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Psychiatric manifestations of inborn errors of metabolism: A systematic review

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ABSTRACT

Inborn errors of metabolism (IEMs) are characterized by deficits in metabolic enzymes as a result of 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 be accompanied by less somatic and more psychiatric manifestations, which often hampers recognition by psychiatrists of the distinction between a primary and secondary psychiatric disorder. To help clinicians in the diagnostic process, we aimed to provide an overview of psychiatric manifestations in IEMs. 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 disorder, 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 multidisciplinary IEM clinics are proposed to help clinicians during the diagnostic process, to prevent diagnostic delay and to raise awareness of the psychiatric manifestations among IEMs.

1. 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 (Saudubray and Garcia-Cazorla, 2018). 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 (Walterfang et al., 2013). 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 (Walterfang et al., 2013).

Although IEMs are rare disorders individually, more than 1000 IEMs have been described and occur in overall 1:800–1:1000 individuals (Saudubray and Garcia-Cazorla, 2018; Pampols, 2010; Ahrens-Nicklas et al., 2015; Gambello and Li, 2018). 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 (Mak et al., 2013) and some IEMs manifest during adolescence or adulthood without preceding symptoms during childhood. These symptoms can emerge most commonly on a somatic level, or manifest themselves by deterioration of cognitive functioning, but they may also manifest as (predominantly) psychiatric symptoms (Nia, 2014). Consequently, a late-onset IEM may even present with isolated psychiatric symptoms before somatic symptoms occur (Sedel et al., 2007). Many psychiatric disorders onset 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,

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the difficulty to distinguish between primary and secondary manifestations of psychiatric disorders may lead to insufficient recognition and diagnostic delay. Consequently, this may lead to under recognition and undertreatment of patients with the combination of a psychiatric condition and an underlying metabolic disease (Walterfang et al., 2013; Bonnot et al., 2014).

This recognition, however, is crucial for several reasons. First, an IEM has consequences for the course of the psychiatric disease. Second, an IEM is sometimes treatable, 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, even when untreatable, is still meaningful and potentially de-stigmatizing for both patients and their families with respect to suffering from a psychiatric condition. Fourth, 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 (Mak et al., 2018).

There is 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 information on the various IEMs and their psychiatric presentations, 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 proposes an algorithm for a screener that can be used in general psychiatric practice. Thereby, this review aims to raise awareness and help psychiatrists or any other clinician in this difficult diagnostic process.

2. Methods

2.1. Literature search methodology

A systematic literature search was performed following Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati et al., 2009). The review protocol was registered in the PROSPERO database (CRD42020161948). An academic librarian supervised the literature search.

2.2. 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 (Schardt et al., 2007). 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.

2.3. Screening

An overview of the screening procedure can be found in Fig. 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.

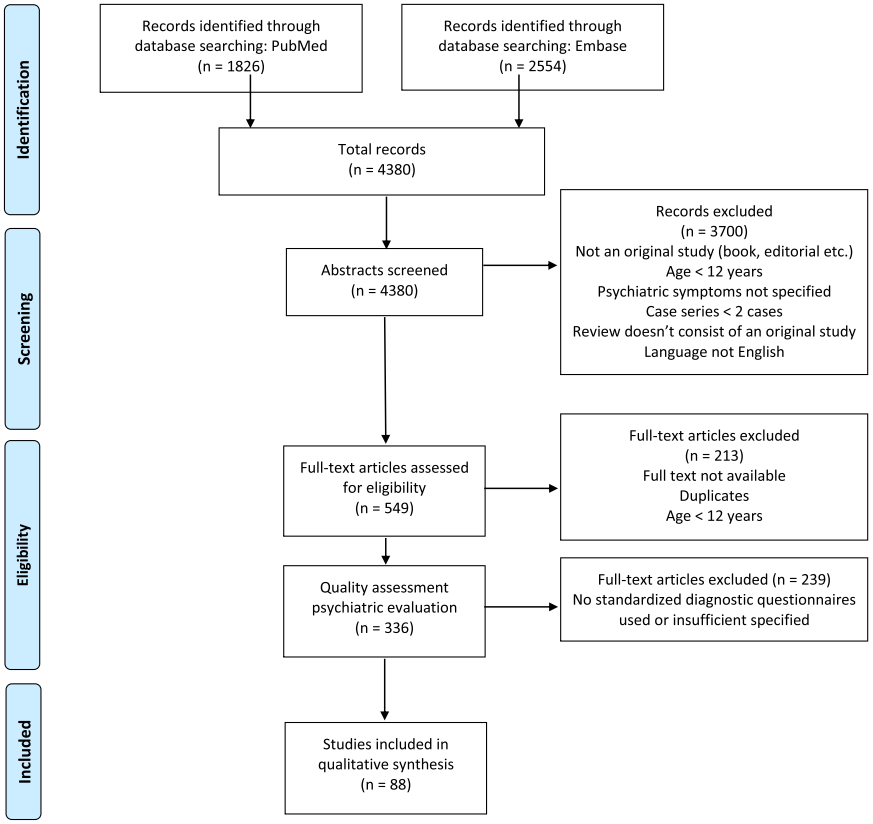

Fig. 1. Flow-chart of this systematic review.

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). Non-English full texts were excluded. 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.

2.5. 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.

3. Results

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 1 and Fig. 2. Included studies were classified according to general type of metabolism involved.

3.1. 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. Classic galactosemia entailed the only disorder in this class of IEM with available literature on these psychiatric symptoms.

3.1.1. 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 when not treated properly, starting with liver failure. Treatment consists of a galactose and lactose restricted diet. Most patients are diagnosed at an early age. However, there are still patients who are diagnosed in adulthood.

3.1.2. Psychiatric manifestations

Galactosemia primarily presents itself with neurological symptoms including movement disorders: ataxia, tremor and dystonia, impaired cognition and speech deficits (Kuiper et al., 2019; Waisbren et al., 2012). Next to these neurological symptoms, psychiatric diagnoses are common in these patients. Only one research paper described these psychiatric symptoms (Kuiper et al., 2019). Kuiper et al. (2019) studied 37 patients with galactosemia and found that 21.6% of these patients had at least one psychiatric diagnosis, including autism spectrum disorder (ASD), 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 (Kuiper et al., 2019).

3.2. 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 from mutations in the *POLG* gene, this review will focus on these MDs.

3.2.1. Psychiatric manifestations

Neuropsychiatric manifestations of MDs include psychosis, anxiety, depression and intellectual disability. In total, ten research papers in a total of 204 patients described these psychiatric symptoms (Inczedy--Farkas et al., 2012; Mancuso et al., 2013, 2008; Fattal et al., 2007; Kaufmann et al., 2009; Parikh et al., 2019; Koene et al., 2009; Morava et al., 2010; Rosebush et al., 2017; Anglin et al., 2012). 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 (Azevedo et al., 2018). 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 negative consequences of the somatic disease itself (Inczedy-Farkas et al., 2012). 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, (Sheehan et al., 1998)). 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 (Mancuso et al., 2013). Consequently, both studies suggest that psychiatric manifestations may be intrinsic to the manifestation of the mitochondrial disorder and not the result of lower quality of life as a consequence of the disorder.

Fattal et al. (2007) 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),

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
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
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,	

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Type of study	IEM	Classification of IEM	Psychiatric manifestations	Red flags
					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)
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
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		Wilson's disease			

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Table 1 (*continued*)

Author	Year	Type of study	IEM	Classification of IEM	Psychiatric manifestations	Red flags
		Original study		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,
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.

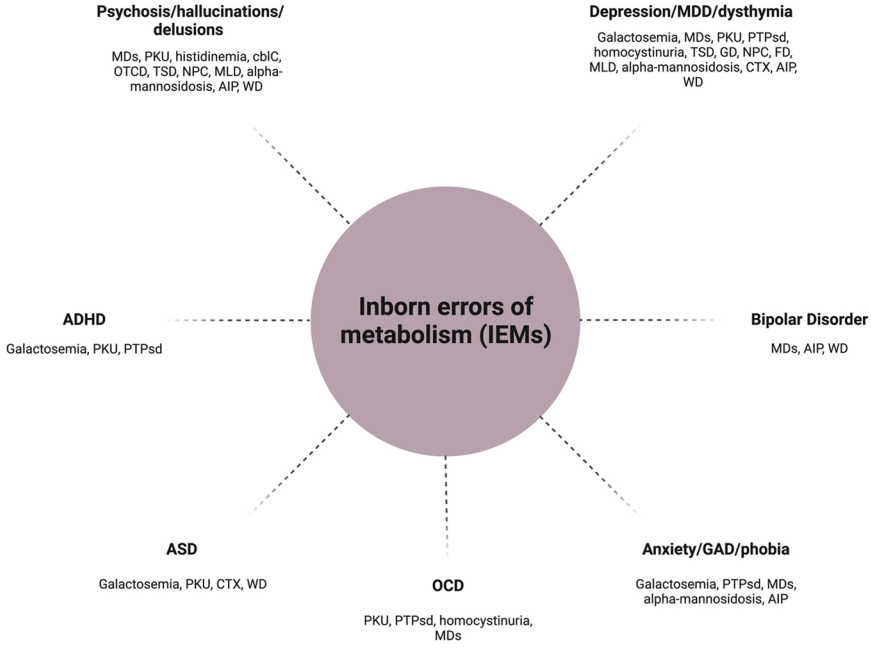

Fig. 2. Overview of psychiatric manifestations of inborn errors of metabolism. MDs = mitochondrial disorders, PKU = phenylketonuria, cblC = cobalamin C disorder, OTCD = ornithine transcarbamylase deficiency, PTPsd = 6-pyruvoyl-tetrahydropterin synthase deficiecy, TSD = tay-sachs disease, GD = Gaucher 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, AHDH = attention deficit hyperactivity disorder.

mitochondrial cytopathy not otherwise specified (n = 7) and other MDs due to mtDNA mutations (n = 14), who all met the criteria of a life-time diagnosis of a psychiatric disorder. Of the patients who had both a MD and a life-time diagnosis of a psychiatric disorder, the 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, including (recurrent) MDD (36 %), dysthymia (11 %), GAD (11 %), social phobia (6 %) and obsessive-compulsive disorder (OCD, 3 %). The somatic symptoms of the patients entailed chronic fatigue, muscle weakness, muscle pain, muscle spasms, headaches and visual problems. Interestingly, patients with a MD and a psychiatric disorder experienced a significantly lower quality of life, more comorbid medical conditions and more hospital admissions, as assessed by the Short-Form 36 Health Survey (SF-36), compared to patients with a MD only (Fattal et al., 2007). These findings contrast with a study by Kaufmann et al. (2009), which described 45 patients with MELAS who did not experience an increase in psychiatric hospitalizations, or in suicide attempts when compared with 78 carrier relatives and 30 controls. However, based on the psychiatric history, patients with MELAS did experience significantly more hallucinations, delusions and depression (Kaufmann et al., 2009).

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 mildly increased blood lactate levels at rest. Genetic analysis revealed that no classified mutation could be identified as a causative factor of the MD, however, a reduction up to 40 % in mitochondrial respiratory chain complexes I, III, and IV activity was observed, as described in MDs (Mancuso et al., 2008). 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 1–4 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 that 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 (Koene et al., 2009). 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 (Parikh et al., 2019), which is in contrast with the findings of Inczedy-Farkas et al. (2012) and Mancusco et al. (2013).

Anglin et al. (2012) 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 1–29 years later. Among these mitochondrial disorders were MELAS, MERRF, chronic progressive external ophthalmoplegia (CPEO) and mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE). Additionally, 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 (Rosebush et al., 2017; Anglin et al., 2012).

Finally, Morava et al. (2010) showed that in 18 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 (Morava et al., 2010). 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 are highly concurrent, with depressive disorders most frequently described, and that somatic symptoms such as chronic fatigue, muscle weakness and exercise intolerance are often part of the clinical manifestation of a MD.

3.3. Disorders of amino acids 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, including the brain. This group of disorders includes disorders such as phenylketonuria, hyperphenylalaninemia and homocystinuria.

3.3.1. Phenylketonuria

Phenylketonuria (PKU, OMIM #261600) is an autosomal-recessive disorder of phenylalanine metabolism characterized by a deficiency of phenylalanine-4-hydroxylase, an enzyme involved in the conversion of phenylalanine into tyrosine (Williams et al., 2008). 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 (Surtees and Blau, 2000).

3.3.2. 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 in a total of 182 patients described these psychiatric symptoms in patients with PKU who either got diagnosed during childhood but discontinued a diet low in phenylalanine (Phe) that is used to treat PKU, or who were diagnosed later in life (Steiner et al., 2003; Daelman et al., 2014; Fisch et al., 1995; Koch et al., 2002; Pietz et al., 1997; Ris et al., 1997). First, Steiner et al. (2003) described 84 patients with a diagnosis of autism spectrum disorder (ASD) according to the DSM-IV criteria. 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 NBS was carried out 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 (Daelman et al., 2014). 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. The patients with PKU combined with 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 (Fisch et al., 1995). 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) (Koch et al., 2002).

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 (Ris et al., 1997). 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 (Pietz et al., 1997).

3.4. 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 (Opladen et al., 2012).

3.4.1. Psychiatric manifestations

Neuropsychiatric manifestations of PTPSd include anxiety, depression and intellectual disability, as described by only one recent research paper (Manti et al., 2020). 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 (Manti et al., 2020).

3.5. 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 (La et al., 1962). 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.

3.5.1. 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 (Lucca et al., 1990). Of all schizophrenic patients, 6 patients were identified as being heterozygous for histidinemia. Although these patients were formally 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 (Lucca et al., 1990).

3.6. 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.

3.6.1. Psychiatric manifestations

Psychiatric manifestations of homocystinuria include depression, behavioral abnormalities including aggression, and personality changes as described in one paper only (Abbott et al., 1987). 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 (Abbott et al., 1987). 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 responders and non-responders to treatment with vitamin B6 support the hypothesis that there may be two types of homocystinuria, caused by different mutations (Abbott et al., 1987).

3.7. 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 unable to absorb and transport vitamin B12 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 (Rosenblatt and Cooper, 1987).

3.8. 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 (Froese and Gravel, 2010). 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 (Rosenblatt et al., 1997).

3.8.1. Psychiatric manifestations

Psychiatric manifestations of late onset forms of cobalamin C disorder include psychosis and anxiety as described in two papers (Roze et al., 2003; Wang et al., 2018). 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 including visual and auditive hallucinations (Roze et al., 2003). 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.

3.9. 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 (Walker, 2014). Cognitive, attention and executive function deficits, learning disabilities, sleep disorders and psychosis have been described in patients with a urea cycle disorder (Gyato et al., 2004).

3.10. 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 (Lee et al., 2018). Because psychiatric symptoms are mainly present in the late-onset form, this review will focus on this subtype of OTCD.

3.10.1. Psychiatric manifestations

Psychiatric manifestations of OTCD may include hallucinations, confusion and irritability as described in one case report of 5 patients (Feighner et al., 1972). Cavicchi et al. (2014) described 5 adult patients with late-onset 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 (Feighner et al., 1972).

3.11. 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 (Rajkumar and Dumpa, 2022). This may result in a wide variation of symptoms.

3.12. 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 (Vanier, 1999, 2010). Psychiatric symptoms are mainly present in late-onset patients (Vanier, 2010). As psychiatric symptoms are mainly present in the late-onset form, this review will focus on this subtype of NPC.

3.12.1. 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 (Josephs et al., 2003; Bauer et al., 2013; Koens et al., 2016; Walterfang et al., 2006; Maubert et al., 2015, 2016). 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 instability, 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 tardive dyskinesia. 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 (Josephs et al., 2003). 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 (Walterfang et al., 2006). In line with these 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 (Maubert et al., 2015).

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 (Bauer et al., 2013). 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) (Koens et al., 2016). Maubert et al. (2016) additionally described 22 patients with NPC. In 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 27 % of the patients, the neurological symptoms manifested after the isolated psychiatric symptoms, and in 9 % of the patients, the psychiatric and neurological symptoms manifested simultaneously. In the remaining number of patients, the chronological order of the psychiatric and neurological symptoms was not described. The authors speculated that actual rates of co-occurrence of psychiatric manifestations in NPC may be even higher, because in some patients these symptoms might have been considered to be part of the clinical manifestation of NPC rather than the result of a primary psychiatric disorder (Maubert et al., 2016).

3.13. 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 (Sipione et al., 2020). A deficiency in this enzyme results in an accumulation of GM2 gangliosides in the brain and nerve cells.

3.13.1. 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 (Rozenberg et al., 2006). 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 diagnosis of TSD after both parents were identified as carriers of the *G269S* and *InsTATC1278* genes (Rozenberg et al., 2006).

3.14. 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).

3.14.1. Psychiatric manifestations

Only one case report described developmental delay, restlessness, aggressive and destructive behavior in patients with MPSs (Valstar et al., 2010) that encompassed Sanfilippo syndrome. A total of 49 patients showed behavioral problems such as restlessness, aggressive and destructive behavior, including temper tantrums and emotional outburst 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 (Valstar et al., 2010).

3.15. 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.

3.15.1. Psychiatric manifestations

Psychiatric manifestations of FD include depression, anxiety and self-injurious behavior in both males and females, as described in 3 papers including a total of 102 patients (Korver et al., 2019; Sigmundsdottir

et al., 2014; Sadek et al., 2004). First, Sigmundsdottir et al. (2014) described significantly increased anxiety and depression in 17 adult male and female patients with FD who did not experience psychiatric manifestations during childhood and received the diagnosis of FD in adulthood (Sigmundsdottir et al., 2014; Sadek et al., 2004). When compared to control individuals, depression and anxiety symptoms were more pronounced in men (n = 12) than in women (n = 5), 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 (Sigmundsdottir et al., 2014). Similarly, Korver et al. (2019) also observed significantly lower processing speed in adult males (35 %) 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 (Korver et al., 2019). 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 (Sadek et al., 2004).

3.16. 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 (Guggenbuhl et al., 2008).

3.16.1. Psychiatric manifestations

Psychiatric manifestations of GD include depression, schizophrenia-like behavior and cognitive impairment. In total, three research papers described both psychiatric manifestation in 63 adult patients with GD (Packman et al., 2006; Beavan et al., 2015; Wilke et al., 2019). Packman et al. (2006) showed that 28 patients with GD scored significantly higher on depression, schizophrenia and hysteria according to the Minnesota Multiphasic Personality Inventory (MMPI-2). Of these patients, 39% of 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 (Packman et al., 2006). 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) (Beavan et al., 2015). 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) (Wilke et al., 2019).

3.17. 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 (Gieselmann and Krageloh-Mann, 2010).

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.

3.17.1. 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 in a total of 16 patients (Baumann et al., 2002). 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 (Baumann et al., 2002; Müller et al., 1969; Kumperscak et al., 2005). A similar observation was done by Müller et al. (1969), who described two patients with the adult form of MLD who mainly experienced 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), Müller et al. (1969). 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 (Kumperscak et al., 2005). Additionally, one of the patients received a diagnosis of severe intellectual disability 10 months after the onset of psychotic symptoms as well.

3.18. 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 (Desnick et al., 1976). Consequently, oligosaccharides accumulate in lysosomes which may result in mild to severe clinical manifestations (Malm and Nilssen, 2008).

3.18.1. Psychiatric manifestations

Psychiatric manifestations of alpha-mannosidosis include psychosis, depression, behavioral problems and intellectual disability as described in two papers in 159 patients (Malm et al., 2005, 2014). Malm et al. (2005) described 11 out of 45 patients with alpha-mannosidosis who experienced episodes of depression, psychosis, anxiety and disturbed sleeping patterns. For most patients, the onset of the psychiatric symptoms started during adolescence, although in one patient, the psychiatric symptoms started at the age of 32 years (Malm et al., 2005). 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 to be 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 (Malm et al., 2014).

3.19. Bile acid synthesis defects

3.19.1. 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.

3.19.2. Psychiatric manifestations

Psychiatric manifestations of CTX includes ASD and cognitive impairment as described in two papers (Stelten et al., 2018a; Yunisova et al., 2019). Stelten et al. (2018a) described 77 patients with CTX inlcuding 9 children and one adult who 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 preceded the diagnosis of CTX and the 10th patient suffered from ASD related symptoms preceding the CTX diagnosis retrospectively. None of these patients experienced neurological symptoms at the time of diagnosis of ASD. However, intellectual disability and 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 ASD should could be considered when ASD is accompanied by cognitive impairment, diarrhea and/or juvenile cataract (Stelten et al., 2018a). Interestingly, the psychiatric manifestations as observed in the patient who was diagnosed during adulthood worsened after treatment with CDCA, while improvement was seen in the patients diagnosed in childhood (Stelten et al., 2018b). Similar findings were published by Yunisova et al. (2019) who studied 7 patients with CTX in Turkish hospitals and found depression and ASD to be one of the first manifestations of this disease (Yunisova et al., 2019). These findings suggest that CTX is among the few IEMs in which psychiatric symptoms can occur as the initial presentation in the absence of any other somatic or neurological symptom.

3.20. Porphyrias

Porphyria consists of a group of autosomal recessive disorders characterized by a disruption of the heme biosynthesis and has been relatively well studied. The disease has been associated with anxiety and psychotic symptoms. Because 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. 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.

3.20.1. Psychiatric manifestations

When patients with porphyria are seen by a psychiatrist, they are often primarily diagnosed with an anxiety disorder, psychosis, drug induced psychosis, schizophrenia, bipolar disorder, depression or conversion disorder (Cross, 1956; Millward et al., 2005). Doctors' delays of six years or more are not unusual, often until neurological signs of AIP appear (Millward et al., 2001). A strong association has been found between porphyria and psychiatric disorders, suggesting shared biological pathways with the psychiatric manifestations in acute porphyria. In total, four studies in 1232 patients with AIP were included.

In a large-scale study in 717 patients diagnosed with AIP and their first-degree relatives, Cederlof et al. (2015) 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. In line with these findings, Patience et al. (1994) who also found an increased risk of psychiatric disease in first-degree relatives (n = 40) of 12 probands carrying latent AIP mutations (Patience et al., 1994). This suggests commonalities (pleiotropy) with respect to genetic pathways involved in the pathophysiology of AIP on the one hand and schizophrenia and bipolar disorder on the other (Cederlof et al., 2015). Possibly latent AIP mutations are responsible for the psychiatric symptoms in first-degree relatives. The kynurenine synthesis pathway is linked to schizophrenia and might, together with the pleiotropic effects of the PBG deaminase gene (which is responsible for the conversion of PBG to hydroxymethylbilane in the heme formation pathway), partially explain the association between AIP and psychotic symptoms (Cederlof et al., 2015).

In contrast to Cederlof et al. (2015), Patience et al. (1994) only found a correlation between patients with AIP and occurrence of anxiety disorders in 344 patients with AIP, but not with symptoms of schizophrenia and bipolar disorder. 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 81 patients with AIP compared to controls (Millward et al., 2001). Anxiety scores and levels of porphyrin metabolites in urine correlated, supporting an association between the two parameters (Patience et al., 1994). 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'. In conclusion, whereas older research has found generalized anxiety and depression symptoms to be common psychiatric symptoms in AIP, more recent findings suggest that symptoms of schizophrenia and bipolar disorder frequently occur as well. Further, the mutual relationship suggests pleiotropy between psychiatric and somatic symptoms of AIP.

4. 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.

4.1. 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 (Bem et al., 2011). 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 (Bem et al., 2011; Akil and Brewer, 1995). Clinicians distinguish hepatic and neurological WD, which indicates the disease progression. In hepatic WD, depositions are confined to the liver characterized by mainly hepatic metabolic symptomatology whereas in the neurological form, depositions are widespread and found in several organs, including the brain. As might be expected, psychiatric manifestations like depression, psychotic symptoms and personality changes are more often seen in patients who present themselves with neurological WD 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) (Akil et al., 1991; Dening and Berrios, 1989a;

Shanmugiah et al., 2008).

4.1.1. Psychiatric manifestations

Psychiatric manifestations of WD include changes in behavior, irritability, disinhibition, obsession, aggressive behavior and deterioration in school or work functioning. In total, 19 papers in 1668 patients have described these psychiatric manifestations (Bem et al., 2011; Akil and Brewer, 1995; Akil et al., 1991; Demily et al., 2017). 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 (Bem et al., 2011; Parker, 1985).

Depressive symptoms are more common than psychosis or schizophrenia-like observations in WD (Akil and Brewer, 1995; Akil et al., 1991; Dening and Berrios, 1989a; Srinivas et al., 2008). Based on an association between WD and the incidence of comorbid bipolar disorder and MDD, (Carta et al., 2012) hypothesized that in some instances metal metabolism disorders including copper and zinc metabolism might be involved in the etiology of these psychiatric disorders. 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. However, depression-like and psychosis-like symptoms may not be adequately estimated, since many observations were made by non-psychiatrists in a non-standardized way (Akil and Brewer, 1995).

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 (Litwin et al., 2013). The researchers hypothesize differences in estrogen and metal metabolism between women and men as a possible cause (Litwin et al., 2012). However, the precise mechanism remains to be elucidated.

Biochemical markers in serum like copper (Cu) and ceruloplasmin (Cp) levels are comparable in hepatic WD and neurological WD (Dening and Berrios, 1989b). 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 is often is seen (Akil and Brewer, 1995; Soltanzadeh et al., 2007). Between 14 % and 20 % of patients is initially seen by a psychiatrist before the diagnosis of WD is established (Dening and Berrios, 1989b).

5. 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 Fig. 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 (Lautenschlager and Forstl, 2001; Waters et al., 2014; Lewandowski et al., 2009). 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 (Mancuso et al., 2013). 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 (Millward et al., 2005). To provide more insight into this matter, future research should possibly focus on including longitudinal prospective cohorts such as the Maastricht study or Lifelines (Scholtens et al., 2015; Schram et al., 2014). 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 (Sheffield et al., 2018; McCleery and Nuechterlein, 2019), progressive memory impairment and attention deficits that deteriorate strongly, should alert to a suspicion of an IEM (Olkinuora, 1982). 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 (Eun and Hahn, 2015). The current review confirms this observation for MPS (Valstar et al., 2010), 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 (Valstar et al., 2010). 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 (Koene et al., 2009; Steiner et al., 2003; Daelman et al., 2014; Fisch et al., 1995; Koch et al., 2002; Pietz et al., 1997; Ris et al., 1997; Manti et al., 2020; Malm et al., 2014). 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 (Steiner et al., 2003; Daelman et al., 2014; Fisch et al., 1995; Koch et al., 2002; Pietz et al., 1997; Ris et al., 1997). A similar observation was done in case of alpha-mannosidosis (Malm et al., 2014). 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 (Kumperscak et al., 2005; Malm et al., 2014).

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 (Sanders and Gillig, 2012; Dhir et al., 2017; Miller and Fleischhacker, 2000), they can be prominent in patients with an IEM (Walterfang et al., 2013; Pan and Vockley, 2013). For example, these motor symptoms have been described in galactosemia, NPC and WD (Kuiper et al., 2019; Akil et al., 1991; Srinivas et al., 2008; Eggink et al., 2014). 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 (Mancuso et al., 2008). Although severe chronic fatigue, sleepiness and muscle weakness were described in patients with a MD as well (Fattal et al., 2007; Koene et al., 2009), 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 (Storjord et al., 2019). 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 (Benque et al., 1984; Stein et al., 2017; Brodie et al., 1977; Forbes, 1995). What is more, our results showed that vomiting has also been described in patients with late-onset OTCD (Benque et al., 1984), 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 (Benque et al., 1984; Hasbaoui et al., 2018). 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 2). 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 (Walterfang et al., 2013).

5.1. *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 Fig. 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.

5.2. *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 (MacDonald et al., 2020; Kumar et al., 2016). 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

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
Other	Vertical supranuclear gaze palsy, Kaiser Fleischer rings

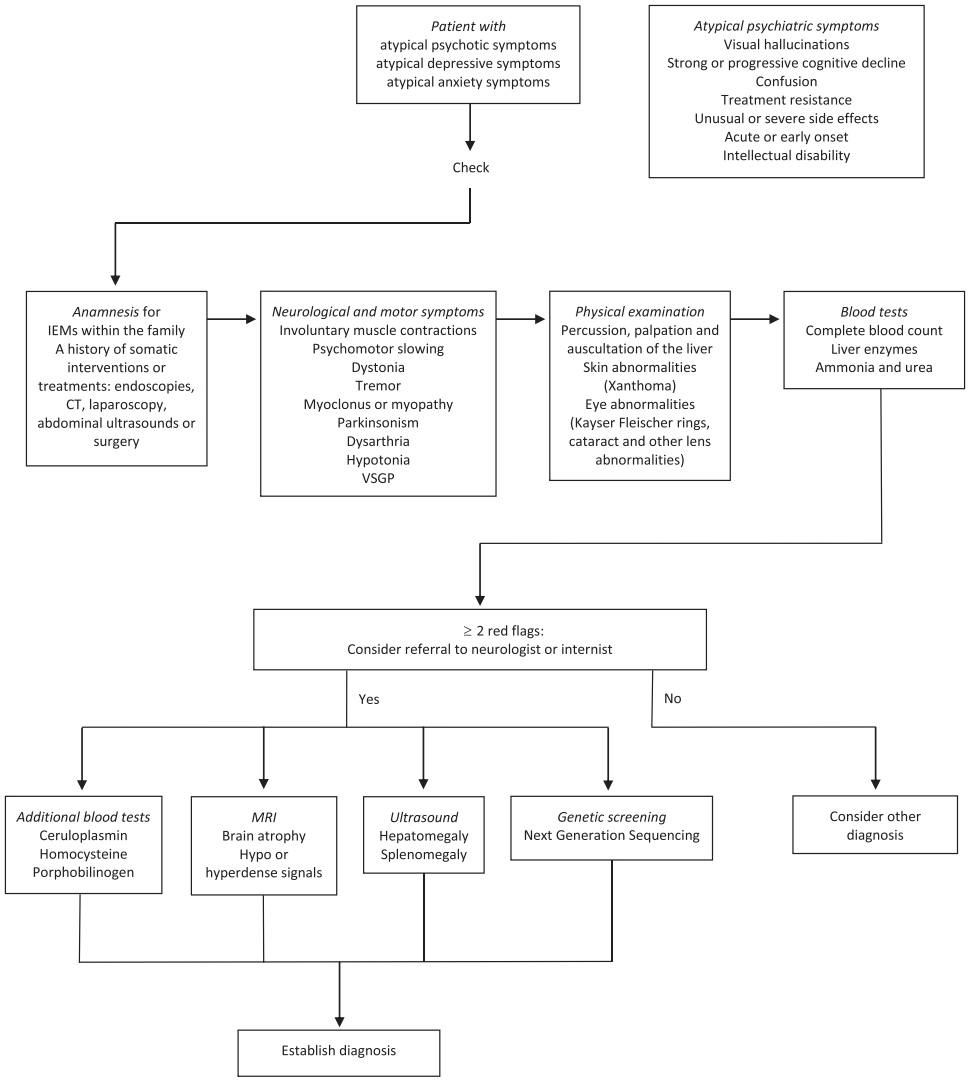

Fig. 3. Diagnostic screener for psychiatrists.

psychological stress, can significantly increase the risk of provoking an attack (Millward et al., 2001). Additionally, treatment is most effective when IEMs are diagnosed early in disease development (Trakadis et al., 2018). 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.

5.2.1. 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.

5.2.2. 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 Fig. 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 (van de Burgt et al., 2021; Malaga et al., 2019; Komlosi et al., 2016) 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.

6. 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 Fig. 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.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104970.

References

Abbott, M.H., Folstein, S.E., Abbey, H., Pyeritz, R.E., 1987. Psychiatric manifestations of homocystinuria due to cystathionine beta-synthase deficiency: prevalence, natural history, and relationship to neurologic impairment and vitamin B6-responsiveness. Am. J. Med. Genet. 26 (4), 959–969.
Ahrens-Nicklas, R.C., Slap, G., Ficicioglu, C., 2015. Adolescent presentations of inborn errors of metabolism. J. Adolesc. Health 56 (5), 477–482.
Akil, M., Brewer, G.J., 1995. Psychiatric and behavioral abnormalities in Wilson's disease. Adv. Neurol. 65, 171–178.
Akil, M., Schwartz, J.A., Dutchak, D., Yuzbasiyan-Gurkan, V., Brewer, G.J., 1991. The psychiatric presentations of Wilson's disease. J. Neuropsychiatry Clin. Neurosci. 3 (4), 377–382.
Anglin, R.E., Tarnopolsky, M.A., Mazurek, M.F., Rosebush, P.I., 2012. The psychiatric presentation of mitochondrial disorders in adults. J. Neuropsychiatry Clin. Neurosci. 24 (4), 394–409.
Azevedo, H., Pupe, C., Pereira, R., Nascimento, O.J.M., 2018. Pain in Charcot-Marie-Tooth disease: an update. Arq. Neuropsiquiatr. 76 (4), 273–276.
Bauer, P., Balding, D.J., Klunemann, H.H., Linden, D.E., Ory, D.S., Pineda, M., et al., 2013. Genetic screening for Niemann-Pick disease type C in adults with neurological and psychiatric symptoms: findings from the ZOOM study. Hum. Mol. Genet. 22 (21), 4349–4356.
Baumann, N., Turpin, J.C., Lefevre, M., Colsch, B., 2002. Motor and psycho-cognitive clinical types in adult metachromatic leukodystrophy: genotype/phenotype relationships? J. Physiol. 96 (3–4), 301–306.
Beavan, M., McNeill, A., Proukakis, C., Hughes, D.A., Mehta, A., Schapira, A.H., 2015. Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. JAMA Neurol. 72 (2), 201–208.
Bem, R.S., Muzzillo, D.A., Deguti, M.M., Barbosa, E.R., Werneck, L.C., Teive, H.A., 2011. Wilson's disease in southern Brazil: a 40-year follow-up study. Clinics 66 (3), 411–416.
Benque, A., Bommelaer, G., Rozental, G., Cales, P., Cathelineau, L., Pham Dinh, D., et al., 1984. Chronic vomiting in a case of citrullinaemia detected after treatment by total parenteral nutrition. Gut 25 (5), 531–533.
Bonnot, O., Klunemann, H.H., Sedel, F., Tordjman, S., Cohen, D., Walterfang, M., 2014. Diagnostic and treatment implications of psychosis secondary to treatable metabolic disorders in adults: a systematic review. Orphanet J. Rare Dis. 9, 65.
Brodie, M.J., Thompson, G.G., Moore, M.R., Beattie, A.D., Goldberg, A., 1977. Hereditary coproporphyria. Demonstration of the abnormalities in haem biosynthesis in peripheral blood. Q. J. Med. 46 (182), 229–241.
Carta, M.G., Sorbello, O., Moro, M.F., Bhat, K.M., Demelia, E., Serra, A., et al., 2012. Bipolar disorders and Wilson's disease. BMC Psychiatry 12, 52.
Cederlof, M., Bergen, S.E., Larsson, H., Landen, M., Lichtenstein, P., 2015. Acute intermittent porphyria: comorbidity and shared familial risks with schizophrenia and bipolar disorder in Sweden. Br. J. Psychiatry.: J. Ment. Sci. 207 (6), 556–557.
Cross, T.N., 1956. Porphyria; a deceptive syndrome. Am. J. Psychiatry 112 (12), 1010–1014.
Daelman, L., Sedel, F., Tourbah, A., 2014. Progressive neuropsychiatric manifestations of phenylketonuria in adulthood. Rev. Neurol. 170 (4), 280–287.
Demily, C., Parant, F., Cheillan, D., Broussolle, E., Pavec, A., Guillaud, O., et al., 2017. Screening of Wilson's disease in a psychiatric population: difficulties and pitfalls. A preliminary study. Ann. Gen. Psychiatry 16, 19.
Dening, T.R., Berrios, G.E., 1989a. Wilson's disease: a prospective study of psychopathology in 31 cases. Br. J. Psychiatry.: J. Ment. Sci. 155, 206–213.
Dening, T.R., Berrios, G.E., 1989b. Wilson's disease. Psychiatric symptoms in 195 cases. Arch. Gen. Psychiatry 46 (12), 1126–1134.
Desnick, R.J., Sharp, H.L., Grabowski, G.A., Brunning, R.D., Quie, P.G., Sung, J.H., et al., 1976. Mannosidosis: clinical, morphologic, immunologic, and biochemical studies. Pedia Res. 10 (12), 985–996.
Dhir, A., Schilling, T., Abler, V., Potluri, R., Carroll, B., 2017. Estimation of epidemiology of tardive dyskinesia in the United States (P2.018). Neurology 88 (16), P2.018.
Eggink, H., Kuiper, A., Peall, K.J., Contarino, M.F., Bosch, A.M., Post, B., et al., 2014. 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. 9, 177.
Elder, G.H., Hift, R.J., Meissner, P.N., 1997. The acute porphyrias. Lancet 349 (9065), 1613–1617.
Eun, S.H., Hahn, S.H., 2015. Metabolic evaluation of children with global developmental delay. Korean J. Pedia 58 (4), 117–122.
Fattal, O., Link, J., Quinn, K., Cohen, B.H., Franco, K., 2007. Psychiatric comorbidity in 36 adults with mitochondrial cytopathies. CNS Spectr. 12 (6), 429–438.
Feighner, J.P., Robins, E., Guze, S.B., Woodruff, R.A.J., Winokur, G., Munoz, R., 1972. Diagnostic criteria for use in psychiatric research. Arch. Gen. Psychiatry 26 (1), 57–63.
Fisch, R.O., Chang, P.N., Weisberg, S., Guldberg, P., Guttler, F., Tsai, M.Y., 1995. Phenylketonuric patients decades after diet. J. Inherit. Metab. Dis. 18 (3), 347–353.
Forbes, D., 1995. Differ. Diagn. Cycl. vomiting Syndr. J. Pedia Gastroenterol. Nutr. 21, Suppl 1, pp. S11–S14.

Froese, D.S., Gravel, R.A., 2010. Genetic disorders of vitamin B(1)(2) metabolism: eight complementation groups–eight genes. Expert Rev. Mol. Med. 12, e37.
Gambello, M.J., Li, H., 2018. Current strategies for the treatment of inborn errors of metabolism. J. Genet. Genom. 45 (2), 61–70.
Gieselmann, V., Krageloh-Mann, I., 2010. Metachromatic leukodystrophy–an update. Neuropediatrics 41 (1), 1–6.
Guggenbuhl, P., Grosbois, B., Chales, G., 2008. Gaucher disease. Jt. Bone Spine 75 (2), 116–124.
Gyato, K., Wray, J., Huang, Z.J., Yudkoff, M., Batshaw, M.L., 2004. Metabolic and neuropsychological phenotype in women heterozygous for ornithine transcarbamylase deficiency. Ann. Neurol. 55 (1), 80–86.
Hasbaoui, B.E., Boujrad, S., Abilkacem, R., Agadr, A., 2018. Vomiting associated with weight stagnation and convulsions: urea cycle disorder should be suspected. Pan Afr. Med. J. 31, 103.
Inczedy-Farkas, G., Remenyi, V., Gal, A., Varga, Z., Balla, P., Udvardy-Meszaros, A., et al., 2012. Psychiatric symptoms of patients with primary mitochondrial DNA disorders. Behav. Brain Funct. 8, 9.
Josephs, K.A., Van Gerpen, M.W., Van Gerpen, J.A., 2003. Adult onset Niemann-Pick disease type C presenting with psychosis. J. Neurol. Neurosurg. Psychiatry 74 (4), 528–529.
Kaufmann, P., Engelstad, K., Wei, Y., Kulikova, R., Oskoui, M., Battista, V., et al., 2009. Protean phenotypic features of the A3243G mitochondrial DNA mutation. Arch. Neurol. 66 (1), 85–91.
Koch, R., Burton, B., Hoganson, G., Peterson, R., Rhead, W., Rouse, B., et al., 2002. Phenylketonuria in adulthood: A collaborative study. J. Inherit. Metab. Dis. 25 (5), 333–346.
Koene, S., Kozicz, T.L., Rodenburg, R.J.T., Verhaak, C.M., de Vries, M.C., Wortmann, S., et al., 2009. Major depression in adolescent children consecutively diagnosed with mitochondrial disorder. J. Affect. Disord. 114 (1–3), 327–332.
Koens, L.H., Kuiper, A., Coenen, M.A., Elting, J.W., de Vries, J.J., Engelen, M., et al., 2016. Ataxia, dystonia and myoclonus in adult patients with Niemann-Pick type C. Orphanet J. Rare Dis. 11 (1), 121.
Komlosi, K., Sólyom, A., Beck, M., 2016. The role of next-generation sequencing in the diagnosis of lysosomal storage disorders. J. Inborn Errors Metab. Screen. 4, 2326409816669376.
Korver, S., Geurtsen, G.J., Hollak, C.E.M., van Schaik, I.N., Longo, M.G.F., Lima, M.R., et al., 2019. Predictors of objective cognitive impairment and subjective cognitive complaints in patients with Fabry disease. Sci. Rep. 9 (1), 188.
Kuiper, A., Grunewald, S., Murphy, E., Coenen, M.A., Eggink, H., Zutt, R., et al., 2019. Movement disorders and nonmotor neuropsychological symptoms in children and adults with classical galactosemia. J. Inherit. Metab. Dis. 42 (3), 451–458.
Kumar, T., Sharma, G.S., Singh, L.R., 2016. Homocystinuria: therapeutic approach. Clin. Chim. Acta 458, 55–62.
Kumperscak, H.G., Paschke, E., Gradisnik, P., Vidmar, J., Bradac, S.U., 2005. Adult metachromatic leukodystrophy: disorganized schizophrenia-like symptoms and postpartum depression in 2 sisters. J. Psychiatry Neurosci. 30 (1), 33–36.
La, Du.B.N., Howell, R.R., Jacoby, G.A., Seegmiller, J.E., Zannoni, V.G., 1962. The enzymatic defect in histidinemia. Biochem. Biophys. Res. Commun. 7, 398–402.
Lautenschlager, N.T., Forstl, H., 2001. Organic psychosis: insight into the biology of psychosis. Curr. Psychiatry Rep. 3 (4), 319–325.
Lee, T., Misaki, M., Shimomura, H., Tanaka, Y., Yoshida, S., Murayama, K., et al., 2018. Late-onset ornithine transcarbamylase deficiency caused by a somatic mosaic mutation. Hum. Genome Var. 5, 22.
Lewandowski, K.E., DePaola, J., Camsari, G.B., Cohen, B.M., Ongur, D., 2009. Tactile, olfactory, and gustatory hallucinations in psychotic disorders: a descriptive study. Ann. Acad. Med. Singap. 38 (5), 383–385.
Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6 (7).
Litwin, T., Gromadzka, G., Czlonkowska, A., 2012. Gender differences in Wilson's disease. J. Neurol. Sci. 312 (1–2), 31–35.
Litwin, T., Gromadzka, G., Czlonkowska, A., Golebiowski, M., Poniatowska, R., 2013. The effect of gender on brain MRI pathology in Wilson's disease. Metab. Brain Dis. 28 (1), 69–75.
Lucca, A., Catalano, M., Valsasina, R., Fara, C., Smeraldi, E., 1990. Biochemical investigation of histidinemia in schizophrenic patients. Biol. Psychiatry 27 (1), 69–75.
MacDonald, A., van Wegberg, A.M.J., Ahring, K., Beblo, S., Belanger-Quintana, A., Burlina, A., et al., 2020. PKU dietary handbook to accompany PKU guidelines. Orphanet J. Rare Dis. 15 (1), 171.
Mak, C.M., Lee, H.C., Chan, A.Y., Lam, C.W., 2013. Inborn errors of metabolism and expanded newborn screening: review and update. Crit. Rev. Clin. Lab Sci. 50 (6), 142–162.
Mak, C.M., Law, E.C., Lee, H.H., Siu, W.K., Chow, K.M., Au Yeung, S.K., et al., 2018. 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 Med. J. = Xianggang yi xue za zhi 24 (3), 226–237.
Malaga, D.R., Brusius-Facchin, A.C., Siebert, M., Pasqualim, G., Saraiva-Pereira, M.L., Souza, C.F.M., et al., 2019. Sensitivity, advantages, limitations, and clinical utility of targeted next-generation sequencing panels for the diagnosis of selected lysosomal storage disorders. Genet. Mol. Biol. 42 (1), 197–206.
Malm, D., Nilssen, O., 2008. Alpha-mannosidosis. Orphanet J. Rare Dis. 3, 21.
Malm, D., Pantel, J., Linaker, O.M., 2005. Psychiatric symptoms in alpha-mannosidosis. J. Intellect. Disabil. Res. 49 (11), 865–871.
Malm, D., Riise Stensland, H.M., Edvardsen, O., Nilssen, O., 2014. The natural course and complications of alpha-mannosidosis–a retrospective and descriptive study. J. Inherit. Metab. Dis. 37 (1), 79–82.
Mancuso, M., Ricci, G., Choub, A., Filosto, M., DiMauro, S., Davidzon, G., et al., 2008. Autosomal dominant psychiatric disorders and mitochondrial DNA multiple deletions: report of a family. J. Affect. Disord. 106 (1–2), 173–177.
Mancuso, M., Orsucci, D., Ienco, E.C., Pini, E., Choub, A., Siciliano, G., 2013. Psychiatric involvement in adult patients with mitochondrial disease. Neurol. Sci.: Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol. 34 (1), 71–74.
Manti, F., Nardecchia, F., Banderali, G., Burlina, A., Carducci, C., Donati, M.A., et al., 2020. Long-term clinical outcome of 6-pyruvoyl-tetrahydropterin synthase-deficient patients. Mol. Genet. Metab. 131 (1–2), 155–162.
Maubert, A., Hanon, C., Metton, J.P., 2015. Niemann-Pick type C disease and psychosis: two siblings. Encephale 41 (3), 238–243.
Maubert, A., Hanon, C., Sedel, F., 2016. Psychiatric disorders in adult form of Niemann-Pick disease type C. Encephale 42 (3), 208–213.
McCleery, A., Nuechterlein, K.H., 2019. Cognitive impairment in psychotic illness: prevalence, profile of impairment, developmental course, and treatment considerations. Dialog. Clin. Neurosci. 21 (3), 239–248.
Miller, C.H., Fleischhacker, W.W., 2000. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf. 22 (1), 73–81.
Millward, L.M., Kelly, P., Deacon, A., Senior, V., Peters, T.J., 2001. Self-rated psychosocial consequences and quality of life in the acute porphyrias. J. Inherit. Metab. Dis. 24 (7), 733–747.
Millward, L.M., Kelly, P., King, A., Peters, T.J., 2005. Anxiety and depression in the acute porphyrias. J. Inherit. Metab. Dis. 28 (6), 1099–1107.
Morava, E., Gardeitchik, T., Kozicz, T., de Boer, L., Koene, S., de Vries, M.C., et al., 2010. Depressive behaviour in children diagnosed with a mitochondrial disorder. Mitochondrion 10 (5), 528–533.
Müller, D., Pilz, H., ter Meulen, V., 1969. Studies on adult metachromatic leukodystrophy. 1. Clinical, morphological and histochemical observations in two cases. J. Neurol. Sci. 9 (3), 567–584.
Nia, S., 2014. Psychiatric signs and symptoms in treatable inborn errors of metabolism. J. Neurol. 261 (2), 559–568.
Olkinuora, M., 1982. Organic brain syndromes from a psychiatric point of view: diagnostic and nosological aspects. Acta Neurol. Scand. 92, 47–57.
Opladen, T., Hoffmann, G.F., Blau, N., 2012. An international survey of patients with tetrahydrobiopterin deficiencies presenting with hyperphenylalaninaemia. J. Inherit. Metab. Dis. 35 (6), 963–973.
Packman, W., Crosbie, T.W., Riesner, A., Fairley, C., Packman, S., 2006. Psychological complications of patients with Gaucher disease. J. Inherit. Metab. Dis. 29 (1), 99–105.
Pampols, T., 2010. Inherited metabolic rare disease. Adv. Exp. Med. Biol. 686, 397–431.
Pan, L., Vockley, J., 2013. Neuropsychiatric symptoms in inborn errors of metabolism: incorporation of genomic and metabolomic analysis into therapeutics and prevention. Curr. Genet. Med. Rep. 1 (1), 65–70.
Parikh, S., Galioto, R., Lapin, B., Haas, R., Hirano, M., Koenig, M.K., et al., 2019. Fatigue in primary genetic mitochondrial disease: No rest for the weary. Neuromuscul. Disord. 29 (11), 895–902.
Parker, N., 1985. Hereditary whispering dysphonia. J. Neurol. Neurosurg. Psychiatry 48 (3), 218–224.
Patience, D.A., Blackwood, D.H., McColl, K.E., Moore, M.R., 1994. Acute intermittent porphyria and mental illness–a family study. Acta Psychiatr. Scand. 89 (4), 262–267.
Pietz, J., Fatkenheuer, B., Burgard, P., Armbruster, M., Esser, G., Schmidt, H., 1997. Psychiatric disorders in adult patients with early-treated phenylketonuria. Pediatrics 99 (3), 345–350.
Ris, M.D., Weber, A.M., Hunt, M.M., Berry, H.K., Williams, S.E., Leslie, N., 1997. Adult psychosocial outcome in early-treated phenylketonuria. J. Inherit. Metab. Dis.: Off. J. Soc. Study Inborn Errors Metab. 20 (4), 499–508.
Rosebush, P.I., Anglin, R.E., Rasmussen, S., Mazurek, M.F., 2017. Mental illness in patients with inherited mitochondrial disorders. Schizophr. Res. 187, 33–37.
Rosenblatt, D.S., Cooper, B.A., 1987. Inherited disorders of vitamin B12 metabolism. Blood Rev. 1 (3), 177–182.
Rosenblatt, D.S., Aspler, A.L., Shevell, M.I., Pletcher, B.A., Fenton, W.A., Seashore, M.R., 1997. Clinical heterogeneity and prognosis in combined methylmalonic aciduria and homocystinuria (cblC). J. Inherit. Metab. Dis. 20 (4), 528–538.
Roze, E., Gervais, D., Demeret, S., Ogier de Baulny, H., Zittoun, J., Benoist, J.F., et al., 2003. Neuropsychiatric disturbances in presumed late-onset cobalamin C disease. Arch. Neurol. 60 (10), 1457–1462.
Rozenberg, R., Kok, F., Burin, M.G., Sa Miranda, M.C., Vasques, C., Henriques-Souza, A. M., et al., 2006. Diagnosis and molecular characterization of non-classic forms of Tay-Sachs disease in Brazil. J. Child Neurol. 21 (6), 540–544.
Sadek, J., Shellhaas, R., Camfield, C.S., Camfield, P.R., Burley, J., 2004. Psychiatric findings in four female carriers of Fabry disease. Psychiatr. Genet. 14 (4), 199–201.
Sanders, R.D., Gillig, P.M., 2012. Extrapyramidal examinations in psychiatry. Innov. Clin. Neurosci. 9 (7–8), 10–16.
Saudubray, J.M., Garcia-Cazorla, A., 2018. Inborn errors of metabolism overview: pathophysiology, manifestations, evaluation, and management. Pedia Clin. North Am. 65 (2), 179–208.
Schardt, C., Adams, M.B., Owens, T., Keitz, S., Fontelo, P., 2007. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med. Inf. Decis. Mak. 7, 16.
Scholtens, S., Smidt, N., Swertz, M.A., Bakker, S.J., Dotinga, A., Vonk, J.M., et al., 2015. Cohort profile: lifelines, a three-generation cohort study and biobank. Int. J. Epidemiol. 44 (4), 1172–1180.

Schram, M.T., Sep, S.J., van der Kallen, C.J., Dagnelie, P.C., Koster, A., Schaper, N., et al., 2014. The Maastricht study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. Eur. J. Epidemiol. 29 (6), 439–451.

Sedel, F., Baumann, N., Turpin, J.C., Lyon-Caen, O., Saudubray, J.M., Cohen, D., 2007. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J. Inherit. Metab. Dis. 30 (5), 631–641.

Shanmugiah, A., Sinha, S., Taly, A.B., Prashanth, L.K., Tomar, M., Arunodaya, G.R., et al., 2008. Psychiatric manifestations in Wilson's disease: a cross-sectional analysis. J. Neuropsychiatry Clin. Neurosci. 20 (1), 81–85.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., et al., 1998. 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 59, 22-33;quiz 4-57.

Sheffield, J.M., Karcher, N.R., Barch, D.M., 2018. Cognitive deficits in psychotic disorders: a lifespan perspective. Neuropsychol. Rev. 28 (4), 509–533.

Sigmundsdottir, L., Tchan, M.C., Knopman, A.A., Menzies, G.C., Batchelor, J., Sillence, D. O., 2014. Cognitive and psychological functioning in Fabry disease. Arch. Clin. Neuropsychol.: Off. J. Natl. Acad. Neuropsychol. 29 (7), 642–650.

Sipione, S., Monyror, J., Galleguillos, D., Steinberg, N., Kadam, V., 2020. Gangliosides in the brain: physiology, pathophysiology and therapeutic applications. Front. Neurosci. 14, 572965.

Soltanzadeh, A., Soltanzadeh, P., Nafissi, S., Ghorbani, A., Sikaroodi, H., Lotfi, J., 2007. Wilson's disease: a great masquerader. Eur. Neurol. 57 (2), 80–85.

Srinivas, K., Sinha, S., Taly, A.B., Prashanth, L.K., Arunodaya, G.R., Janardhana Reddy, Y.C., et al., 2008. Dominant psychiatric manifestations in Wilson's disease: a diagnostic and therapeutic challenge! J. Neurol. Sci. 266 (1–2), 104–108.

Stein, P.E., Badminton, M.N., Rees, D.C., 2017. Update review of the acute porphyrias. Br. J. Haematol. 176 (4), 527–538.

Steiner, C.E., Guerreiro, M.M., Marques-de-Faria, A.P., 2003. Genetic and neurological evaluation in a sample of individuals with pervasive developmental disorders. Arq. De Neuro-Psiquiatr. 61 (2a), 176–180.

Stelten, B.M.L., Bonnot, O., Huidekoper, H.H., van Spronsen, F.J., van Hasselt, P.M., Kluijtmans, L.A.J., et al., 2018a. Autism spectrum disorder: an early and frequent feature in cerebrotendinous xanthomatosis. J. Inherit. Metab. Dis. 41 (4), 641–646.

Stelten, B.M.L., Bonnot, O., Huidekoper, H.H., van Spronsen, F.J., van Hasselt, P.M., Kluijtmans, L.A.J., et al., 2018b. Autism spectrum disorder: an early and frequent feature in cerebrotendinous xanthomatosis. J. Inherit. Metab. Dis. 41 (4), 641–646.

Storjord, E., Dahl, J.A., Landsem, A., Ludviksen, J.K., Karlsen, M.B., Karlsen, B.O., et al., 2019. Lifestyle factors including diet and biochemical biomarkers in acute intermittent porphyria: results from a case-control study in northern Norway. Mol. Genet. Metab. 128 (3), 254–270.

Surtees, R., Blau, N., 2000. The neurochemistry of phenylketonuria. Eur. J. Pedia 159, S109–S113.

Trakadis, Y.J., Fulginiti, V., Walterfang, M., 2018. Inborn errors of metabolism associated with psychosis: literature review and case-control study using exome data from 5090 adult individuals. J. Inherit. Metab. Dis. 41 (4), 613–621.

V. Rajkumar V. Dumpa Lysosomal Storage Disease StatPearls. Treasure Isl. (FL) 2022.

Valstar, M.J., Bruggenwirth, H.T., Olmer, R., Wevers, R.A., Verheijen, F.W., Poorthuis, B. J., et al., 2010. Mucopolysaccharidosis type IIIB may predominantly present with an attenuated clinical phenotype. J. Inherit. Metab. Dis. 33 (6), 759–767.

van de Burgt, N., van Koningsbruggen, S., Behrens, L., Leibold, N., Martinez-Martinez, P., Mannens, M., et al., 2021. Screening for inborn errors of metabolism in psychotic patients using next generation sequencing. J. Psychiatr. Res. 138, 125–129.

Vanier, M.T., 1999. Lipid changes in Niemann-Pick disease type C brain: personal experience and review of the literature. Neurochem. Res. 24 (4), 481–489.

Vanier, M.T., 2010. Niemann-Pick disease type C. Orphanet J. Rare Dis. 5, 16.

Waisbren, S.E., Potter, N.L., Gordon, C.M., Green, R.C., Greenstein, P., Gubbels, C.S., et al., 2012. The adult galactosemic phenotype. J. Inherit. Metab. Dis. 35 (2), 279–286.

Walker, V., 2014. Ammonia metabolism and hyperammonemic disorders. Adv. Clin. Chem. 67, 73–150.

Walterfang, M., Fietz, M., Fahey, M., Sullivan, D., Leane, P., Lubman, D.I., et al., 2006. The neuropsychiatry of Niemann-Pick type C disease in adulthood. J. Neuropsychiatry Clin. Neurosci. 18 (2), 158–170.

Walterfang, M., Bonnot, O., Mocellin, R., Velakoulis, D., 2013. The neuropsychiatry of inborn errors of metabolism. J. Inherit. Metab. Dis. 36 (4), 687–702.

Wang, S.J., Yan, C.Z., Liu, Y.M., Zhao, Y.Y., 2018. Late-onset cobalamin C deficiency Chinese sibling patients with neuropsychiatric presentations. Metab. Brain Dis. 33 (3), 829–835.

Waters, F., Collerton, D., Ffytche, D.H., Jardri, R., Pins, D., Dudley, R., et al., 2014. Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye disease. Schizophr. Bull. 40 (4), S233–S245.

Wilke, M., Dornelles, A.D., Schuh, A.S., Vairo, F.P., Basgalupp, S.P., Siebert, M., et al., 2019. Evaluation of the frequency of non-motor symptoms of Parkinson's disease in adult patients with Gaucher disease type 1. Orphanet J. Rare Dis. 14 (1), 103.

Williams, R.A., Mamotte, C.D., Burnett, J.R., 2008. Phenylketonuria: an inborn error of phenylalanine metabolism. Clin. Biochem. Rev. 29 (1), 31–41.

Yunisova, G., Tufekcioglu, Z., Dogu, O., Bilgic, B., Kaleagasi, H., Akca Kalem, S., et al., 2019. Patients with lately diagnosed cerebrotendinous xanthomatosis. Neurodegener. Dis. 19 (5–6), 218–224.