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The neuropsychiatry of inborn errors of metabolism

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Abstract A number of metabolic disorders that affect the central nervous system can present in childhood, adolescence or adulthood as a phenocopy of a major psychiatric syndrome such as psychosis, depression, anxiety or mania. An understanding and awareness of secondary syndromes in metabolic disorders is of great importance as it can lead to the early diagnosis of such disorders. Many of these metabolic disorders are progressive and may have illness-modifying treatments available. Earlier diagnosis may prevent or delay damage to the central nervous system and allow for the institution of appropriate treatment and family and genetic counselling. Metabolic disorders appear to result in neuropsychiatric illness either through disruption of late neurodevelopmental processes (metachromatic leukodystrophy, adrenoleukodystrophy, GM2 gangliosidosis, Niemann-Pick type C, cerebrotendinous xanthomatosis, neuronal ceroid lipofuscinosis, and alpha mannosidosis) or via chronic or acute disruption of excitatory/inhibitory or monoaminergic neurotransmitter systems (acute intermittent porphyria, maple syrup urine disease, urea cycle disorders, phenylketonuria and disorders of homocysteine metabolism). In this manuscript we review the evidence for neuropsychiatric illness in major metabolic disorders and discuss the possible models for how these disorders result in psychiatric symptoms. Treatment considerations are discussed, including treatment resistance, the increased propensity for side-effects and the possibility of some treatments worsening the underlying disorder.

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Introduction

Metabolic disturbance can have wide-ranging effects on the central nervous system (CNS), as highly metabolically active neurons are variably sensitive to derangements in metabolic processes (Schreiber and Baudry 1995). Disruption to metabolic processes results in marked disruption to normal CNS function and development, with presentations ranging from gross neurodevelopmental disruption, seizures and coma when disruption is severe, to intermittent and/or subtle cognitive and behavioural disturbance when disruption is mild. Inborn errors of metabolism (IEM) result from the absence or deficiency of an intrinsic component of a metabolic pathway, often an enzyme, which disrupts cellular function due to impairment in synthesis of cellular components essential to neuronal function, or the accumulation of neurotoxic substances (Saudubray 2009). Many IEMs have attenuated forms that present for the first time in adulthood (Sedel et al 2007) without preceding overt clinical symptoms in childhood. Three quarters of all psychiatric illness presents prior to the age of 24 (Kessler et al 2005) and the majority of these disorders have strong genetic and biological underpinnings (Inoue and Lupski 2003). It could be therefore expected that IEMs that present in adolescence or early adulthood will have a greater likelihood of presenting with psychiatric illness (Walterfang et al 2009b).

It has long been recognised that mental illness can result directly from organic brain disease and that psychiatric disorder may be the first presentation of a more systemic illness (Lipowski 1984). A number of brain disorders can produce an accurate *phenocopy* of psychiatric illness, where

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the presentation is indistinguishable from a primary psychiatric disorder. As many disorders that cause organic psychiatric syndromes have their own definitive non-psychiatric treatment, many of the secondary psychiatric syndromes may be partially or totally reversible. This is particularly true in metabolic disorders, many of which are treatable with dietary modification, enzyme replacement, or other specific biochemical therapy. Awareness of the types of disorders that may present as psychiatric illness phenocopies and their associated physical, cognitive or neurological concomitants allow clinicians to recognise an underlying systemic or metabolic illness. Conversely, failure to recognise the underlying illness whilst focussing on treatment for the secondary psychiatric syndrome alone can delay the institution of appropriate treatment and result in potentially irreversible CNS change.

The purpose of this review is to describe the major metabolic disorders that are associated with secondary psychiatric illness. Given that most psychiatric illness has its onset in adolescence or early adulthood, our focus is on disorders that present in or persist into adulthood. We will then propose a number of neurobiological models that allow an understanding of how metabolic disorders can result in secondary psychiatric syndromes and describe general principles of management of these syndromes.

Metachromatic leukodystrophy

In younger patients with metachromatic leukodystrophy (MLD, OMIM: 250100), seizures, mental retardation and motor symptoms predominate while psychiatric manifestations and dementia frequently present prior to motor or cognitive symptoms in adult-onset patients. The adult form presents as one of two distinct phenotypes, one with a predominantly motor (cerebello-pyramidal) presentation and the other with a predominantly psychiatric presentation. The latter appears to be strongly associated with the I179S mutation (Rauschka et al 2006). Up to half of patients with onset between 10 and 30 years of age present with psychotic symptoms, including auditory hallucinations, delusions, formal thought disorder, and catatonia (Rosebush et al 2010). As the illness progresses, other neurological symptoms supervene, including seizures, chorea or dystonia. Neurological symptoms commonly present *after* the development of psychiatric symptoms (Black et al 2003; Hyde et al 1992; Rosebush et al 2010). Patients often present with attentional disturbance, reduced speed of processing and executive impairment, typical of reduced frontal-subcortical connectivity (Shapiro et al 1994). Some adult-onset patients may initially be diagnosed as frontotemporal dementia (Kozian et al 2007). MRI generally demonstrates typical confluent periventricular white matter changes sparing subcortical U-fibres, with leukodystrophy frequently showing a frontotemporal preponderance with only minimal involvement of grey matter (Reider-Grosswasser and Bornstein 1987).

Adolescent/adult MLD provides an intriguing model for the understanding of the neurobiology of psychosis, as it interrupts myelinative processes that occur during this critical period of neurodevelopment, in particular frontotemporal myelination (Hyde et al 1992; Walterfang et al 2005). As frontotemporal connectivity is known to be impaired at both structural and functional levels in schizophrenia (Friston and Frith 1995; Pettersson-Yeo et al 2011), the unique predilection of MLD for frontotemporal anatomical connections appears to confer its psychotogenic propensity. This suggests that any CNS process that interrupts the normal development of connectivity between these cortical regions in this crucial "psychotogenic window" can produce psychosis (Black et al 2003; Walterfang et al 2005). It is notable that some treatment-refractory patients with schizophrenia have been shown to have ASA pseudo-deficiency or intermediate ASA levels (Fluharty 1990), suggesting that this may be an independent risk factor in the population for psychotic illness.

GM2 gangliosidosis: Tay-Sachs disease

In Tay-Sachs disease (TSD, OMIM: 272800), HEX-A deficiency in lysosomes impairs the catabolism of gangliosides from the neuronal cell membrane, resulting in accumulation of lysosomal gangliosides. This results in neuronal ultrastructural change, particularly axon hillock outgrowth to form meganeurites with ectopic dendritogenesis (Purpura and Suzuki 1976) and axonal spheroids (Walkley 1988), which may alter neuron-to-neuron microconnectivity initially before neuronal death occurs. Neurons in the thalamus, substantia nigra, cerebellum and brainstem are particularly affected (Suzuki 1991). Unlike early-onset cases, late-onset patients' cortical neurons show little to no excess ganglioside storage (Kornfeld 2008).

The neurological presentation of late-onset TSD is quite variable and no distinct phenotype-genotype correlations exist (Federico et al 1991). Patients will frequently present with gait disturbance, dysarthria and tremor (MacQueen et al 1998). Many patients have normal or near-normal cognitive function (MacQueen et al 1998), although subtle deficits in executive function, processing speed and verbal memory may be present in up to half of patients (Elstein et al 2008; Frey et al 2005; Zaroff et al 2004). Neuroimaging findings in TSD describe cerebellar atrophy in most patients (Frey et al 2005; Neudorfer et al 2005; Streifler et al 1989), although cerebral atrophy may be present in up to a quarter

of patients (Frey et al 2005). Diagnosis generally rests on demonstration of deficient hexosaminidase activity.

Neuropsychiatric presentations occur in up to half of late onset TSD patients described in unselected series (Gravel et al 2001) and the most common neuropsychiatric presentation is psychosis (Frey et al 2005; Navon et al 1986; Neudorfer et al 2005; Oates et al 1986; Streifler et al 1993). The rate of schizophrenia-like psychosis in late-onset TSD patients ranges from 30 % (Oates et al 1986) to 50 % (Navon et al 1986). In a review of all published cases prior to 1998, a conservative estimate of prevalence of psychosis in late-onset patients was one third (MacQueen et al 1998). Catatonia may be the initial presenting feature (Renshaw et al 1992; Rosebush et al 1995; Streifler et al 1989). Mania or depression has also been described (Argov and Navon 1984; Federico et al 1991; Hamner 1998).

The treatment of psychosis in TSD can be problematic, with often only partial response to neuroleptics and mood stabilisers such as lithium (Hurowitz et al 1993; MacQueen et al 1998; Rosebush et al 1995; Streifler et al 1989). Importantly, patients with late-onset TSD are exquisitely sensitive to the motor side-effects of typical neuroleptic medications (Manor et al 1997; Rosebush et al 1995; Streifler et al 1989). For severe psychotic or affective illness, electroconvulsive therapy (ECT) appears to be a safe and effective treatment (Hurowitz et al 1993; Renshaw et al 1992).

Adrenoleukodystrophy

In X—linked adrenoleukodystrophy (ALD, OMIM: 300100), the adult cerebral form shows a predilection for neuropsychiatric presentations. Demyelinative changes are most prominent in parietal and occipital cortex as well as the thalamus, callosum and brainstem (Patel et al 1995), although more anterior cortical regions can be involved in a minority of patients (Castellote et al 1995; MacDonald et al 1984). MRI generally shows symmetrical hyperintensity beginning in the posterior callosum and spreading into parieto-occipital regions on T2-weighted imaging (Poll-The and Gartner 2012).

At presentation, the majority of adult-onset cerebral ALD patients present with psychiatric disturbance, most commonly behavioural changes (Rosebush et al 2010). Mania and affective psychosis appear to be the most common neuropsychiatric presentations, more so than schizophreniform illnesses, although the latter do occur (Rosebush et al 2010; Walterfang et al 2005). Patients are not infrequently treatment-resistant (Rosebush et al 2010). As in MLD, psychiatric presentations in ALD may precede frank motor or cognitive changes by some years (Rosebush et al 1999).

The andrenomyeloneuropathy (AMN) form of ALD, the most common form of ALD amongst adults and long thought to affect only the peripheral nervous system, subtle cerebral manifestations of the disorder are often present, and the rate of depressive illness appears to be elevated at least two-fold (Walterfang et al 2007). Some patients may present with mood changes subsequent to adrenal insufficiency, which reverse with appropriate corticosteroid replacement therapy. As patients progress, most will develop significant neuropsychological disturbance, characterised by a frontal-subcortical pattern of impairment (Luda and Barisone 2001), a pattern which may also appear in an attenuated form in many AMN patients (Edwin et al 1990). As in MLD, when white matter changes occur in anterior cortical regions, patients may present with a clinical presentation that initially may be indistinguishable from frontotemporal dementia (Inoue et al 2012).

Niemann-Pick type C disease

Niemann-Pick Type C disease (NPC, OMIM: 607625) is characterised neuropathologically by axonal spheroid formation, hypomyelination and eventual demyelination (Karten et al 2003) and impaired synaptic function (Byun et al 2011; Pressey et al 2012). White matter tracts are severely affected (Ong et al 2001; Palmeri et al 1994; Zervas et al 2001) with the corpus callosum showing the most striking axonal loss (German et al 2002). The neuronal cells most vulnerable to these pathological processes are the Purkinje cells of the cerebellum, striatum, and thalamus followed by neurons in hippocampal and other cortical regions (Elleder et al 1985; Harzer et al 1978; March et al 1997; Ong et al 2001).

Structural imaging in NPC commonly shows diffuse cerebral and/or cerebellar atrophy (Fink et al 1989; Lossos et al 1997; Schiffman 1996; Shulman et al 1995b; Tedeschi et al 1998), atrophy of striatum, thalamus and hippocampi (Walterfang et al 2010, 2012b), midbrain atrophy (Walterfang et al 2012a) and pathology in major white matter tracts including the corpus callosum (Grau et al 1997; Palmeri et al 1994; Walterfang et al 2011, 2010). Neuropsychological testing in adolescent/adult-onset cases often reveals a steady decline in function throughout adulthood with significant deficits in executive function and memory (Campo et al 1998; Schiffman 1996; Shulman et al 1995a, b).

Psychosis is a common initial presentation of adolescent or adult-onset NPC and may present alongside motor symptoms and cognitive impairment as an initial manifestation in 25–40% of adult-onset cases (Josephs et al 2003; Walterfang et al 2006a). When psychosis has been reported, features have included persecutory delusions, auditory hallucinations and ideas of reference (Breen et al 1981; Campo et al 1998; Josephs et al 2003; Shulman et al 1995a, b; Walterfang et al 2009a, 2006b). A small number of cases

have been reported where psychosis was the sole initial manifestation (Shulman et al 1995a, b; Turpin et al 1991; Vanier 1999; Walterfang et al 2006a), and these patients may be treated with neuroleptics alone for a number of years before gait impairment and cognitive decline result in a diagnostic revision (Josephs et al 2003; Shulman et al 1995b; Walterfang et al 2006a, 2009a). We have also described a presentation in adulthood with rapid-cycling bipolar disorder that responded to anticonvulsant medication (Sullivan et al 2005).

Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosisis (CTX, OMIM: 213700) results in cholestanol accumulation in white and grey matter, leading to neuroaxonal dystrophy, axonal dropout and severe white matter pathology (Soffer et al 1995) and accelerated apoptosis (Moghadasian et al 2002). Global reduction in grey and white matter volume, reduced white matter integrity and callosal atrophy are noted on structural imaging (Berginer et al 1994; Chang et al 2010; Dotti et al 1994; Guerrera et al 2010; Su et al 2010; Wallon et al 2010). MRS findings suggest that axonal metabolic dysfunction rather than demyelination are responsible for the diffuse white matter findings (De Stefano et al 2001).

Two case series of CTX patients with psychiatric disturbance have been reported. In the first, 4 of 35 cases suffered psychiatric disturbance, three of these being neuroleptic-responsive psychotic illness (Berginer et al 1988). A further series found psychiatric disturbance in 7 of 10 CTX patients, predominantly agitation and psychosis (Dotti et al 1991). Other authors have reported depression in CTX sufferers (Chen et al 2012b; Lee et al 2002; Shapiro 1983) and more recently a fronto-temporal dementia picture in a compound heterozygote has been described (Guyant-Marechal et al 2005).

Neuronal ceroid lipofuscinosis

The characteristic neuropathology of adult neuronal ceroid lipofuscinosis (ANCL) is accumulation of lipofuscin-like material in lysosomes in neuronal and extraneuronal tissue (Wisniewski et al 2001). The distribution of abnormal lysosomal inclusions in neurons is commonly diffuse through cortical and subcortical neurons, but may be localised to the cerebral cortex in a quarter of cases (Constantinidis et al 1992). Hippocampal/enterorhinal cortex may be particularly susceptible (Braak and Braak 1993). MRI often shows cerebral and cerebellar atrophy, callosal thinning, and may show other features such as altered signal in subcortical nuclei, whilst SPECT commonly shows regional cortical hypoperfusion (D'Incerti 2000; Sayit et al 2002; Schreiner et al 2000).

Neuropsychiatric disturbance in adolescent or adult-onset cases is very common (Berkovic et al 1988; Goebel and Braak 1989). ANCL presents with psychosis in up to 20 % of patients, with ages of onset between 13 and 41 (Augustine et al 1993; Callagy et al 2000; Charles et al 1990; Gospe and Jankovic 1986; Hinkebein and Callahan 1997; Lewandowska et al 2009; Reif et al 2003; Tobo et al 1984; Waldman 1992), with psychotic symptoms also described in juvenile patients (Vercammen et al 2003). Backman et al, in a series of juvenile NCL patients (mean age 15 years), described five adolescent patients with psychotic symptoms warranting psychotropic medication, although affective symptoms (predominantly depression) were more common (Backman et al 2005). Nijssen et al described a pedigree with an autosomal dominant inheritance where three of six affected family members presented with psychosis (Nijssen et al 2009). Characteristic psychotic symptoms appear to be auditory hallucinations, delusions and thought disorder (Callagy et al 2000), although occasionally catatonic motor changes can present (Reif et al 2003). In older patients, ANCL may also present with a frontotemporal dementia-like picture (Zini et al 2008), or with the hyperorality and sexual disinhibition characteristic of Kluver-Bucy syndrome (Alonso-Navarro et al 2005). Neuropsychological impairments are common, often with a mixed frontal/subcortical picture of psychomotor slowing, impaired new learning and executive and attentional impairments (Hinkebein and Callahan 1997; Zini et al 2008).

Sensitivity to the motor side effects of neuroleptic medication complicates the treatment of ACNL psychosis, with an increased propensity towards EPSE including dystonia (Gospe and Jankovic 1986; Hinkebein and Callahan 1997) and neuroleptic malignant syndrome (Reif et al 2003; Vercammen et al 2003). This sensitivity has been attributed to a combination of subcortical neuropathology and muscle membrane pathology (Reif et al 2003). The treatment of psychosis, notwithstanding motor side effects, is usually with neuroleptic medication although electroconvulsive treatment has proven effective in a number of cases (Reif et al 2003; Tobo et al 1984).

Alpha mannosidosis

In type II alpha mannosidosis (AM; OMIM: 248500) which presents in later childhood or adulthood, the predominant features are cerebellar ataxia, hearing loss, neuropsychological impairment and retinopathy (Gutschalk et al 2004). MRI scanning shows periventricular T2-hyperintensities in white matter (Gutschalk et al 2004; Vite et al 2001), which have been suggested to be secondary to demyelination

(Dietemann et al 1990) although it may to be an effect of myelin vacuolation (Sung et al 1977). Cortical and cerebellar atrophy is also not uncommon in type II patients (Ara et al 1999; Gutschalk et al 2004). Diagnosis is established by the combination of a suggestive urinary pattern of oligosaccharides and demonstration of significantly reduced enzyme activity in leukocytes or cultured skin fibroblasts, and the only treatment option is bone marrow transplantation (Sun and Wolfe 2001).

As in some other lysosomal disorders, patients with type II AM may be diagnosed with schizophrenia prior to the onset of frank neurological symptomatology (Seidl et al 2004), or psychosis may follow the development of other symptoms (Gutschalk et al 2004). Malm et al described a series of 45 patients over the age of 15, and found clearly diagnosable mental illness in 25%, with the majority presenting with a psychotic disorder characterised by delusions, hallucinations, confusion and a prolonged period of post-psychotic somnolence (Malm et al 2005). Psychosis in AM often presents with "organic" features, such as concurrent cognitive and neurological signs at the time of presentation.

Fabry disease

Fabry disease (FD; OMIM: 301500) causes accumulation of the glycolipid globotriaosylceramide (Gb3) in blood vessels and other tissues (Schiffmann 2009), resulting in a range of end-organ vascular disease (Mehta et al 2009; Mehta 2009). Brain MRI often reveals subcortical ischemia in basal ganglia, brainstem, thalamus, and particularly periventricular white matter (Reisin et al 2011).

Depressive disorders, often meeting criteria for a severe clinical depression, occur in up to half of all FD patients. The first series of FD patients highlighted an elevated rate of depression in both hemizygous males and female carriers (Grewal 1993; Sadek et al 2004). More recent systematic studies of larger cohorts have shown rates of major depression as high as 60 % (Cole et al 2007; Laney et al 2010; Schermuly et al 2011). Depression and anxiety in FD patients predicts significant impairment in social and vocational functioning (Bouwman et al 2011; Laney et al 2010). There is no clear link between white matter lesion load and depression (Schermuly et al 2011), although depression in FD appears to be predicted by the persistence of chronic pain and anhidrosis into adulthood (Cole et al 2007). There is very little data on the response to antidepressants in this group. Psychosis has been occasionally described (Shen et al 2007), although it is unclear whether this is causally related to the CNS pathology of FD (Gairing et al 2011). Neuropsychologically, FD patients are frequently normal (Low et al 2007) but may demonstrate attentional and executive deficits (Schermuly et al 2011; Segal et al 2010), commensurate with the effects of subcortical cerebrovascular disease.

Acute intermittent porphyria

Acute intermittent porphyria (AIP; OMIM: 176000) has a lengthy historical association with mental illness. The periodic "madness" of King George III has been attributed to AIP (Ho et al 2003), with the illness also implicated in Van Gogh's psychiatric history (Rose 2006). AIP has been shown to be significantly over-represented in large samples of psychiatric inpatients, at a rate up to 50–200× higher than the general population (McEwin et al 1972; Tishler et al 1985). The "classical triad" consists of abdominal pain, psychiatric disturbance, and peripheral neuropathies during episodes, although psychiatric symptoms alone may be the single presenting feature. Of clinically symptomatic patients, psychiatric disturbance occurs up to half of all cases (Crimlisk 1997), half of which are psychotic episodes (Santosh and Malhotra 1994), although depression, anxiety and delirium may also be the main presenting syndrome (Santosh and Malhotra 1994). The intermittent "attacks" of neuropsychiatric disturbance may result in a misdiagnosis of schizophrenia (Crimlisk 1997), and occasionally psychosis is the sole initial manifestation (Crimlisk 1997; Ellencweig et al 2006; Kumar 2012). Additionally, because of the high likelihood of abdominal pain during periods of acute distress, patients may be diagnosed with a somatoform disorder or histrionic personality disorder (Ellencweig et al 2006).

Although porphobilinogen (PBG) and amino-levulinic acid (ALA) accumulation is thought to be neurotoxic (Pierach and Edwards 1978), exactly how this results in neuropsychiatric disturbance is unclear. Explanatory hypotheses have included oxidative stress, vascular change and demyelination, although it may be that ALA's structural similarity to GABA results in impaired release of GABA from synapses of GABAergic inhibitory neurons (Muller and Snyder 1977), and reductions in heme dependent enzymes resulting in increased serotonin turnover and reduced nitric oxide activity (Meyer et al 1998).

Psychopharmacological management of AIP involves judicious use of medication that will not worsen the biochemical deficit, which for psychosis includes chlorpromazine and droperidol, fluoxetine or sertraline for depression, lithium for mania, and lorazepam, triazolam and temazepam for anxiolysis and sedation (Holroyd and Seward 1999).

Maple syrup urine disease

In the milder forms of maple syrup urine disease (MSUD; OMIM: 248600) that present in adulthood, altered leucine

metabolism alters astrocyte function (Funchal et al 2005; Yudkoff et al 1996) and induces neuronal apoptosis (Jouvet et al 2000). Elevated leucine can block the transport across the blood–brain barrier of other large, neutral amino acids (LNAAs), including precursors of most monoamines, causing significant disruptions to dopaminergic, noradrenergic, serotonergic and histaminergic metabolism and thus neurotransmission (Zinnanti et al 2009). Altered BCAA metabolism also results in depletion of gluatamate, GABA and aspartate, significantly altering excitatory/inhibitory neurotransmission across the CNS (Korein et al 1994; Zinnanti et al 2009). The BCAA-restricted diet also results in chronic cerebral valine deficiency, which itself may impair neuronal and oligodendrocyte function (Strauss et al 2010). As a result, MSUD patients with poor dietary management will show reduced synaptogenesis and dendritic arborisation, and dysmyelination (Kamei et al 1992; Kinney et al 1994; Prensky and Moser 1966) and, in acute metabolic crisis, cerebral edema (Strauss and Morton 2003). These pathological changes may manifest on MRI as reductions in grey matter volume, abnormal T2 signal in white matter, and diffusion restriction (Jan et al 2003; Schonberger et al 2004) and altered spectroscopy during metabolic decompensation (Jan et al 2003).

As in PKU, the advent of dietary restriction has modified illness course significantly, allowing survival of MSUD patients well into adulthood, albeit with a suggestion of subtle cognitive deficits and an elevated rate of some neuropsychiatric disorders (le Roux et al 2006). MSUD patients who transition to adulthood may have impaired neurological and psychosocial outcomes. Many may be left with subtle pyramidal and extrapyramidal signs (Carecchio et al 2011). As in a number of metabolic disorders where childhood dietary restriction is essential, MSUD patients perceive a significant strain from dietary management and resultant peer isolation, in addition to an impact on intimate/family relationships, education and employment (Packman et al 2012; Simon et al 2007). As in PKU, adult neuropsychological impairment appears more related to the age at institution of, and adherence to, dietary treatment (Hilliges et al 1993; Hoffmann et al 2006; Kaplan et al 1991).

Despite strict metabolic control, many children suffer from attentional-deficit disorders, whereas adolescents and adults commonly present with depression and anxiety (Strauss and Morton 2003). Limited neurocognitive data exists, although it is suggestive of executive and attentional deficits, with impairments to nonverbal reasoning and spatial functioning (le Roux et al 2006; Walsh and Scott 2010).

Urea cycle disorders

The hyperammonemia that characterises urea cycle disorders (UCDs) causes hyperglutaminemia in the CNS, leading to cerebral edema and astrocytic swelling (Norenberg et al 2005), altered axonal function and growth (Braissant et al 2002) and NMDA-mediated excitotoxicity (Gropman et al 2007; Robinson et al 1995). MRI during the acute phase may show cerebral edema, particularly on T2-weighted imaging; repeated episodes of hyperammonemia may result in atrophy and gliosis visible on MRI (Gaspari et al 2003; Panlaqui et al 2008), and asymptomatic patients demonstrate alterations to white matter in frontal and parietal regions subserving executive and working memory functioning (Gropman 2010). Patients with deficient arginase show alterations to corticospinal tracts (Oldham et al 2010).

In older children/adolecents or adults, the presentation may be of recurrent episodes of encephalopathy, or with a more chronic encephalopathy; there may be a history of meat avoidance/refusal, and episodic headaches, vomiting, extreme lethargy and altered consciousness in the setting of metabolic stress or protein load (Legras et al 2002; Nassogne et al 2005). Arginase deficiency is the exception, as it presents with progressive spasticity and dementia. Psychiatric presentations in UCDs may initially occur as behavioural disturbance, with development to frank psychosis, and then acute encephalopathy (Belanger-Quintana et al 2003; Eather et al 2006; Lien et al 2007; Nassogne et al 2005; Thurlow et al 2010). Affected or carrier females may present with adult-onset illness, particularly in the setting of pregnancy, and postpartum presentations may be misdiagnosed as postpartum psychosis (Enns et al 2005; Fassier et al 2011; Peterson 2003; Tonini et al 2011). In patients where acute-onset psychosis and confusion is associated with vomiting, lethargy, and seizures or other neurological symptoms, elevated plasma ammonia is crucial in excluding or confirming a UCD.

Sodium valproate is known to result in hyperammonemic encephalopathy, and as it is used as a mood stabiliser in psychiatric patients, it needs to be used carefully in patients with an atypical presentation of psychiatric illness, particularly when associated with confusion, lethargy and gastrointestinal symptoms as numerous case reports exist of severe medical compromise in this clinical circumstance (Bogdanovic et al 2000; Chopra et al 2012).

Disorders of homocysteine metabolism

In homocystinuria (OMIM: 236200), the accumulation of homocysteine and methionine, two sulphur-containing amino acids (SCAAs) in the CNS alters the release of monoamines (Selema et al 1997) and may effect neurotoxicity via agonism of NMDA receptors (Schurr et al 1993). Brain imaging may show leukodystrophy secondary to disrupted myelination (Vatanavicharn et al 2008). While isolated case reports have identified patients with psychosis and

homocystinuria (Bracken and Coll 1985; Eschweiler et al 1997; Li and Stewart 1999; Ryan et al 2002), studies investigating large case series of patients have reported that personality disorder, behavioural disturbance (such as aggression), depression and obsessive compulsive disorder are the most common psychiatric findings and that aggression and behavioural disturbances were commoner in patients with mental retardation (Abbott et al 1987).

Methylenetetrahydrofolate reductase (MTHFR) deficiency (OMIM: 236250) has been strongly associated with psychosis in its less severe form, which presents in adolescents and adults (Birnbaum et al 2008; Michot et al 2008), and may result in impairment to myelination (Engelbrecht et al 1997) and dopamine synthesis (Muntjewerff et al 2008). Notably, the C677T variant of the MTHFR gene, which causes a 35 % reduction in MTHFR function, has been associated with an increased risk for schizophrenia in some (Arinami et al 1997; Regland et al 1997; Reif et al 2005) but not all (Kunugi et al 1998) populations; two recent meta-analyses suggest it confers a 70 % increased risk of schizophrenia (Muntjewerff et al 2006), which may be part of a broader vulnerability for both mood and psychotic disorders (Peerbooms et al 2011).

Phenylketonuria

In phenylketonuria (PKU; OMIM: 261600), two metabolic processes affect the CNS. Elevated cerebral phenylalanine (Phe) levels inhibit tyrosine and tryptophan hydroxylase, altering monoaminergic neurotransmitter synthesis (particularly dopamine), but also reduce protein and cholesterol synthesis, impair synaptogenesis and alter glutamatergic transmission (de Groot et al 2010; van Spronsen et al 2009). Reduced large neutral amino acid (LNAA) availability results in reduced protein synthesis, impaired oligodendrocyte development and function, and severely disrupts normal neurodevelopment (Dyer 1999; Hoeksma et al 2009; van Spronsen et al 2009). While altered cholesterol and protein synthesis particularly affect myelination, as evidenced by human post-mortem and in vivo MRI studies (Bauman and Kemper 1982; Bick et al 1991). Hypomyelination occurs in untreated PKU and in early-treated patients, this appears to relate to intramyelinic edema (Anderson and Leuzzi 2010). Increased T2 signal on MRI scanning is seen in most patients in frontal and parieto-occipital white matter (Cleary et al 1994), and diffusion and spectroscopy imaging demonstrates altered diffusion and an increase in cerebral Phe that tightly correlates with serum Phe levels (Manara et al 2009; Scarabino et al 2009), particularly in anterior white matter (Christ et al 2010b). Functional MRI has demonstrated impaired functional connectivity within and between pre-frontal cortical regions (White et al 2010). In animal PKU models, hypomyelination has been partially restored with dietary phenylalanine restriction (Joseph and Dyer 2003), and reversal of T2 signal abnormalities has been shown with a return to dietary management (Cleary et al 1995).

Early-treated patients are described as showing elevated rates of depression, anxiety disorders (particularly agoraphobia), attention-deficit disorder and more non-specific psychosocial adjustment issues in adolescence when compared to matched healthy individuals (Brumm et al 2010). Poor metabolic control, or early discontinuation, are associated with a higher incidence of behavioural problems in childhood (Holtzman et al 1986; Smith et al 1988). PKU patients who discontinued treatment in middle childhood demonstrate elevated rates of anxiety and mood disorders in adulthood (Koch et al 2002; Ris et al 1997; Waisbren and Zaff 1994) and a persecutory stance in social contexts compared to continuously treated patients (Waisbren and Zaff 1994). These higher rates of psychiatric and cognitive illness appear to directly negatively affect psychosocial outcomes (Gentile et al 2010). A much higher proportion of PKU sufferers remain unmarried, childless, and/or living with their parents (Simon et al 2008).

From a cognitive perspective, untreated patients will show mental retardation (with IQ<50) and developmental delay (Scriver and Kaufman 2001). Much of the cognitive impairment can be attenuated with dietary control, although even early-treated patients may have subtle reductions in IQ, executive and attentional impairment (Weglage et al 1996), although non-executive impairment is less consistently present (Janzen and Nguyen 2010). The degree of dietary control in early-treated patients has a significant impact on ultimate cognitive outcome (Christ et al 2010a; Gonzalez et al 2011). However, perhaps less than 20 % of adults maintain dietary control throughout adulthood (Walter et al 2002), with the impact of diet on social interactions being a particular impediment to adherence (Cazzorla et al 2012). Discontinuation in adult life is associated with poorer educational, socioeconomic and health outcomes (Koch et al 2002), but re-engagement of "lost" patients may lead to improved outcomes (Burton and Leviton 2010).

The origin of neuropsychiatric illness in inborn errors of metabolism

As we have seen in the preceding section, metabolic disorders that result in neuropsychiatric illness alter CNS function and/or structure via a number of neuropathological processes. We postulate that the causality of psychiatric illness is the result of two processes: 1. The interruption of childhood/early adulthood neurodevelopmental trajectories in progressive illness, 2.

The acute alteration of monaminergic or excitatory/inhibitory neurotransmitter systems in acute or episodic illness.

Altered neurodevelopment in progressive metabolic illness

For a number of disorders, different mutations can disrupt protein function to varying degrees, with severe disruption causing more severe impairment in neuronal function, and thus early onset of illness—usually in infancy or early childhood and a rapid course. Conversely, when function is only mildly disrupted, onset may be much later, such as late adolescence or early adulthood. As exemplified by progressive neurometabolic disorders such as MLD and NPC, the nature of the presentation relates to the relative maturity of the underlying CNS and the nature of the neurodevelopmental processes that are currently underway when neuronal function becomes significantly impaired (Hyde et al 1992; Walterfang et al 2006a){Shaw, 2010 #416}. An understanding of neurodevelopment in adolescence and early adulthood, the period of onset of most mental illness, is thus crucial to understanding how metabolic disorders can lead to major psychiatric disorders.

In adolescence, the human brain undergoes great structural change, driven by a number of late neurodevelopmental processes. Grey matter reductions occur throughout the brain in a back-to-front direction, initially in sensorimotor, then association, and finally higher-order cortical areas such as prefrontal and superior parietal cortex (Gogtay et al 2004), with similar changes also occurring in subcortical regions (Sowell et al 2002), putatively driven by a pruning of the overproliferation of synapses that occurs in early childhood and then again in early puberty (Zecevic and Rakic 2001). This reduction in grey matter is matched by a linear increase in white matter, which continues through adolescence and adulthood (Bartzokis et al 2003; Sowell et al 2003), and which is driven by increasing myelination of cortico-cortical connections between prefrontal regions and between dorsolateral prefrontal cortex and temporal, parietal and occipital association areas (Fuster 2002; Gogtay et al 2004; Paus et al 1999).

The long association fibres connecting frontal and temporal cortex are crucial in this period. Disrupted frontotemporal connectivity is thought to be central to the neurobiology of schizophrenia (Benes et al 1994), and white matter disorders that disrupt these connections are particularly psychotogenic (Walterfang et al 2005), although altered myelination may also occur in major mood disorders (Regenold et al 2007). The refinement of prefrontal function allows a number of executive cognitive functions to mature and/or develop during this period, including processing speed, working memory, self-regulation, and cognitive control (Tau and Peterson 2010). Myelination, and the refinement of cortico-cortical and cortico-subcortical connectivity, is affected in MLD, ALD, NPC, CTX, AM, AIP, MSUD, homocysteine metabolism disorders and PKU. Interference in this normal process is likely to underpin the elevated rate of mood and psychotic disorders, in addition to executive impairment, in these metabolic disorders. This is particularly exemplified in the leukodystrophies that present in adolescence or adulthood such as MLD and ALD, where rates of major mental illness such as psychosis or mood disorders occur in one quarter to one half of patients (Hyde et al 1992; Rosebush et al 1999).

These metabolic disorders lead to a disruption to *macroconnectivity,* whereby long association corticocortical and cortico-subcortical fibres are disrupted. The high-level temporal synchrony between these regions that is required for reality testing and behavioural and emotional regulation is thus compromised. This type of dysconnectivity is thought to be central to the pathogenesis of schizophrenia (Friston and Frith 1995; Walterfang et al 2006c), and schizophrenia-like psychoses are frequent presentations of metabolic illness (Sedel et al 2007). Given the aforementioned widespread developmental synaptodendritic changes that occur during late adolescence and early adulthood, disruption of *microconnectivity*, i.e. connectivity between neurones may be a further pre-disposing factor to psychosis. Disturbed microconnectvity has been described as a possible neurodevelopmental "pathway" to schizophrenia (McGlashan and Hoffman 2000). The dendritic changes in GM2 gangliosidosis (Purpura and Suzuki 1976; Walkley et al 1990) and consequent disruption in microconnectivity may underpin the elevated rates of psychosis in this disorder (Frey et al 2005; Gravel et al 1995; Neudorfer et al 2005) while in a disorder such as NPC, where both micro- and macroconnectivity are impaired (Walterfang et al 2010, 2012b), the rates of psychosis are even higher (Walterfang et al 2006a).

Significant alterations to the dopaminergic system occur during this developmental period and largely involve the frontal cortex. Increases in dopaminergic fibre and dopamine transporter density (Kalsbeek et al 1988; Spear 2000) and differential (striatal > prefrontal) dopamine receptor pruning (Spear 2000) leads to a relative dominance of the mesocortical dopaminergic system (Davey et al 2008). Synaptic plasticity, pruning and myelination are partially dependent on dopaminergic innervation so that the refinement of cortico-cortical connections depends on the integrity of this system (Gurden et al 1999).

A similar overproduction of other monaminergic receptors, which are then pruned and refined, also occurs in adolescence (Brenhouse and Andersen 2011; Lidow and Rakic 1992). Developmental disruption of monoaminergic systems contributes to the development of mood disorders (Davey et al 2008) as well as psychosis (Di Forti et al 2007). Inhibitory GABAergic and glutamatergic systems show ongoing changes, with a steady linear increase in levels of the former across adolescence (Lidow and Rakic 1992) and substantial pruning from their early adolescent peak of NMDA receptors in frontotemporal regions (Insel et al 1990).

Disruption to the dopaminergic system occurs in MSUD (Zinnanti et al 2009) and disorders of homocysteine metabolism (Selema et al 1997), but is perhaps most central to PKU (de Groot et al 2010; Puglisi-Allegra et al 2000), where prefrontal depletion appears to directly disrupt the development of dopamine-dependent executive functioning. Other monoaminergic systems are variably affected by MSUD (Zinnanti et al 2009) and PKU (de Groot et al 2010; Puglisi-Allegra et al 2000). Given that reduced or dysregulated transmission in monoaminergic systems is integral to anxiety and depression (Gorman et al 2002; Ruhe et al 2007), these alterations to monoaminergic availability may underpin the higher prevalence of anxiety and depression in these metabolic disorders.

This model represents a shift away from a more traditional "neurodegenerative" model of neuropsychiatric illness, whereby mental disorders are described as resulting from the impaired function or loss of specific neuronal populations that have largely matured and which subserve mental functions such as reality testing or emotional regulation. Whilst psychiatric disorders do not infrequently occur in neurodegenerative disorders such as cortical and subcortical dementias, the vast majority of psychiatric disorders have their onset in adolescence or early adulthood, largely a distinct epoch from that in which the majority of neurodegenerative disorders have their onset. Secondly, as can be seen in disorders which have a varying age of onset of illness dependent on the degree of metabolic disturbance, such as NPC or MLD, when illness presents later in life, the presentation is more likely to be of a dementing-type illness rather than a typical psychiatric illness such as schizophrenia-like psychosis, major depression or bipolar disorder. Additionally, a neurodegenerative process can disrupt a normal neurodevelopmental trajectory, as these are not discrete processes and can interact if neurodegeneration occurs within the timeframe of ongoing neurodevelopment. Thus, whilst typical neurodegeneration alone may present with neuropsychiatric illness in a proportion of patients with metabolic disorders, it is most likely to be the disruption of neurodevelopmental trajectories that results in typical psychiatric illness.

Neurotransmitter disruption in acute/episodic illness

In addition to those metabolic disorders that impact upon neurodevelopment, a number of metabolic disorders are associated with episodic but potentially reversible metabolic disturbances in the setting of an otherwise largely intact and normally-developed CNS. In disorders such as AIP, MSUD or the UCDs, acute decompensation can occur in the setting of particular metabolic states, such as situations requiring increased protein or heme synthesis, or when dietary management of a metabolic illness lapses or is disrupted.

These disorders result in acute alterations to the balance between excitatory and inhibitory systems via alteration of GABAergic and/or NMDA-mediated glutamatergic transmission, and/or alteration of monoaminergic transmission involving dopamine, serotonin or noradrenaline. Acute alteration of the excitatory/inhibitory balance between GABAergic and glutamatergic systems is exemplified by anti-NMDA receptor encephalitis and gamma-hydroxy butyric acid (GHB) intoxication. The former is a paraneoplastic syndrome that causes acute-onset psychosis, frequently catatonic, in mostly young women (Dalmau et al 2011), and its psychotogenic effects relate to acute loss of NMDA receptors that disrupt glutamatergic transmission (Hughes et al 2010). Similarly, potent NMDA antagonists such as phencyclidine and ketamine can produce psychotic symptoms, potentially by secondary dysregulation of prefrontal and striatal dopaminergic systems (Javitt 2007). Similarly, alterations of the GABAergic system have been implicated in substance-induced psychosis (Cagnin et al 2011; Kruszewski et al 2009) and delirium, particularly that secondary to alcohol withdrawal (Hughes 2009). Thus, rapid dysregulation of either or both of these systems may result in psychosis and/or an acute confusional state, such as that seen in UCDs (Nassogne et al 2005), MSUD (Strauss and Morton 2003) and AIP (Muller and Snyder 1977).

Similarly, monoaminergic depletion or reduced turnover can occur in a number of metabolic disorders, such as AIP (Meyer et al 1998), MSUD (Zinnanti et al 2009), or in untreated PKU (de Groot et al 2010). Animal studies show that depression can result from acute depletion of dopamine (Santiago et al 2010) and dopamine depleting agents used for movement disorders not infrequently cause depression (Chen et al 2012a). Similarly, noradrenaline depletion has been reliably shown to lead to depression or depressive relapse (Miller et al 1996). Both depression and anxiety can also be caused by serotonin depletion (Fernandez and Gaspar 2012). Thus, the elevated rates of anxiety and depression seen in many of these disorders is not unexpected. Although the effect of depletion on different monoaminergic systems is complex, with interactions between different monoaminergic systems that occur differentially in different circuits (and which also interact with glutamatergic and GABAergic systems), disruption in these systems—particularly secondary to reduced monoaminergic synthesis or availability—is likely to result in alterations to mood, anxiety levels, and thus behaviour.

Management of neuropsychiatric disturbance

Management of neuropsychiatric disturbance in metabolic syndromes is generally symptomatic. For many disorders, little clear treatment data exists, and clinicians will generally treat a secondary psychiatric syndrome with the standard

psychotropic medications: antidepressants for depression and anxiety; antipsychotics for psychosis; antipsychotics and mood stabilisers for mania and antipsychotics and/or benzodiazepines for agitation. However, a number of caveats apply in the management of neuropsychiatric symptoms in the setting of metabolic illness.

Metabolic disorders that disrupt neurodevelopment can result in psychiatric syndromes that are at initially, or may later become, treatment-resistant. This has been well-described in ALD (Rosebush et al 2010), MLD (Hermle et al 1997) and Niemann-Pick type C disease (Walterfang et al 2006a, 2009a). It may be that secondary or "organic" psychiatric illness is less likely to respond to traditional treatments as the underpinning neurobiology of secondary presentations differs from the primary psychiatric illness in which the particular treatment has shown to be beneficial. A phenocopy of an illness does not guarantee that both the phenocopy and the primary illness will respond to the same treatments. Additionally, as many of these illnesses are progressive, patients may be initially responsive to treatment but less responsive to treatment over time as neurobiological change ensues. Furthermore, treatment response may depend on the maintained integrity of brain systems outside those thought to be disrupted in psychosis. If these systems become illness-affected, then this may impact upon illness presentation and treatment response (Hyde et al 1992). This is not uncommon in progressive disorders that result in secondary psychiatric syndromes, particularly as frank dementia supervenes (Walterfang et al 2009b).

The second main issue relates to an increased propensity for side effects of psychiatric treatments, particularly dopamine blockers used to treat psychosis. If metabolic disorders affect the striatum, then these patients will have a significantly elevated rate of extra-pyramidal side effects. This has been well-described in TSD (Manor et al 1997; Rosebush et al 1995; Streifler et al 1989), ACNL (Gospe and Jankovic 1986; Hinkebein and Callahan 1997) and NPC (Sandu et al 2009). The anticholinergic side-effects of many antipsychotics and some antidepressants may worsen already compromised cognition in patients with moderate to advanced illness, as may the sedation caused by many of these medications' antihistaminic effects. Thus, careful consideration of agent choice is crucial in treating patients with secondary psychiatric syndromes, to minimise motor and cognitive side effects that may worsen the concomitant neurological manifestations of the underlying metabolic disorder.

Medications used to manage psychiatric symptoms such as aggression, agitation or mood elevation may also directly impact upon the underlying metabolic condition. The greatest caution should be exercised with valproate, which can precipitate or worsen the clinical presentation of AIP (Crimlisk 1997) or UCDs (Bogdanovic et al 2000; Chopra et al 2012). Other porphyrogenic psychotropic medications which should be avoided include carbamazepine and imipramine. It has been suggested that tricyclic antidepressants and phenothiazines may worsen the underlying biochemical deficit of TSD (Hurowitz et al 1993). In these circumstances however, there are generally a number of other available pharmacological options, including modern selective serotonergic antidepressants for depression and anxiety, and atypical antipsychotics for psychosis, mania and acute agitation (Walterfang et al 2009b).

The most important treatment consideration in psychiatric presentations of metabolic disease is the detection of—and, where possible, institution of treatment for—the underlying disorder. In a patient presenting for the first time with a psychiatric syndrome, a metabolic disorder should be suspected when:

1. There is a significant family history of metabolic or other neurological disorder
2. The presentation of psychiatric symptoms occurs coincident with neurological, cognitive or other systemic symptoms that suggest a more widespread neurological or systemic disease
3. The course is episodic and triggered by specific conditions that result in metabolic stress such as surgery, elevated protein intake or fever (Sedel et al 2007).

If clinicians are aware of the aforementioned disorders and how they present, they can initiate either a specialist referral or commence an investigative path including brain MRI, examination of biofluids for specific metabolic intermediates or endproducts, or direct testing for enzymatic disorders. Sedel et al have described a useful diagnostic algorithm for both acute and chronic presentations of secondary psychiatric illness in a previous version of JIMD (Sedel et al 2007). Accurate diagnosis may allow treatment and attenuation of the primary disorder, which may itself result in abatement of the psychiatric syndrome and reduce the requirement for psychotropic medication.

Conclusion

A number of metabolic disorders can present at differing illness timepoints with major psychiatric illness. For many progressive disorders that present in adolescence or early adulthood, the disruption of late neurodevelopmental processes—which occur during the period of greatest vulnerability to major mental illness—appear to underpin the development of psychiatric illness. Disruption to myelination, and the resultant impairments in cortico-cortical and subcortical connectivity that ensue, is common to many of these disorders. For a range of other disorders that can cause acute metabolic disruption, disruption to inhibitory/excitatory

neurotransmission, or monoaminergic neurotransmitter turnover and availability, appears to cause acute presentations of psychiatric illness. An awareness of these disorders, and the nature of how they may present, can allow clinicians to accurately diagnose a secondary psychiatric illness and institute appropriate treatment for the underlying disorder.

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