Neuropsychiatric Symptoms in Inborn Errors of Metabolism: Incorporation of Genomic and Metabolomic Analysis into Therapeutics and Prevention

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Abstract

Inborn errors of metabolism may present as a spectrum ranging from neonatal lethality to non-specific symptoms. Neuropsychiatric manifestations have been identified in three groups: those presenting as emergencies, those with chronic fluctuating symptoms, and those associated with mental retardation. Milder central nervous system specific inborn errors of metabolism may also present later in life with isolated psychiatric symptoms. Inborn errors of metabolism presenting with neuropsychiatric symptoms are described with illustrative case examples. Metabolomic and genomic approaches to identification and treatment are described.

Keywords

inborn error of metabolism; neuropsychiatric; CNS-specific; genomics; metabolomics; psychosis; depression; suicide

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Introduction

Inborn errors of metabolism (IEMs) are traditionally defined as defects in a single gene leading to a physiologically relevant decrease in the function of an enzyme. They can present with a spectrum of symptoms ranging from neonatal lethality due to accumulation of an intoxicating compound to onset of non-specific symptoms later in life. Delayed diagnosis in the latter situation can lead to significant morbidity and mortality. Neuropsychiatric manifestations in IEM's have historically been grouped into three classifications, those presenting as emergencies (delirium, confusion), those with chronic, fluctuating psychiatric symptoms, and those presenting in the setting of mild mental retardation [1]. Early identification when psychiatric symptoms are present is crucial to prevent permanent neurologic damage in these settings (Table 1).There is, however, a fourth group of milder central nervous system (CNS) specific IEM's presenting later in life with isolated neuropsychiatric symptoms, currently not identified by most diagnostic paradigms. In addition, psychiatric symptoms, neurocognitive difficulties, and learning disability are well

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documented in patients with known inborn errors of metabolism, even in the setting of appropriate treatment. Examples include phenylketonuria [2, 3], maple sugar urine disease [4, 5], Wilson's Disease [6], the porphyrias [7], Wolfram's Syndrome [8], and homocysteinuria [9, 10]. Imbalances in dopamine and serotonin pathways related to mood, anxiety, learning and cognition (for review see 11 and 12) may contribute to the development of these symptoms in patients with IEM's.

Consideration of single gene defects leading to IEM's with psychiatric manifestations almost certainly underestimates the scope of the problem. The human genome consists of 3 billion nucleotide base pairs encoding 25,000 genes, and more than 4,000 specific genetic disorders affecting 1% of all live births. Nonetheless, single gene effects do not explain all genetic disease, as genotype-phenotype correlates are imperfect [13]. Dysfunction at multiple gene loci can also result in disease, and disease modifying factors complicate our understanding of IEMs [14]. For example, multiple partial enzyme deficiencies have been shown to lead to clinically relevant dysfunction in muscle energy metabolism, with evidence of an additive effect of heterozygous mutations in multiple genes in functionally related pathways [15]. Heterozygosity for multiple defects in a metabolic pathway or functionally related pathways has been termed "synergistic heterozygosity" [15], a concept with potential implications in the diagnosis, treatment, and understanding of CNS specific IEM's leading to psychiatric symptoms. Physiologically, this reflects reduction of flux through pathways, or a dominant negative model in which one protein with an unstable mutation disrupts the structure of a complex needed for appropriate function of the pathway. Such epistasis or multigenic inheritance can just as easily lead to a CNS specific disease phenotype. Relevant examples include dihydrofolate reductase in the folate metabolism pathway [16], and guanosine triphosphate (GTP) cyclohydrolase and associated tetrahydrobiopterin deficiencies in the serotonin, dopamine, and nitrous oxide pathways [17, 18, 19].

Disorders of metabolism in psychiatric disease, particularly aberration of flux through metabolic pathways rather than complete deficiencies, may be far more common than we are aware. A study of 34 adult psychiatric patients with severe major depressive disorder revealed that 21% had previously unrecognized reduced folate levels (less than 150 ng/ml), which correlated with lower cerebrospinal fluid (CSF) 5-HIAA [20]. Of 673 children with elevated phenylalanine screened for biopterin synthesis defects with HPLC of urine pterins and a biopterin load test, one child with GTP cyclohydrolase I deficiency, 36 children with dihydrobiopterin synthetase deficiency (DHBS), and 14 children with dihydropteridine reductase (DHPR) were identified [21]. In this sample, 7.5% were found to have an IEM.

Over the past two decades, improvements in the diagnosis of IEMs have been driven by the development of new technologies to identify groups of metabolites indicative of a specific diagnosis. Gas chromatography of urine organic acids revolutionized the identification of the organic acidemias, and tandem mass spectrometry (MS/MS) analysis of the blood has extended the range of disorders that can readily be identified in clinical practice, with the advantage of requiring very small sample volumes. Linking both technologies to a variety of front-end columns for sample fractionation dramatically expands their ability and can lead to the identification of literally thousands of physiologically and clinically relevant compounds in body fluids. Metabolomics is a relatively new and rapidly evolving field that focuses on the relationship of metabolites to physiologic and pathophysiologic processes, but the relationship of metabolic balance to deficiencies to mental health disorders is understudied. One metabolomic study of nine geriatric patients with depression suggested that the depressed state may be associated with alterations in the metabolism of lipids and neurotransmitters, particularly GABA, but cause and effect could not be determined [22]. Blood biopterin level and inflammatory compounds have been correlated with depression in older adults as well (for review see 23). Metabolomics techniques have also been utilized to

study Huntingdon's disease, Parkinson's disease, and schizophrenia (for review see 24). In addition to deficiency of specific cofactors having the potential to adversely affect monoamine synthesis (Figure 1), disorders of mitochondria have also been implicated in psychiatric disorders (for review see 25). Mitochondria are the main intracellular producers of oxidants, and mitochondrial disorders may impact the metabolism of monoamines and lead to an increased risk of depression. Mitochondria are also involved directly in monoamine synthesis (Figure 1) via monoamine oxidases (MAO) in the mitochondrial membrane. Finally, individual structural genetic variants have been identified in genomics studies both in studies of schizophrenia [26] and in large scale studies seeking drug targets [27]. These structural variants are abundant and may contribute to deleterious effects similar to the cases described below.

Illustrative Clinical Cases

Guanosine triphosphate-cyclohydrolase (GTPCH) (Figure 1) deficiency is an autosomal-recessive genetic disorder associated with neurologic abnormalities. Type I includes hyperphenylalaninemia due to deficiency of tetrahydrobiopterin (BH4).In milder variants, defective monoamine production is prominent because of tetrahydrobiopterin dependent tyrosine and tryptophan hydroxylases. Biopterin is a cofactor for three enzymes: the conversion of phenylalanine-4-hydroxylase (to phenylalanine), tyrosine-3-hydroxylase (to catecholamines) and tryptophan-5-hydroxylase (to serotonin). Nearly 200 different mutant alleles in GTPCH have been identified. Treatment with sapropterin (Kuvan) and/or the deficient monoamine may be successful. We have recently reported the treatment of a 19-year-old patient with treatment-refractory suicidal ideation and severe major depressive disorder who had a CSF metabolite profile consistent with GTPCH deficiency. He had an IQ in the gifted range and other neurologic abnormalities were absent. He presented at 14 years of age with suicide attempt by overdose, and by 15, he overdosed again requiring treatment in the pediatric intensive care unit. Despite treatment with serotonin-norepinephrine reuptake inhibitors (SNRIs), riluzole, antipsychotics, mood stabilizers and electroconvulsive therapy (ECT) (Figure 1), the patient did not improve. Serotonin reuptake inhibitors (SSRIs) resulted in worsening. At age 17, after 32 treatments of ECT, he remitted for only one week followed by immediate onset of suicidal intent and an aborted suicide attempt. The patient refused further ECT due to non-response. He demonstrated significant suicidality during a 49-day hospitalization. With maximal dose polypharmacy, the patient experienced neither improvement nor side effects. Neurologic examination remained normal throughout.

Metabolic testing revealed normal cytochrome P450 (3A4, 2D6 and C19) metabolism and homozygous long allele of the serotonin transporter promoter gene (SLC64A) locus. Brain MRI was normal. CSF showed undetectable neopterin, biopterin 10 nM/l (12–30), 5-hydroxyindoleacetic acid (5-HIAA) 38 nM/l (67–140) and homovanillic acid (HVA) 116 nM/l (145–324), indicative of GTPCH deficiency, and thus a defect in the pterin biosynthetic pathway. Blood phenylalanine level was 6 μmol/dl (nl<12) and sequencing of the GTPCH gene showed no pathogenic mutation. CSF 5MTHF was normal (levels 93 and 98, range 40–120).

The patient was started on sapropterin 800 mg (10 mg/kg) supplementation. Beginning treatment day 6, he reported euphoric mood, then euthymia; on day 17, hyperactivity, euphoria and normal sleep. By day 24, mood fluctuated markedly with gradually decreasing frequency. The patient endorsed mood incongruent impulses and strong feelings of love and emotion. By day 31, the effect plateaued. Sapropterin was increased to 800 mg orally twice daily (20 mg/kg). On day 40, the CSF neurotransmitter pattern revealed little change (Figure 1). He began to have episodes of shaking, insomnia and word finding difficulty. Sapropterin was reduced to 800 mg orally, in the morning and 400 mg orally, at bed time. After 2.5

months, the patient reported stable improvement, but mood remained low. He received 5-hydroxytryptophan (5-HTP) supplementation with carbidopa to block peripheral effects of serotonin and increase conversion to serotonin in the CNS. Sapropterin was stabilized at 700 mg orally twice daily and carbidopa 25 mg daily was added. 5-HTP was started at 50 mg and titrated to 200 mg, the patient had normal sleep duration and continuity, and at 250 mg, he reported improved mood and continued relief of suicidal ideation. Mood remained euthymic for 4 months with titration of 5-HTP to 400 mg orally twice daily. Nausea responded to promethazine. Eight months status-post sapropterin treatment, CSF neopterin and biopterin were in the normal range (10 and 12 nM/l respectively). The patient continues to report only minimal residual symptoms and improved function presently. To our knowledge, this is the first report of a severe biopterin metabolic defect and a pattern of metabolites consistent with GTPCH deficiency presenting with isolated severe psychiatric symptoms in the absence of neurologic abnormality. The etiology of the patient's severe CNS biopterin deficiency remains unclear, as GTPCH molecular studies were normal. However, this enzyme requires an additional protein subunit for activation, a defect that would reduce GTPCH activity. Previously unrecognized negative regulatory mechanisms on the enzyme may also be at play and could be identified through additional genome sequencing studies. The metabolic profile reported here is unique to GTPCH deficiency or a defect in the GTP activator protein with other enzymatic defects in the pterin synthetic pathway showing with very different metabolic patterns. It should be noted that little is known about alterations or responses in this pathway with neuroactive metabolic agents. For example, there could be non-specific secondary changes mimicking deficiencies that are not clinically relevant. Alterations in the pathway could be related to a pathophysiologic process or even pharmacotherapy, emphasizing the need for additional metabolomics studies. While it is possible that the discovery of a defect in the pterin biosynthetic pathway is coincidental to symptoms of severe, treatment-resistant depression and suicidality, the patient's clinical response to replacement of BH4 with 5-HTP supplementation makes this unlikely. Successful reversal of life-threatening depression refractory to known interventions does suggest that metabolic abnormalities should be considered in similar cases.

A second case of a more common metabolic disorder, cerebral folate deficiency [5-methyltetrahydrofolate (5-MTHF) deficiency] presenting with primarily psychiatric symptoms has also identified by our team. Cerebral folate deficiency has been described as a CNS specific syndrome with low 5-MTHF in CSF and normal folate in plasma [28]. Folate is involved in nearly 100 metabolic reactions [29], and because folate is involved in the purine synthetic pathway, there may be an association between low 5-MTHF and impaired tetrahydrobiopterin synthesis leading to impairment of serotonin, norepinephrine, and dopamine synthesis [28] (Figure 1). In addition to its contribution to synthesis of monoamines implicated in psychiatric disorders, screening for low CSF 5-MTHF levels has been recommended in neurologic disorders of unknown origin [30,31].

Definitive diagnosis of cerebral folate deficiency requires CSF sampling. Our patient was a young woman with a significant major depressive disorder and sudden mood fluctuations. She had history of non-suicidal self-injury and five suicide attempts. Her symptoms partially remitted with high dose serotonin reuptake inhibitor and cognitive behavioral therapy, but she continued to have sudden dips in mood with significant suicidal ideation and recurrence of non-suicidal self injury despite treatment. CSF testing revealed low 5MTHF level of 35 (normal range 40–120). CSF 5-HIAA, HVA, neopterin, and biopterin were within normal limits. Plasma testing revealed normal hemoglobin (13.8), hematocrit (40), serum B12 (937), and folate (14.4) levels. Serine, glycine, and homocysteine levels were within normal limits. In light of her low CSF 5-MTHF, we initiated treatment with folinic acid [29] at 5 mg PO daily. Folinic acid bypasses deconjugation and reduction steps for folic acid metabolism, i.e., metabolism occurs without dihydrofolate reductase. The patient reported reduction in

mood fluctuation, resolution of suicidal ideation, and improvement in mood after 8 weeks. She denied side effects. Folinic Acid was increased to 10 mg po daily at 8 weeks. In the following months, the patient reported continued stable improvement of mood.

Conclusion

A diagnosis of an inborn error of metabolism is often made in the setting of a family history of a known disorder, symptoms that are exacerbated by significant physiologic changes (such as fever, fasting, surgeries, or extremes of temperature), and otherwise unexplained multi-system disease. However, it is also important to consider isolated psychiatric symptoms as a sign of an IEM at times of stress or physiologic change such as puberty, a time of onset for many IEM's associated with psychiatric symptoms [1], childbirth (such as ornithine transcarbamylase disorder [32], and urea cycle disorders [33], and in times of physical trauma. In addition, expansion to other clinical situations is necessary, especially in the setting of a treatment resistant psychiatric disorder. As demonstrated by our patients, it is possible that adolescent and adult onset milder variants of inborn metabolic disease can escape diagnosis for many years, leading to ineffective or inadequate management of symptoms. Identification of a treatable inborn error of metabolism early in the course of psychiatric illness may reduce emotional stress, cognitive impairment, and developmental delay. At the very least, it can reduce stigma, and prevent adverse effects of ineffective treatments. Identification of new inborn errors of metabolism leading to psychiatric illness ultimately may allow us to repurpose currently approved standard and orphan drugs. Finally, with the identification of sentinel cases of IEM's contributing to psychiatric illness, we may be able to develop new peripheral screening tests for patients with severe or atypical psychiatric symptoms [34].

Acknowledgments

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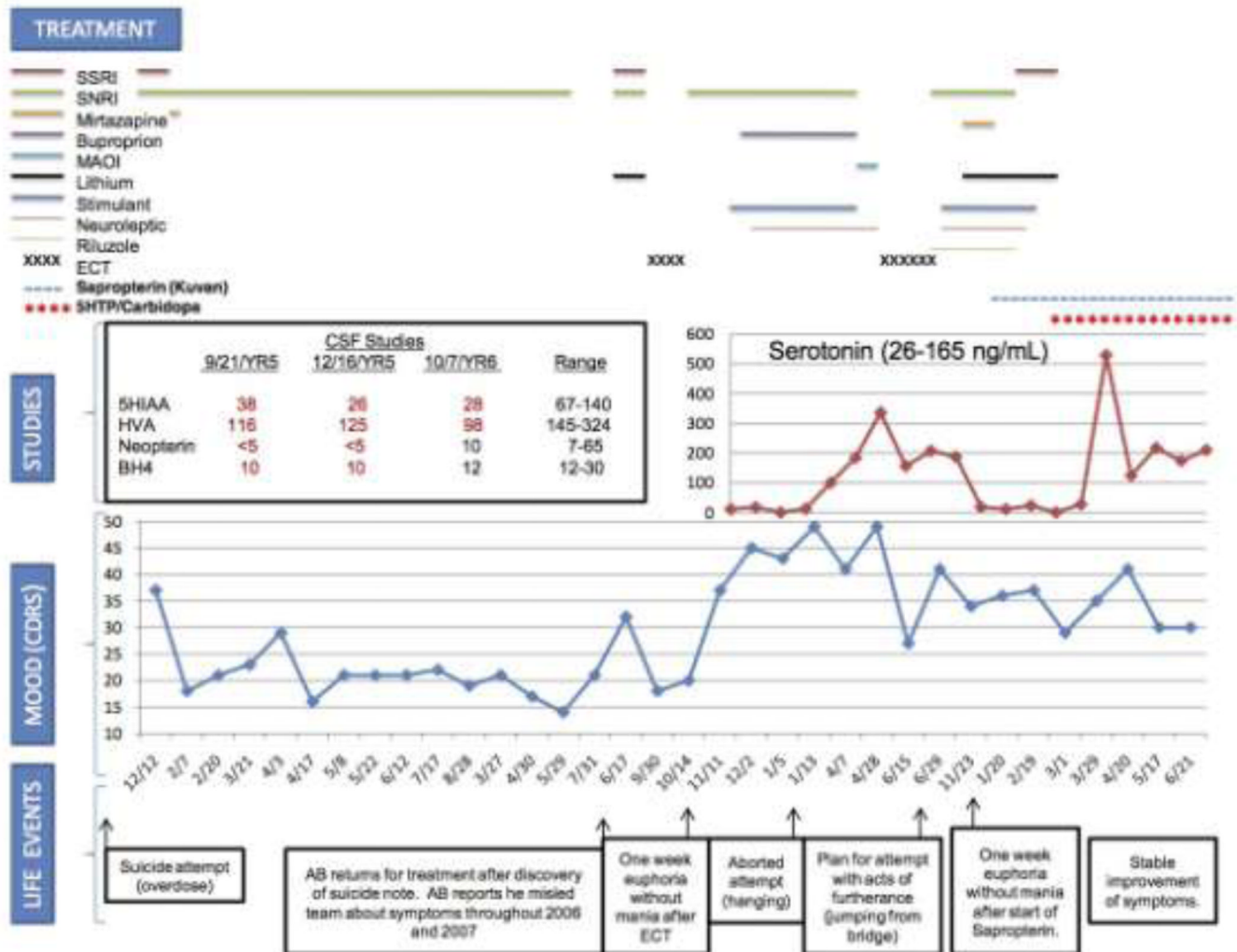
Figure 1.
Course and treatment of treatment refractory depression in a patient with a new variant of GTP-Cyclohydrolase Deficiency [19]
CDRS Children's Depression Rating Scale, SSRI Selective Serotonin Reuptake Inhibitor, SNRI Serotonin-Norepinephrine Reuptake Inhibitor, MAOI Monoamine Oxidase Inhibitor, ECT Electroconvulsive Therapy, 5HTP 5-Hydroxytryptophan, 5HIAA 5-Hydroxyindoleacetic Acid, HVA Homovanillic Acid, BH4 Tetrahydrobiopterin

Table 1

Known inborn metabolic disorders that may present with psychiatric symptoms

Disorder	Symptoms	Signs	Psychiatric presentation
Intoxication Syndromes			
Urea cycle disorders	Liver dysfunction, emesis	NH3, AA, Orotic Acid	Confusion Behavioral changes Psychosis Delirium
Homocysteine remethylation defects	Stroke, seizures, myelopathy	Homocystinuria	
Cystathionine- synthase deficiency	Seizure, osteoporosis, thromboembolism, eye d/o	Homocystinuria,	
Acute intermittent porphyrias	Abdominal pain, emesis, neuropathy	Dark urine, plasma/ urine porphyrins	
Phenylketonuria	Seizure, developmental delay	Hyperphenylalanemia	
Lipid Storage/Oligosaccharidoses/ mucopolysaccaridoses			
Niemann-Pick C	Vertical opthalmoplegia	Bone marrow foam cells	Psychosis Delusions Disorganization Catatonia Cognitive decline (mimics schizophrenia)
GM2 gangliosidosis	Ataxia, dystonia, polyneuropathy	Enzyme testing, CSF GM2	
Metachromatic leukodystrophy	Ataxia, dystonia, demyelinating polyneuropathy	Leukocyte arylsulfatase A; MRI symmetrical white matter changes	
Adrenoleukodystrophy	Paraparesis, adrenal insufficiency, neuropathy	MRI may show leukoencephalopathy	
Cerebrotendinous xanthomatosis	Variable neurological symptoms, osteoporosis, xanthomas,	Cerebellar atrophy, low Vit. D	
-mannosidosis	Ataxia	Leukoencephalopathy	
Ceroid lipofuscinosis	Seizures, retinitis pigmentosa	None	
-methyl-acyl-CoA racemase deficiency	Encephalopathy, seizure, neuropathy, retinopathy	Elevated serum pristanic acid	
Metal Storage Disorders			
Wilson disease	Liver disease, movement disorder	Low serum ceruloplasm, copper	Impulsivity Irritability Psychosis
Aceruloplasminemia	Retinal degeneration, Diabetes mellitus, Neurological changes	Low serum ceruloplasm, iron, copper, high serum ferritin, Brain MRI iron deposits	
Neuroferritinopathy	Extrapyramidal symptoms	Low plasma ferritin	
PANK2 (pantothenate kinase 2)	Neurodegeneration	MRI iron deposits in the basal ganglia	
Central Nervous System Specific Disorders			
Disorders of Neurotransmitter Metabolism	Neuropsychiatric	CSF HVA, 5-HIAA, neopterin, biopterin	Depression Suicide
Cerebral Folate Deficiency	Neuropsychiatric	CSF 5MTHF	Variable

Adapted from [35]