For this purpose, this thesis is divided into three sections, each focusing on one of these rare causes of psychotic symptoms. In these sections, several techniques are combined, both genetic and molecular methods. These techniques are combined to determine how these causes relate to psychotic symptoms.

The first section of this thesis focused on IEMs. It is known that EMs may manifest with psychiatric symptoms, especially in the case of more mild forms. The more mild variants usually manifest during adolescence, making distinguishing between psychiatric symptoms due to an IEM or a primary mental disorder difficult. To gain more insight into the variety of psychiatric manifestations among IEMs, to determine whether there is a difference between psychiatric manifestations due to an IEM or a primary mental disorder, and to determine whether the described manifestations are based on standardized clinical scales, we conducted an extensive literature review in **chapter 2** of this thesis. In this review, we discuss the different IEMs associated with psychiatric manifestations and describe the standardized clinical scales used to measure the severity of these manifestations. We emphasize the combination of atypical psychiatric symptoms, such as visual hallucinations, confusion, and cognitive impairment, together with developmental delay, gastrointestinal complaints, and exercise intolerance. Therefore, a suspicion of an IEM should be raised in case a combination of these symptoms is observed in a patient within the psychiatric field. In order to help and guide psychiatrists or other clinicians, a diagnostic screener has been proposed, which consists of several steps and diagnostic methods. By combining standardized clinical scales with the proposed diagnostic screener within the psychiatric field, patients with an underlying IEM should be recognized sooner, and diagnostic delays may be prevented in the future.

Subsequently, in **chapter 3**, we screened for IEMs in blood samples of 60 patients with a psychotic disorder by using next generation sequencing (NGS), a method to sequence (parts of the) DNA with only one blood sample. In this chapter, we aimed to investigate whether this screening tool could act as an alternative for the currently used methods, usually invasive and extensive, to detect IEMs. Blood samples of 60 patients with a psychotic

disorder were used to detect various homozygous and heterozygous mutations associated with IEMs and compared to a reference genome, GoNL, as a control. No homozygous mutations were found in the patients with a psychotic disorder, although several pathogenic heterozygous mutations were observed. Additionally, no differences were observed in the number of heterozygous mutations found in the patients with a psychotic disorder and the controls. However, we did confirm that NGS could be used as an alternative to detect mutations that are associated with IEMs.

In section 2 of this thesis, the focus shifted to the presence of antibodies against neuronal receptors, complexes, and proteins as a rare underlying cause of psychosis. These autoantibodies may cause an autoimmune response after binding to surface proteins, leading to neuroinflammation and a variety of (psychiatric) symptoms, of which psychosis is one of them. In **chapter 4**, we discuss the results of a clinical study in which the blood of 45 patients with at least one psychotic episode was tested for the presence of these autoantibodies by immunohistochemistry (IHC). Additionally, in 19 out of these patients, cerebrospinal fluid (CSF) was used to screen for these autoantibodies as well. Initial analysis showed that one patient's blood tested positive for the presence of these autoantibodies, resembling already known patterns. This patient was initially diagnosed with a psychotic disorder not otherwise specified, and the duration of illness was less than one year. To determine the specific antigen to which these autoantibodies bind and to determine whether these antibodies bind to the surface of the neurons, cell-based assays, and primary hippocampal neurons will be used in the future.

In **chapter 5** of this thesis, we screened for the presence of autoantibodies against myelin oligodendrocyte glycoprotein (MOG). This protein is located on the surface of oligodendrocytes and myelin and was recently associated with (isolated) psychotic symptoms. In this study, we screened for the presence of autoantibodies against MOG in blood samples of 262 patients with at least one psychotic episode by using cell-based assays and flow cytometry. Additionally, we compared our findings of these two methods with the blood samples of 163 controls. In total, four patients and none of the controls tested positive for the presence of MOG autoantibodies. In the case of 3 out of 4 patients, their psychotic symptoms included visuals, hallucinations, and/or strong cognitive decline. The final section of this thesis, section 3, investigates if there are changes in lipid levels in the CSF in patients with psychotic symptoms. In **chapter 6**, we investigated whether a disbalance in lipids in the CSF of 18 patients with psychotic symptoms compared to 18 controls could be observed. Our results showed changes in levels of lipids in specific lipid classes and individual lipid species in patients with psychotic symptoms compared to controls. However, whether these changes are unique to psychotic symptoms and whether

they are associated with other specific clinical characteristics is yet to be determined.

Finally, in **chapter 7** of this thesis, the different studies are integrated and their relevance within research and the clinic, as well as their limitations, are discussed. Additionally, possibilities for future research are proposed.

A

Samenvatting

Een psychotische stoornis wordt gekenmerkt door een of meerdere psychotische episodes, welke zich uiten in klachten zoals hallucinaties, waanbeelden, een gebrek aan motivatie en cognitieve achteruitgang. Het is vaak niet duidelijk hoe een psychotische stoornis precies ontstaat, ondanks dat er wel een aantal risicofactoren zijn beschreven. In een aantal zeldzame gevallen, ligt er echter een onderliggende ziekte ten grondslag aan de psychotische symptomen. Dit proefschrift heeft zich gefocust op een aantal van deze zeldzame onderliggende oorzaken van psychose, waaronder aangeboren stofwisselingsziekten en de aanwezigheid van antistoffen tegen receptoren en andere antigenen in de hersenen. Ook hebben we onderzocht welke rol sfingolipiden spelen in het hebben van psychotische symptomen. Dit proefschrift is onderverdeeld in drie secties, waarin elke van deze zeldzame onderliggende oorzaken worden besproken en onderzocht. Hierbij worden een aantal verschillende technieken gecombineerd, zowel genetisch als moleculair, om te onderzoeken hoe deze oorzaken samenhangen met de symptomen die patiënten met een psychotische stoornis ervaren.

De eerste sectie focust zich op zeldzame stofwisselingsziekten, welke in het Engels inborn errors of metabolism worden genoemd. Het is bekend dat deze stofwisselingsziekten, met name de meer mildere vormen die zich later in het leven manifesteren, zich kunnen uiten in psychiatrische klachten. Om meer inzicht te krijgen in de variëteit aan psychiatrische klachten, te kunnen beoordelen hoe goed gestandaardiseerde psychiatrische hulpmiddelen zijn geïntegreerd in de tot nu toe gepubliceerde wetenschappelijke onderzoeken en te kunnen beoordelen hoe deze klachten zich onderscheiden van primaire psychotische symptomen, bevat **hoofdstuk 2** een kritisch literatuuroverzicht waarin we de relatie tussen deze zeldzame stofwisselingsziekten en psychiatrische klachten bespreken. De verschillende stofwisselingsziekten die zijn geassocieerd met psychiatrische klachten en de gebruikte gestandaardiseerde psychiatrische hulpmiddelen worden samengevat. Dit kritische literatuuroverzicht benadrukt dat de psychiatrische klachten vaak atypisch zijn, zoals het ervaren van visuele hallucinaties, verwarring, grote cognitieve achteruitgang, een (lichte) ontwikkelingsachterstand en het niet reageren op psychotrope geneesmiddelen zoals verwacht. Bovendien ervaren patiënten vaak andere klachten, zoals gastro-intestinale klachten en/of inspanningsintolerantie, naast de psychiatrische klachten. De combinatie van psychiatrische en lichamelijke klachten dient de behandelend psychiater of arts alert te maken op het feit dat een mogelijke stofwisselingsziekte ten grondslag ligt aan de psychiatrische klachten. Om clinici te helpen hebben we op basis van de resultaten van het kritisch literatuuroverzicht een beslisboom gemaakt, waarin de verschillende stappen en meetmethodes worden genoemd om te bepalen of er inderdaad sprake is van een onderliggende stofwisselingsziekte. Door gestandaardiseerde psychiatrische hulpmiddelen te combineren met deze beslisboom hopen we dat patiënten met een stofwisselingsziekte

binnen de psychiatrie in de toekomst sneller worden herkend en zo sneller een adequate behandeling krijgen, waarin de focus ligt op het behandelen van de stofwisselingsziekte, in plaats van alleen de psychiatrische klachten.

In **hoofdstuk 3** hebben we onderzocht of een vernieuwende manier van DNA sequencen, namelijk next generation sequencing (NGS), een alternatief zou kunnen zijn voor de invasieve en vele meetmethoden die in de huidige klinische praktijk worden gebruikt om een zeldzame stofwisselingsziekte te diagnosticeren. In dit onderzoek hebben we bloedmonsters van 60 patiënten met een psychotische stoornis onderzocht op een variëteit aan mutaties die zijn geassocieerd met een zeldzame stofwisselingsziekte en deze resultaten vergeleken met "het genoom van Nederland", een zogenaamd referentiegenoom. Dit referentiegenoom bevat een digitale database met nucleïnezuursequenties van 498 Nederlanders. De aanwezigheid van homozygote en heterozygote mutaties tussen patiënten met een psychotische stoornis en de gemiddelde Nederlander zijn vergeleken. Er werden geen homozygote mutaties, maar wel een aantal pathogene heterozygote mutaties in de patiënten met een psychotische stoornis gedetecteerd. Het verschil tussen het aantal heterozygote mutaties tussen patiënten met een psychotischte stoornis en het referentiegenoom was niet significant. Onze resultaten laten ook zien dat NGS een geschikte methode is om mutaties, die zijn geassocieerd met een zeldzame stofwisselingsziekte, te detecteren.

In sectie 2 hebben we ons vervolgens gefocust op de aanwezigheid van antistoffen en hun associatie met psychotische klachten. Deze antistoffen kunnen zich binden aan antigenen in de hersenen en zorgen voor een auto-immuun reactie, wat kan resulteren in een verscheidenheid aan (psychiatrische) klachten. In **hoofdstuk 4** bespreken we de resultaten van een studie waarin we het bloed 45 patiënten hebben onderzocht op de aanwezigheid van deze antistoffen door middel van immunohistochemie (IHC). Van 19 van de 45 patiënten is ook het hersenvocht getest. In totaal is één patiënt positief getest op de aanwezigheid van deze antistoffen, met een patroon wat lijkt op het patroon zoals beschreven bij antistoffen tegen de NMDAR of DPPX. Deze patiënt is een man van 20 jaar met een diagnose psychotische stoornis niet anders gespecificeerd met een ziekteduur van minder dan een jaar. Het bloedmonster zal nog verder worden onderzocht door middel van cel-gebaseerde tests en een primaire neuronale cellijn om te bepalen aan welk specifiek antigen deze antistoffen zijn gebonden.

In **hoofdstuk 5** hebben we onderzoek gedaan naar de aanwezigheid van een relatief nieuwe antistof binnen de psychiatrie, namelijk de antistof die zich bindt aan myelin oligodendrocyte glycoprotein, ofwel MOG. Dit eiwit bevindt zich aan de oppervlakte van de

myeline en de oligodendrocyten in ons zenuwstelsel. In deze studie hebben we de aanwezigheid van deze antistoffen in bloedmonsters van in totaal 262 patiënten die minimaal één psychotische episode hebben doorgemaakt onderzocht door middel van cel-gebaseerde tests en flowcytometrie. Deze bevindingen hebben we vervolgens vergeleken met de aanwezigheid van deze antistof in bloedmonsters van 163 controle proefpersonen. In totaal zijn er 4 patiënten positief getest op de aanwezigheid van deze antistoffen.

In sectie 3 van dit proefschrift verschuift de focus naar de rol van lipiden in psychotische klachten. In **hoofdstuk 6** hebben we het hersenvocht van patiënten met psychotische klachten geanalyseerd door middel van vloeistofchromatografie-massaspectrometrie (LC-MS/MS) en deze vergeleken met die van controle proefpersonen. Een verschil in zowel individuele lipiden als een verschil in een aantal lipide klassen werd gedetecteerd, alhoewel het nog niet duidelijk is of deze verschillen uniek zijn voor patiënten met psychotische symptomen en of deze verschillen een associatie vormen met andere klinische kenmerken.

In **hoofdstuk 7** worden vervolgens de verschillende studies uit dit proefschrift besproken en geïntegreerd om de wetenschappelijke en klinische implicaties als ook de beperkingen te bespreken. Bovendien worden er suggesties gedaan voor vervolgonderzoek.

A

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.

A

Curriculum Vitae

Nikita van de Burgt was born on September 3rd, 1994 in Leiden, the Netherlands. Determined to learn more about the human body and the brain, she started her bachelor's degree in Health and Life Sciences with a specialization in Biomedical Sciences and Neuroscience at the Vrije Universiteit Amsterdam in 2012. During her bachelor, she decided to move to Maastricht to follow an internship with a focus on electroencephalogram (EEG) measurements and schizophrenia. Intrigued by the field of psychiatry and neuropsychology, she decided to continue her studies by following a master in Neuropsychology at Maastricht University in 2015. During her master, she learned more about healthy ageing and neuropsychological testing. What fascinated her most was how behavior and disorders are caused on a molecular and cellular level. Consequently, she decided to continue her studies by following a second master in 2016: Biomedical Sciences at Maastricht University. During her internships, she investigated the role of inflammation within the placenta in women with pregnancy complications and the influence of plant sterols on inflammation in Niemann-Pick disease. After her second internship, Nikita was awarded best poster presentation at the MOSA conference. With the vision to combine both clinical psychiatry, neuropsychology and fundamental neuroscience, she started her PhD at the department of Psychiatry and Neuropsychology at Maastricht University, under the supervision of prof. dr. Pilar Martinez-Martinez and prof. dr. Therese van Amelsvoort in September 2018. Throughout her PhD, she worked at three main projects; the first project aimed to determine the prevalence of psychotic disorder in individuals with an underlying inborn error of metabolism. The second project aimed to learn more about the role of autoantibodies in patients with a psychotic disorder and finally, the third project aimed to elucidate the role of sphingolipids in these patients. She was a PhD representative during her entire PhD, was involved in the Educational Committee and supervised several bachelor and master students. Upon completion of her PhD, Nikita will continue her career within academia as a teacher at the faculty of Psychology and Neuroscience.

List of publications

PUBLISHED

2023 **Nikita van de Burgt**, Willem van Doesum, Mirjam Grevink, Stephanie van Niele, Tom de Koning, Nicole Leibold, Pilar Martinez-Martinez, Therese van Amelsvoort, Danielle Cath. Psychiatric manifestations of inborn errors of metabolism: a systematic review. Neurosci Biobehav Rev. 2023 Jan; 144: 104970. doi: 10.1016/j.neubiorev.2022.104970.

2021 **Nikita van de Burgt**, Silvana van Koningsbruggen, Leonie Behrens, Nicole Leibold, Pilar Martinez-Martinez, Marcel Mannens, Therese van Amelsvoort. Screening for inborn errors of metabolism in psychotic patients using Next Generation Sequencing. J Psychiatr Res. 2021 Jun; 138: 125-129. doi: 10.1016/j.jpsychires.2021.03.060.

SUBMITTED

2023 **Nikita van de Burgt**, Laila Kulsvehagen, Marina Mané-Damas, Luc Lutz, Anne-Catherine Lecourt, Clara Monserrat, Anita Vinke, Cem İ. Küçükali, Shenghua Zong, Carolin Hoffmann, Emiliano González-Vioque, Celso Arango, Nicole Leibold, Mario Losen, Peter Molenaar, Erdem Tüzün, Nico van Beveren, Anna Mané, Rob Rouhl, For Genetic Risk and Outcome of Psychosis (GROUP) Investigators Therese van Amelsvoort, Anne-Katrin Pröbstel, Pilar Martinez-Martinez. Autoantibodies against myelin oligodendrocyte glycoprotein associated with psychosis in a subgroup of patients.

IN PREPARATION

2023 **Nikita van de Burgt**, Daan van Kruining, Therese van Amelsvoort, Pilar Martinez-Martinez, Nicole Leibold. Altered levels of phospholipids and sphingolipids in cerebrospinal fluid of patients with psychotic symptoms.

2023 Marina Mané-Damas, **Nikita van de Burgt**, Anita Vinke, Bea Campforts, Carolin Hoffmann, Shenghua Zong, Peter Molenaar, Mario Losen, Rob Rouhl, Nicole Leibold, Therese van Amelsvoort, Pilar Martinez-Martinez. Prevalence of neuronal surface antibodies in a cohort of recent-onset psychosis: The PSYANTIB study – an update.

PRESENTATION RELATED TO THIS THESIS

2023	Oral presentation	MHeNS Research Day	Maastricht (NL)
2022	Poster presentation	Novel Mechanisms, Tools and Therapies in Neuroinflammation workshop	London (UK)
2021	Oral presentation	MHeNS Research Day	Online
2019	Poster presentation	Get the VIBE symposium	Eindhoven (NL)
2019	Oral presentation	Unwrapped Psychology	Maastricht (NL)
2019	Poster presentation	MHeNS Research Day	Maastricht (NL)

Acknowledgements

First, I would like to start by thanking my promotion team. Dear Therese, dear Pilar, thank you for giving me the chance to start my career under your supervision. Thank you for creating a PhD position in which I was able to combine both patient and laboratory work. After 5 years I still believe that such collaborations are essential to make a difference in the lives of patients in the future. You both have taught me so much regarding the importance of translational research and I am happy to complete my PhD with both of you as my supervisor. You are both examples that being successful in science as a woman is definitely possible and that being the head of your own research group is something that one can achieve. Additionally, I would like to thank you for always seeing possibilities and opportunities in all of our projects. Even when projects weren't progressing as expected, you both stayed optimistic and were confident that completing projects was possible. IT turned out... you were right. ☺ Furthermore, thank you for adding Nicole to the promotion team.

Secondly, I would like to thank you, Nicole, for everything. Honestly, I don't even know where to start. I am so happy that you joined our promotion team as a co-promotor during my second year. Thank you for being only a text or call away when I needed advice on whatever was going on at the moment. Even on Wednesdays, when I always seemed to forget that it was your day off after Max was born (again: sorry for that). Somehow, this was something I always realized after I have already sent the text, haha. But my questions were never too much and you always answered them kindly. Especially during my last year, I must have sent you so many messages. Not only with questions, but also to share what was going on or what was going through my mind. You were always there and only a text or call away. Thank you for all your advice on both research-related topics, as advice on student guidance, advice on practical matters and your support on a daily basis. It really means a lot. Without you, those papers would not be finished and this thesis would not have been written. Although you are a co-author on several papers, this does not reflect by far what you have done for me during the last three years of my PhD. Thank you for being an exemplary human being and to show that not being perfect is good enough. I hope I will be a person like you for someone else at least once in my life. I think you make the world a better place and I hope more people like you will join academia every day.

DIVISION TWO (VIJVERDAL)

First, I would like to thank all the secretaries at division two. Thank you Trees, Jolanda, Ine and Nancy for all your help with practical issues. Thank you for arranging everything regarding meetings, invitations and fun events. Without you as secretaries, things at the department would not run as smoothly. So a big thank you for all your work!

Furthermore, I would like to thank all our research assistants for their help over the years. Thank you Nele, Nele, Truda and Bea. Thank you for all your help with the recruitment, screening and testing of patients. And thank you Bea in particular, for all your help with PSYANTIB. Without you, it would not have been possible to test all these patients. I am happy that you managed to create a PhD position and I wish you all the best. I am looking forward to reading your work and to applaud at your defense in the future.

Thank you, Claudia V., for the nice conversations when you were around on Wednesdays during my first few years. It was always nice to see you and to hear your stories, both research-related as cat- and bunny-related. ☺ And thank you for being able to use the SMURF samples for our IEM study. And thank you, Claudia S., for all your help with getting the approval to use the GROUP samples for our MOG study. Thank you for being so kind and patient. You always answered my (million) questions with a smile. Thank you for that!

Especially thanks to you, Maud, for all the laughter and listening to everything we went through the first years. Sadly, we haven't seen each other as much in the last year(s) due to COVID-19, but nevertheless, thank you so much for being part of my journey at the beginning of my PhD. You were always there to listen, and I am still laughing about our 5-minute moments of complaining after our meetings before we continued our work. Because of you I looked forward to lunch in the morning, learned a lot about triathlons and even improved my planking skills for a while. You are definitely an example both professionally and person-wise. I admire your perseverance and ability to make me (and others!) laugh in every situation. I am happy that you were able to continue within the division as a research coordinator and were always there for me when I needed advice during the last months of my PhD. I am definitely going to miss you while I am teaching and if I would ever be able to do so, I would vote for a Maud in every department to make the day. Please stay true to who you are and keep being the amazing go-to person for laughter, pets, fish and of course, lunch. ☺

Thank you, Kobus and Emma, for taking over Maud her role as office buddies. Thank you for the laughter, with you guys "gedeelde smart is halve smart" really makes sense. I am happy that we could share anything and I am going to miss you guys as well. I hope that your research will lead to amazing results and breakthroughs and I can't wait to applaud at your defense in a few years Emma. You got this and if you ever need someone to help you with writing an amendment to the METC (because we all know you will do this at least once during your PhD, hahaha ☺) you know where to find me. Kobus, I think it is really brave that you decided to follow your heart. Keep doing what makes you happy and I am sure everything will work out. Enjoy travelling in South-America and don't hesitate to share your

adventures and beautiful pictures with us. ☺

And thank you Stella, Sam, Chaira and Emma for being great next-door office buddies! I really enjoyed our nice conversations, lunching together and some occasional drinks. ☺

And finally, thank you to all other PhD students, staff and other individuals that work(ed) or were/are affiliated at/to division two. Thank you for the laughter and nice conversations.

DIVISION THREE (LAB)

First, I would like to thank Rachelle for all her help with all the practical issues during these five years. Thank you for arranging meetings, invitations and the final steps of the PhD. Furthermore, thank you for being involved in all the fun activities all those years.

Second, I would like to thank our NEURIM research group. I have learned so much from all of you in the past few years. Thank you for all your hard work and efforts. Marina and Shenghua, thank you for teaching me everything I know about blood and CSF processing, immunohistochemistry, cell-based assays, animal studies, neurons and so much more. Thank you for every discussion about our results and ideas for future research. Shenghua, thank you for always being so friendly and patient. I think you are a great teacher and I am happy that you always made time, even though you explained something already a hundred times. ;). I think I can speak for the entire group that we were sad that you left to go back to China, although we wish you all the best. We are happy that you are still a bit connected to us and that you will still be involved in many projects. Thank you, Peter, for all your help with everything that had to do with the METC. Furthermore, I would like to thank you for all your help with checking all our work and improving our papers. And thank you to all of the PhD students that have already left or joined our team during my PhD; Tanya, Caterina, Daan, Anja, Qian, Britt, Houan, Peng, Michelle and Beatriz. Thank you, Carolin, for being able to use your samples, our discussions and all the ideas that led to finalizing some projects of this thesis. I am really curious about the new project that you started and I am already looking forward to the results. And thank you Mario for sharing all of your knowledge and your endless patience when explaining new concepts or techniques. Finally, I would like to thank all of you for being able to grow, both as a researcher and a person, within our group. Additionally, I would like to thank a few people individually.

Dear Caterina, thank you that you were always genuinely interested in our lives and that we were always welcome to come into your office for a chat. You are such a nice person and I am really happy for you that you finished your PhD, you deserved it. You worked really hard

for it and although it sometimes felt like it would take forever, I think you can't be anything but proud. You did it!!! I am also really happy that you found a job that you really enjoy and that you can finally be with Luca full-time. I hope you can both build a happy home and be happy together as long as you live. ☺

Dear Daan, thank you for your help with the sphingolipids project, without you I would not have written such a nice chapter. I have always admired you for your relaxed and positive attitude. I am sure you will do great at your defense and your career afterward will be amazing. The group was lucky to have you and I think I can speak for all of us that we were happy that you were always so organized and shared that characteristic with us. I wish you all the best and I hope your future with Sanda and Tommy will be bright.

Dear Tanya, I would like to thank you for always being there for me, for listening to all my stories and your advice. You were and are my go-to person when I needed to talk to someone or to simply share my experiences and sometimes frustration in the lab (all those failed experiments without knowing why they actually failed… ☺). Thank you for all the coffees, chats, hugs and laughter. Thanks to you the long days in the lab became better. So, thank you, thank you, thank you! I hope we will still be in touch in the upcoming years.

Dear Anja, thank you for letting me use your scissors, stapler and perforator (or hole puncher?! ☺) all those years when all of our office supplies seemed to go missing every once in a while. Even though we never really worked together in the lab, I enjoyed the time we spend as office buddies, especially in the last half year while I was trying to finish this PhD (now for real, haha). I hope you will be able to finish your PhD in the upcoming academic year as well and write a thesis you can be proud of. P.s. thank you for the staple certificate, I am sure it will be of great value during the upcoming years and later in my career! ☺

Dear Britt, I am so happy that you joined our group after covid. It was nice to have another Dutchie join the team and to share our love for (iced) coffee! Bringing the Nespresso machine was really one of the best ideas ever. I really appreciate you as a person, so please stay true to who you are. I am sure you will do amazing in the upcoming few years and if you ever need help with METC-related questions… You know where to find me. ☺ I am definitely going to miss you as an office buddy!

Dear Peng, I really hope that the next PhD in this office will be a guy to balance out all the girls in the office so you don't have to hear conversations about clothes and make-up all the time, haha. You are doing great in the lab and I wish you all the best of luck with your

experiments and in life. You've got this!

Additionally, I would like to thank the tech team. Without you, our department wouldn't function and projects would never be completed. Thank you for all your hard work and for all the advice that you have given throughout the years.

Dear Hellen, thank you so much for helping out when a staining didn't work or when the results turned out unexpectedly. Thank you for all your great tips and ideas, without you we would never be able to improve our staining protocols like we did. Thank you for making me feel confident and supported in my lab work. I honestly believe that with your advice I have grown both as a PhD student and as a person. Without your knowledge, not even half of the stainings at our department would succeed. Oh, and thank you for arranging the new keyboard and new chair, they really made writing in the last few months way more comfortable! ☺

Dear Sandra, thank you for sharing all your knowledge within the field of cell biology, your ideas and your help to improve my laboratory skills and our research. You were always there to listen and help, and I really appreciate that. Whether we were talking about research or life in general, you always had time to catch up and offer advice. I am kind of sad that we didn't work closely together more often, as I had a great time learning from you and testing those SepMate tubes and learning your tricks for blood processing. I am also really grateful that you are responsible to give the labs a big upgrade in all the machines and tools that we were using, they really made our life easier. And let's not forget your help with the cells, you were always a text away to discuss how the cells look like and whether or not it was going in the right direction. Furthermore, discussions about research with you were always so fun and really made me feel passionate about research again. With you, projects were actually fun. So if I will ever go back to research... I know who would be the best person to discuss research ideas with. ☺ And thank you that I could always ask you a question, no matter how big or small. Thank you for making me feel appreciated at work and as a person in general. With you, I felt appreciated as a human being and I am happy that, being around you, being myself was good enough. And of course, I would like to thank you for all the nice coffee breaks and nice pictures of Guusje. They always made my day! ☺ I wish you all the best and happiness in life and I hope we will still have more coffee breaks in the future.

And of course, I would like to thank all of the other technicians, Denise, Wouter and Barbie. Denise, thank you for your help and nice conversations. I admire you for your kindness and willingness to help. Thank you for always asking how I was doing and being genuinely interested in the answer. Not a day passed by without you being happy at work. I think that

we all benefit from that. So, please stay such a kind person, always. And let's not forget about your help with cleaning the freezers. Thank you! Wouter and Barbie, although my research didn't really allow me to work closely together with one of you, I really appreciate you for all your help and efforts in the last few years of my PhD. I know you have played a huge role in some of the studies in our research group. Thank you, thank you, thank you. Where would be without our technicians? Probably nowhere. ;)

Anna, I am happy that I got to know you during my third year as a PhD student. Thank you for the nice conversations, for sharing your ideas and for listening to everything I told you. I really appreciate your passion to share the importance of mental health in academia and to show that vulnerability is something that can be used for good purposes. Please, keep going and stay the nice person that you are.

Ellis, thank you so much. For everything. Because of you I survived the last years of this PhD, haha. ☺ Thank you for improving my level of sarcasm (or is it irony?), the million nice coffee and hot chocolate breaks. For being able to share everything professionally and personally. I am still surprised that you never get tired of all my stories, lol. No, with all the jokes aside, I am happy that you are a person that I can turn to, always. And know that this is likewise. I really hope your life will be filled with happiness and I believe you can do anything you set your mind to. You are incredibly smart and a kind person as well. I really hope we will stay in touch the upcoming years because I really need someone in my life that understands my humor and shares the love for silly memes, haha. P.s. thank you for helping with the part of my thesis that people will actually read ;)

Dear Daniël, I would like to thank you for being an example within our department and our university. I fully support your ideas and appreciate that you would like to make academia a place where everyone should feel supported and were working hard can be combined with family, boundaries and good mental health. I really believe that you can make a difference, so please continue sharing your passion for research and a healthy work-life balance.

And finally, thank you to all other PhD students, staff and other individuals that work(ed) at division three. Thank you for the laughter and nice conversations. I really enjoyed talking to you and teaching together. I am not going to mention everyone's names here, because I am afraid I will forget someone's name. But know that you all made a difference in doing a PhD at this department, big or small. For everyone that still needs to finish their PhD: you've got this! It is a cliché, but if I can do this… you can (definitely) do so too.

COLLABORATORS

Dear Leonie, Silvana and Marcel, thank you for our really interesting collaboration on IEMs in patients with a psychotic disorder. Especially thank you Silvana, for answering all my questions regarding NGS and its application. Even though none of the patients were affected, I am very proud that we made this contribution to this field, as this technique is really promising for diagnosing patients with an IEM (in the future). I hope this work will be used for future research and in the end, the clinic.

Dear Willem, Mirjam, Stephanie, Tom, Danielle and Ineke, thank you for our GIPSY collaboration. I think we can all agree that the review that we wrote was a lot of work and that there was a time that we felt like it was never-ending, but the end result is something to be proud of. I really hope it will impact the scientific community and the patient lives for the better.

Dear Laila, dear Anne-Katrin, thank you for your work on the MOG paper and your support and ideas during our MOG project. I really enjoyed working on this project and I am happy that we managed to write a nice paper about our findings. So let's hope it will be published soon. ☺

And thank you to everyone at the MUMC+ that I had the pleasure to work with during those five years. Not only at the department of Psychiatry and Neurology but also for the nice conversations within the CDL and the biobank. Thank you for all the help and all the interest in our studies. This genuine interest and our conversations really made doing research more fulfilling. And of course, I would like to thank everyone at the department of Pathology, for the use of the Ventana scanner (and the scanner after that) and all the help and kindness within the department.

Finally, I would like to thank all professionals within all the psychiatric departments throughout the Netherlands and Belgium. Thank you for sharing our research, your help with referring patients and your genuine interest in the results of our studies. Without your efforts we were never be able to complete our studies. Additionally, I would like to thank Pieter(-Bas) Kantebeen from GGzE in particular. Thank you for seeing the importance of our research and referring the large number of patients to our university.

FPN

Thank you Anke and Arie, for the pleasant job interview and for creating a nice atmosphere in which I felt welcome immediately. I am happy that you gave me the opportunity and will give me the opportunity in the future to work within STIL as a teacher and I am looking forward to the years ahead!

And for everyone that I already had to pleasure to work with at STIL: Thank you for making me feel so welcome and inviting me to all the fun activities. I am happy that I found colleagues who love alpacas (or any other animals for that matter..) as much as I do! Our day out and pet assignment still makes me laugh.

FAMILY AND FRIENDS

And thank you mom, dad and my (not so) little sister Emily. Thank you, mom and dad, for the opportunity to study and move from Amsterdam to Maastricht. It was honestly the best decision ever. Thank you for all the times that I moved, even though I was sure I wouldn't move anymore for the upcoming years (but did anyway). Thank you for the ability to follow my passion, my dreams and for supporting my wishes. Thank you, Emily, for being such an amazing sister. I am happy that we seem to bond more the older that we get. You are an amazing person, inside and out. I am so proud of who you are and what you have achieved so far in life. And thank you, Kimberly, for always being a big sister to me. Know that you will always be part of our family and that I love you dearly.

Thank you, Kim, Eline and Thijs, for being such amazing friends. Thank you for accepting and appreciating me for who I am, it means the world. Kim, thank you for being there during tough times and making me feel welcome at your place for a talk, drinks or a shoulder to cry on. Thank you for being an inspiration to follow your dreams no matter what. I am happy that our bond only got stronger during the past 8 years. Thank you, thank you, thank you. I will never be able to express in words how much you mean to me and I am very grateful for our friendship. And thanks Jonny, for making me feel welcome too. Thank you for all the laughter and just being there to listen – or to make snacks. ☺ I am happy that Kim and you are happy together, I wish you nothing but the best.

Eline, thank you for all these years you have been by my side (I can't believe it has been ten years already!). The trident during our bachelor camping weekend still makes me laugh, what a weekend that was, haha ☺. I am happy that we met on that Friday and that we turned out to be quite alike. Thank you for all those hours of listening and being so

understanding in whatever situation I found myself in. I never had a friend who could just listen and make me feel better by just being there. And thank you for all your advice, which you only gave me when I asked for it, or when you knew I could use it. You always knew the right words to say to make me feel heard, thank you. So far, I could never find the words to thank you for everything you have done for me and I am happy that the acknowledgment of this thesis gives me the possibility to give words to our friendship. I really hope that all your dreams will come true because you deserve it. You are the strongest person I know and you deserve the best! I may never say this enough, but you are truly the best friend I ever had and the world is a better place because you are in it. Thank you, sweetie, from the bottom of my heart. I love you!

Thank you, Thijs, for being there for me during good and bad times. Thank you for always listening, cheering me up and your kind words. I would even like to thank you for saying the things that I did not want to hear, haha. I appreciate your honesty. You are an amazing friend and know that I will always be there for you as well.

Finally, I would like to thank Björn. Thank you for being the most supportive person I could ever imagine during the three years we were together. I will never be able to express how much you have helped me throughout the past years, by supporting me and just being you. It may sound like a cliché, but I have never met anyone before who could make me laugh as much and make me feel so at ease at the same time. You have brought so much joy to my life, more than anyone else ever did. Being together was often the only thing that was needed to make me feel loved, appreciated and cared for. You were always there for me, whatever was going on or whatever choice I decided to make. You made me feel like I could do anything I had set my mind to. And more importantly, you have shown me what is important in life and how to be a better person, every day. Thank you for providing a safe space to be myself and to be able to learn who I am, what I like and who I would like to be. Thank you for making me feel like being myself was good enough. Without you, I would not stand here today, and I am grateful for every day that we were together. And even though we had to let go of each other, you will always have a special place in my heart. I am eternally grateful for all your support all those years because, without you, this thesis would not have been written.