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What is new for monoamine neurotransmitter disorders?

Clara Marecos · Joanne Ng · Manju A. Kurian

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Abstract The monoamine neurotransmitter disorders are increasingly recognized as an expanding group of inherited neurometabolic syndromes caused by disturbances in the synthesis, transport and metabolism of the biogenic amines, including the catecholamines (dopamine, norepinephrine, and epinephrine) and serotonin. Disturbances in monoamine metabolism lead to neurological syndromes that frequently mimic other conditions, such as hypoxic ischemic encephalopathy, cerebral palsy, parkinsonism-dystonia syndromes, primary genetic dystonia and paroxysmal disorders. As a consequence, neurotransmitter disorders are frequently misdiagnosed. Early and accurate diagnosis of these neurotransmitter disorders is important, as many are highly amenable to, and some even cured by, therapeutic intervention. In this review, we highlight recent advances in the field, particularly the recent extensive characterization of known neurotransmitter disorders and identification of novel neurotransmitter disorders. We also provide an overview of current and future research in the field focused on developing novel treatment strategies.

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C. Marecos · J. Ng · M. A. Kurian
Department of Neurology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

J. Ng · M. A. Kurian (✉)
Developmental Neurosciences, UCL-Institute of Child Health, Room 111 Level 1 CMGU, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
e-mail: manju.kurian@ucl.ac.uk

Introduction

Neurotransmitters disorders are an expanding group of neurometabolic syndromes. Diagnosis is made through detailed clinical assessment, analysis of cerebrospinal fluid (CSF) neurotransmitters and further supportive diagnostic investigations. Early and accurate diagnosis of neurotransmitter disorders is paramount, as many are amenable to therapeutic intervention. Complete amelioration of motor symptoms is achievable in some disorders, such as Segawa's syndrome [autosomal dominant guanosine triphosphate cyclohydrolase I (GTP) cyclohydrolase deficiency], and in other conditions, significant improvement in motor symptoms and quality of life can be attained with pharmacotherapy.

Disruption of monoamine neurotransmitter metabolism leads to diverse neurological manifestations in childhood, such as neurodevelopmental delay, pyramidal and extrapyramidal motor disorders, epilepsy, autonomic dysfunction, and neuropsychiatric features. More specifically, clinical features suggestive of dopamine deficiency include dystonia, fluctuation of symptoms (including diurnal variation), tremor, oculogyric crises, ptosis, axial hypotonia, hypersalivation, developmental delay, feeding difficulties, excessive sweating, and temperature instability. These features overlap clinically with many other neurological syndromes, such as cerebral palsy (including that due to hypoxic ischemic encephalopathy), primary genetic dystonia, early-onset parkinsonian syndromes, paroxysmal disorders, and epileptic encephalopathies, thereby making the diagnosis of neurotransmitter disorders somewhat challenging (Fernandez-Alvarez 2009).

In this review, we highlight advances in the field over the last 5 years, as listed below, particularly the extensive characterization of known neurotransmitter disorders, as well as recent identification of novel neurotransmitter disorders. We also provide an overview of current and future research in the field, mainly focused on developing novel treatment strategies for the more pharmacoresistent neurotransmitter disorders.

What is new in neurotransmitter disorders
• **Sepiapterin reductase deficiency** A treatable cerebral palsy mimic Axial hypotonia, motor and language delay, oculogyric crisis, weakness and dystonia with diurnal fluctuation of symptoms are the core clinical symptoms Parkinsonian features, sleep disturbance, behavioural and psychiatric abnormalities are also frequent Most patients respond to L-dopa and 5-hydroxytryptophan combination
• **Tyrosine hydroxylase deficiency** New distinct phenotypic classification (A, B and intermediate phenotypes) Myoclonus-dystonia syndrome described as a new phenotype Slow gradual increment of L-dopa aims to minimise risk of dyskinesia Consider amantadine for treating l-dopa induced dyskinesias
• **AADC deficiency** Genotype-phenotype correlations are described L-dopa restricted usage for AADC deficiency to patients with mutations affecting binding or catalytic sites Transdermal rotigotine may benefit some patients Gene therapy was safe with some efficacy in 4 children
• **Report of new diseases –the "transportopathies"** Dopamine transporter deficiency syndrome (*SLC6A3*) Vesicular monoamine transporter disease (*VMAT2*)
• **Secondary neurotransmitter disorders** Secondary low HVA, 5-HIAA and 5-MTHF can be found in a broad spectrum of neurological disorders. L-dopa, 5-HTP and folinic acid, respectively, may have a role in symptomatic patients

Clinical update on known neurotransmitter disorders

Clinical research of sizeable patient cohorts has successfully led to improved characterization of many primary neurotransmitter disorders due to defects in dopamine synthesis (Fig. 1). Increased disease awareness has also led to expansion of the phenotypic spectrum to include both classic and atypical/unusual phenotypes.

Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy

Sepiapterin reductase deficiency (SRD) is an underrecognized dopa-responsive disorder of pterin synthesis without hyperphenylalaninemia. Friedman et al. (2012) describe the clinical features of the largest SRD series to date (43 cases) and report a significant delay in diagnosis for many patients, with frequent misdiagnosis of cerebral palsy. Core clinical features of SRD are axial hypotonia, motor and language delay, oculogyric crisis, weakness and dystonia with diurnal fluctuation of symptoms (Friedman et al. 2012). Recently, Leuzzi et al. (2013) reported tremor of the limbs and head at rest, inhibited by skin contact and spontaneous movement as presenting symptoms of the disease during the first months of life. Parkinsonian features, sleep disturbance, behavioral, and psychiatric abnormalities are also frequently reported in SRD. Only 8 % of such individuals have normal cognitive abilities, with the majority having mild to moderate learning disability (Friedman et al. 2012; Neville et al. 2005). Diagnosis is made through the characteristic CSF findings of low HVA and 5-HIAA, with raised total biopterin, dihydrobiopterin (BH2), and sepiapterin (Zorzi et al. 2002). Urine pterins and plasma phenylalanine levels are normal, but the phenylalanine load test is frequently positive (Bonafé et al. 2001a, b); sepiapterin reductase enzyme activity is reduced (Bonafé et al. 2001a, b).

For SRD, therapeutic approaches involve dopamine and serotonin precursor supplementation. Most patients seem to respond to combination therapy with L-dopa and 5-HTP; most significantly, many patients display a dramatic response to L-dopa/carbidopa, with improvement in motor and sleep symptoms (Friedman et al. 2006). A combination of L-dopa and carbidopa at a ratio 1:5 was reported in two siblings with global amelioration, including resolution of stiffening and ocular deviation (Verbeek et al. 2008). Benserazide is an alternative to carbidopa (Friedman et al. 2012). Some patients experience side effects, such as dose-related dyskinesia; therefore, a very low starting dosage of L-dopa ~0.5–2 mg/kg per day in three to four doses, with slow increment to the target dose, is recommended. The independent benefits of 5-HTP have been difficult to assess, but modest improvement in

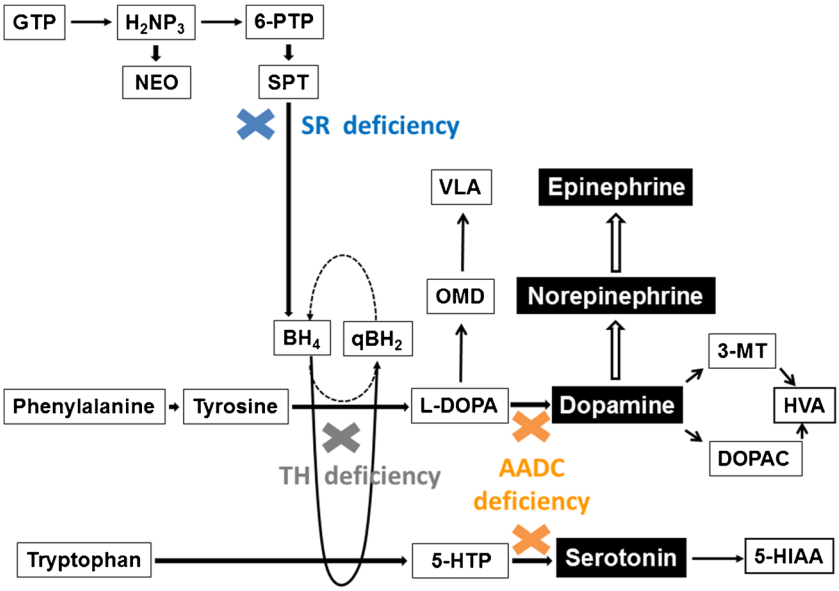

Fig. 1 Metabolic pathways of tetrahydrobiopterin and the monoamine neurotransmitters. The biogenic amines are *boxed in black*. BH4 is synthesized de novo in four steps from GTP and recycled via qBH2. BH4 is a cofactor for the hydroxylation of tyrosine to L-dopa and tryptophan to 5-HTP. AADC enzyme, with its cofactor pyridoxal-5-phosphate, catalyses the conversion of L-dopa to dopamine and 5-HTP to serotonin. Dopamine is metabolized to HVA and serotonin to 5-HIAA. The enzymatic steps affected by SR deficiency, TH deficiency and AADC deficiency are illustrated. *AADC* aromatic L-amino acid decarboxylase, *BH2* 7,8-dihydrobiopterin, *BH4* tetrahydrobiopterin, *DOPAC* 3,4-dihydroxyphenyl-acetic acid, *GTP* guanosine triphosphate cyclohydrolase I, *HVA* homovanillic acid, *H2NP3* dihydroneopterin triphosphate, *NEO* neopterin, *OMD* 3-O-methyldopa, *SPT* sepiapterin, *SR* sepiapterin reductase, *TH* tyrosine hydroxylase, *VLA* vanillactic acid, *3-MT* 3-methoxytyramine, *5-HIAA* 5-hydroxyindoleacetic acid, *5-HTP* 5-hydroxytryptophan, *6-PTP* 6-pyruvoyl-tetrahydropterin

sleep, motor and cognitive aspects have been reported, with 5-HTP doses ranging from 1 to 6 mg/kg per day. Dopamine agonists, such as bromocriptine, other agents blocking neurotransmitter reuptake (sertraline) or reducing neurotransmitter catabolism (selegiline), and symptomatic therapy (trihexyphenidyl/baclofen for dystonia, melatonin for disturbed sleep pattern) were used in a smaller fraction of patients with benefit in some, whilst BH4 was not useful (Friedman et al. 2012). Lohmann et al. (2012) also described the successful use of pramipexole in association with L-dopa.

The key finding of our report on sepiapterin reductase deficiency emphasizes the importance of increasing awareness and recognition of this treatment-responsive neurotransmitter disorder and to consider CSF neurotransmitter analysis and a trial of L-dopa in children with cerebral palsy of undefined etiology.

Tyrosine hydroxylase deficiency: disease classification, novel phenotypes and treatment strategies

Willemsen et al. (2010) report the largest cohort of 36 tyrosine hydroxylase deficiency (THD) patients defining the clinical features, genotype–phenotype correlation, prognosis and treatment response. The clinical phenotypes are classified into type A (infantile hypokinetic rigid syndrome with dystonia) and type B (severe neonatal encephalopathy) subtypes. The majority of patients (69 %) have type A THD. At the severe end of the spectrum, patients are profoundly disabled from early infancy, with motor delay, truncal hypotonia, limb rigidity, hypokinesia, ptosis, oculogyric crises, and diurnal variation of motor symptoms (Swoboda and Furukawa 2008). Intermediate phenotypes with disease severity between types A and B have also been described (Pons et al. 2013), and it is likely that, in reality, there is a phenotypic continuum from the milder type A THD to more severe type B THD. Atypical clinical cases of THD have also been reported, including those presenting with early-onset spastic paraplegia and dopa-responsive myoclonus dystonia (Giovanniello et al. 2007; Stamelou et al. 2012; Espay and Chen 2013).

It has long been recognized that the CSF signature of THD comprises a low HVA and 3-methoxy-4-hydroxyphenylethylene glycol (3-MHPG) with normal 5-HIAA, leading to a HVA:5-HIAA ratio <1 (normal 1.0–3.7) (Hyland et al. 1992; Willemsen et al. 2010; Yeung et al. 2011). Hyperprolactinemia is observed in 50 % of cases, leading occasionally to galactorrhoea (Yeung et al. 2011). Willemsen et al. (2010) report that the HVA:5-HIAA ratio correlates with severity of clinical phenotype (lower ratios of <0.7 are more associated with type B THD). Genotype–phenotype analysis reveals that patients with promoter mutations had type A THD and responded well to L-dopa (Willemsen et al. 2010).

The dosing regimen for L-dopa treatment in THD needs to be tailored specifically to minimize L-dopa hypersensitivity,

otherwise, intolerable side effects of dyskinesia are observed, even at lower dose ranges. In type B THD, the initiating dose should be very guarded, <0.5 mg/kg per day (in four to six divided doses per day), with slow titration (over weeks to months) to 3–10 mg/kg per day, according to response. In type A disease, slow titration of L-dopa doses from 0.5 to a target 3–10 mg/kg per day is also recommended. In a cohort of six patients treated with L-dopa (dose range 0.5–5 mg/kg/day), dyskinesias developed in the first months of treatment and consisted of chorea involving the face, limbs and trunk (Pons et al. 2013). Dyskinesias were precipitated by L-dopa increment, intercurrent febrile illness, tiredness, and overexcitement. There was no relation between dyskinesia and age at treatment onset or HVA levels. In two patients, dyskinesias were successfully treated with amantadine (Pons et al. 2013). Striatal supersensitization to dopamine and excessive excitatory influences of glutamatergic corticostriatal projections on the direct pathway are putative mechanisms causing dyskinesia in these patients.

The impact of treatment strategies in THD has become increasingly well defined. In those who tolerate L-dopa well, there is a moderate to good response, with improvement of both motor symptoms and involuntary movements (Willemsen et al. 2010). Cognitive abilities remain reduced but stable in the majority of patients. Selegiline, a selective monoamine oxidase (MAO) B inhibitor, and the dopamine agonists bromocriptine and pramipexole, were prescribed in a child with type A THD and in five children with type B THD, with limited additional effect. Combination of L-dopa with selegiline, with or without biperiden (a selective central M1 cholinoreceptor blocker), has been reported to be helpful in some more pharmacoresistent THD patients (Chi et al. 2012; Yeung et al. 2011). A single case of deep-brain stimulation for refractory dystonia has been reported to show significant clinical improvement of dystonia and parkinsonian symptoms in a 6-year old boy with THD (Tormenti et al. 2011). Carbidopa/L-dopa requirement was reduced, but the right intracranial electrode was removed due to subgaleal fluid collection. Improvement in dystonia was maintained despite this electrode removal.

Aromatic L-amino acid decarboxylase deficiency: clinical phenotypes, genotypes, and treatment approaches

Aromatic L-amino acid decarboxylase (AADC) is the key enzyme in decarboxylation of L-dopa and 5-HTP for yielding active dopamine and serotonin neurotransmitters (Fig. 1). AADC activity is dependent on cofactor pyridoxal-5-phosphate. To date, AADC deficiency has been identified in approximately 100 patients. Brun et al. (2010) published clinical and biochemical features of 78 children with AADC deficiency. Key clinical features at presentation include hypotonia (95 %), oculogyric crises (86 %), and developmental retardation (63 %); 50 % of patients presented with other movement disorders, including hypokinesia, chorea, dystonia, and bulbar dysfunction. Associated features of monoamine neurotransmitter deficiency, such as sleep disturbance, autonomic dysfunction, labile temperature regulation, and irritability are also observed with cognitive impairment in the majority (Brun et al. 2010; Pons et al. 2004). Clinical presentation and phenotype of AADC deficiency is highly variable, with onset ranging from 4 months to adulthood (although the majority of patients present in childhood). A milder AADC phenotype consisting of fatigability, hypersomnolence, dystonia, and excellent response to MAO inhibitor and dopamine agonist treatment was reported in a pair of siblings (Tay et al. 2007). CSF signature consists of low HVA, 5-HIAA, and 3-MHPG, with raised 3-O-methyl-l-dopa, L-dopa, and 5-HTP, in the presence of a normal pterin profile. Plasma AADC activity is markedly reduced (deficiency range from 0 to 5.3 pmol/min per milliliter, normal ranges 20–130 pmol/min per milliliter), with raised urinary vanillylactic acid.

AADC deficiency is caused by mutations in the *DDC* gene, with a common founder mutation identified in Taiwanese Chinese patients (IVS6+4A>T) and one third of known patients being of southern Chinese origin (Lee et al. 2009). Small hands and feet as additional AADC features were described in eight children from Taiwan with an IVS 6+4 A>T splicing mutation (Lee et al. 2009).

Treatments in AADC deficiency are variable due to variable patient response. Significantly, Brun et al. (2010) report that treatment is only reported to be satisfactory in 19 % of patients, signifying a need for novel therapeutic strategies for this pharmacoresistent disorder. Therapeutic approaches consist of AADC cofactor supplementation [pyridoxine/pyridoxal phosphate (PLP)], folinic acid (the folate pool may be depleted in the metabolism of excessive L-dopa, and folate supplementation aims to avoid this depletion), dopamine agonists to counteract dopamine deficiency, and MAO B inhibitors to boost endogenous serotonin and dopamine levels. Clinicians should be aware that L-dopa is generally not used for the majority of patients, as further L-dopa accumulation causes depletion of S-adenosylmethionine that is enhanced by the AADC defect (Allen et al. 2009). However, Chang et al. (2004) described three siblings with a homozygous point mutation (c.387 G→A) in exon 3 that showed significant dystonia improvement with a combination of L-dopa and carbidopa but persistence of behavioral problems. The mutation proved to cause decreased affinity of the AADC enzyme for L-dopa affecting the catalytic site or on the binding site for the PLP cofactor. The best clinical response occurred with a combination of L-dopa and pyridoxal-5-phosphate.

Clinical benefit with newer-generation dopamine agonists (such as pramipexole) has been observed in a number of patients. Transdermal rotigotine, a dopamine agonist with

activity across D1–D5 dopaminergic receptors, as well as serotoninergic and noradrenergic receptor effects, is being increasingly used in clinical practice as the dopamine agonist of choice (Cawello et al. 2013). The aim of transdermal application and continuous drug release is easy administration and avoidance of dopamine agonist peak/troughs throughout the day. Mastrangelo et al. (2013) report rapid and persistent reduction of bradykinesia, improved gross motor function, and amelioration in on–off phenomena in one child with AADC deficiency, though the response was not so evident in his affected sibling.

Newly described monoamine neurotransmitter disorders

Dopamine transporter deficiency syndrome

Hereditary dopamine transporter deficiency syndrome (DTDS) is the first biogenic amine "transportopathy" to be described. It is an autosomal recessive condition leading to infantile parkinsonism–dystonia caused by pathogenic mutations in the *SLC6A3* gene encoding the dopamine transporter (DAT) (Kurian et al. 2009). All children present with irritability, axial hypotonia, and feeding difficulties in infancy, with a hyperkinetic movement disorder that evolves into hypokinetic parkinsonism–dystonia. Ocular abnormalities included eye flutter, saccade initiation failure, slow saccadic eye movements, eyelid myoclonus, and oculogyric crises (Kurian et al. 2011a, b, 2009). All children showed global developmental delay, with severe gross-motor delay; and none were able to speak. Many children had good receptive language and situational understanding and were able to learn methods of alternative communication (Kurian et al. 2011a, b). Autonomic features, such as hypersalivation, sweating, hyperthermia, and sleeping difficulties were also present in every child, as were feeding difficulties and failure to thrive.

CSF studies showed a raised ratio of HVA:5-HIAA>5 (normal range 1.3–4.0, Kurian et al. 2011a, b) and is a key finding in DTDS diagnosis (Kurian et al. 2011a, b). The majority of children with DTDS were misdiagnosed with dyskinetic, spastic, and mixed cerebral palsy, as frequently observed in SRD and other neurotransmitter disorders.

The *SLC6A3* gene encodes the presynaptic DAT that mediates the active reuptake of dopamine and regulates the amplitude and duration of dopamine neurotransmission (Kurian et al. 2009). Reported mutations cause loss of transporter function and impaired dopamine reuptake, with likely consequences of depleted presynaptic stores of intracellular dopamine and excessive extracellular dopamine (Kurian et al. 2011a, b, 2009; Blackstone 2009, 2011).

The phenotypic spectrum of this condition is expanding, with the first adults diagnosed with DTDS now recognized, and the condition is now considered as a differential for juvenile and early-onset parkinsonism (Ng et al. 2014; Henriksen et al. 2012).

The majority of patients are unresponsive to nearly all available therapeutic agents, including L-dopa, anticholinergics, benzodiazepines, and deep brain stimulation. L-dopa and dopamine agonists, such as ropinirole, have been used, with limited improvement in motor symptoms in a minority of patients (Kurian et al. 2011a, b).

Vesicular monoamine transporter disease

Rilstone et al. (2013) described a single extended consanguineous kindred consisting of eight affected individuals, who presented with an infantile-onset movement disorder caused by a homozygous loss-of-function mutation (P387L) in *SLC18A2,* encoding the dopamine–serotonin vesicular transporter. The mutation is predicted to impair packaging of dopamine and serotonin into vesicles for subsequent synaptic transmission. Affected individuals show clinical features of dopamine deficiency, such as severe parkinsonism, dystonia, and oculogyric crisis. In addition, features of epinephrine and norepinephrine deficiency presented as temperature instability, sweating, postural hypotension, and ptosis. Mood disturbance, especially depression, and sleep disturbance were features attributed to serotonin deficiency. All children had global developmental delay. The index patient was first evaluated at 4 months of age due to hypotonia, loss of acquired head control, and recurrent oculogyric crises, with subsequent development arrest and progression of motor symptoms in childhood and adolescence.

CSF neurotransmitter profile was reported to be normal in one individual, whereas urinary monoamine metabolites (5-HIAA, HVA) were elevated and urinary norepinephrine and dopamine were low. Magnetic resonance imaging (MRI) and (MRS) spectroscopy of the brain were normal (Rilstone et al. 2013). Following identification of the disease-causing gene, an initial trial of L-dopa was undertaken and resulted in intense chorea and worsening of dystonia after 1 week. These symptoms rapidly settled after L-dopa was suspended, and the children returned to baseline function. Subsequent treatment with the dopamine agonist, pramipexole, resulted in significant and sustained clinical improvement. In 1 week, there was full resolution of parkinsonism, dystonia attacks ceased, and three previously nonambulant children started walking after a few days. Cognition and fine-motor skills also improved in some of the affected children (Rilstone et al. 2013).

Secondary neurotransmitter diseases

Abnormal neurotransmitter profiles, such as low CSF HVA suggesting dopamine deficiency, are recognized in association with other neurological conditions and are not an exclusive feature of primary disorders of dopamine synthesis or metabolism. These so-called secondary

neurotransmitter abnormalities are increasingly biochemically and clinically recognized.

One of the most detailed studies on this subject to date is that by Molero-Luis et al. (2013), who investigated low levels of HVA in 1,388 children with neurological disorders. This study showed low CSF HVA as a secondary finding in various neurological diseases, including pontocerebellar hypoplasia, perinatal asphyxia, infections, mitochondrial disorders and other genetic diseases. Biochemical distinction between the two groups was difficult, as there was considerable overlap in the level of low HVA seen in the primary and secondary neurotransmitter disorders. The authors report that many children with secondary low-level HVA did not often present classic clinical symptoms of dopamine deficiency.

In 606 patients with neurological disorders, De Grandis et al. (2010) reported secondary low 5-HIAA, suggestive of low serotonin turnover, in 19.3 % of patients. Epileptic encephalopathies (26.4 %), mitochondrial disorders (10.2 %), pontocerebellar hypoplasia (4.3 %), Rett syndrome (4.3 %), leukodystrophies (6.8 %), and neuropsychiatric disturbances (4.2 %) were the most frequent etiologies associated with low 5-HIAA. In the study by Molero-Luis et al. (2013), reduced 5-HIAA was frequently reported in association with low HVA. This finding is suggestive of a close structural–functional relationship between dopamine and serotonin metabolism pathways, which may both therefore be affected in a broad spectrum of diseases (Molero-Luis et al. 2013).

Mitochondrial disorders frequently mimic both the clinical presentation (e.g., hypokinetic rigid syndrome, generalized dystonia) and biochemical profile (low HVA/5-HIAA) of primary neurotransmitter disorders (Garcia-Cazorla et al. 2008; Moran et al. 2011). The authors report that treatment with L-dopa for low HVA resulted in little or no clinical improvement in patient symptoms in this group. Molero-Luis et al. (2013) reported that mitochondrial disorders with parkinsonism may also present with high HVA. It is not completely understood why mitochondrial diseases affect dopamine/serotonin turnover, but it may possibly be due to structural defects in the serotonin/dopamine neuronal pathways as well as secondary impairment of dopamine/serotonin synthesis, metabolism, and transport.

Clinical interpretation of HVA levels and developing therapeutic strategies can be challenging, and results will often require discussion with both the neurometabolic laboratory and neurologist with neurotransmitter expertise (Kurian 2013). In patients with low HVA of undetermined or secondary origin, the role of L-dopa remains unclear. Certainly, in some patients with obvious symptoms and signs of dopaminergic deficiency (such as parkinsonism, dystonia, oculogyric crises, and other movement disorders), there may be a role for the slow introduction and gradual increase of L-dopa to tolerated doses. A proportion of these patients show improvement in motor function (Ng et al. 2013). The possibility of treating such patients with L-dopa and 5-HTP for central dopamine and serotonin deficiency to improve clinical symptoms and neurological outcome should therefore be considered (Kurian 2013). The use of neurotransmitter replacement therapy in patients with CSF neurotransmitter abnormality in the absence of classic features of dopaminergic deficiency remains controversial.

Novel therapeutic strategies and future research

A proportion of dopamine metabolism disorders responds satisfactorily to monoamine replacement and enhancement, whereas others (including AADC deficiency, type B THD, and DTDS) show much less satisfactory response. Research and development of novel treatments is therefore essential for many monoamine neurotransmitter disorders.

Alternative novel treatment strategies are already in the early stages of in vitro development, including studies on pseudoexon-exclusion therapy with antisense morpholino oligonucleotides. Using this approach, 6-pyruvoyltetrahydropterin synthase (PTPS) enzyme activity in fibroblast cell lines from three PTPS-deficient patients with intronic mutations resulting in splicing defects was restored (Brasil et al. 2011).

Furthermore gene transfer technologies have been developed to deliver an adeno-associated virus (AAV) encoding hAADC for stable expression of AADC enzyme in the striatum. This experimental technology was used in clinical trials for adult Parkinson's disease. AA2-hAADC was reported to show stable expression with improved parkinsonian rating scores, reduced dosages of dopaminergic therapy, and showing clinical safety (Eberling et al. 2008). Such studies paved the way for clinical trials in gene therapy for AADC deficiency. Recently, four Taiwanese children underwent AAV-mediated transfer of the human *AADC* gene through stereotactic injection bilaterally to the putamen. This has shown promising results, predominant clinical safety, with improved motor symptoms in all patients, and increased dopamine and serotonin levels following gene transfer (Hwu et al. 2012). Larger clinical trials will be more informative in relation to the relative benefit of gene therapy in this group of patients. Whether gene therapy in AADC deficiency proves to be curative or an adjunct to medical therapies remains to be determined.

It is clear that a significant proportion of children with neurological disease have undetermined neurotransmitter abnormalities and that other primary neurotransmitter disorders are yet to be identified. Further research into etiologies underpinning neurotransmitter abnormalities in children will likely lead to the discovery of novel primary neurotransmitter disorders, as well

as a further understanding of pathogenic mechanisms by which to direct future novel therapeutic approaches. Research into dopamine metabolism and dopaminergic neurons was previously limited by the availability of in vitro models of dopaminergic neuronal disease. With the advent of dopaminergic neuronal modelling (through reprogramming of patient-derived fibroblasts into induced pluripotent stem cells and differentiation into dopaminergic neurons) (Chambers et al. 2009), there is huge potential for research to inform disease mechanisms. The prospects of developing new treatments, such as novel molecules to modulate protein function in these cell models, enzyme replacement therapy, and gene therapy, appear highly promising.

Conclusion

Neurotransmitter disorders are underrecognized, and it is vital to increase clinical recognition of these diseases, as many are treatable, with good long-term prognosis. There have been a number of recent seminal studies defining clinical phenotypes and genotypes of these disorders [namely, THD, SRD, AADC deficiency, as well as the newly described transportopathies DTDS and vesicular monoamine transporter (VMAT) deficiency], which aim to promote increased recognition, knowledge, and understanding of monoamine neurotransmitter disorders. The secondary neurotransmitter disorders provide evidence that aberrant dopamine and serotonin metabolism may also be apparent in other neurological disorders. It is clear from studies reviewed that treatment responses can be variable and, for some neurotransmitter disorders, have little impact on motor and cognitive symptoms. Future study into successfully understanding pathological mechanisms in monoamine neurotransmitter disorders will be the first step toward developing new therapeutic approaches.

Conflict of interest None.

References

Allen GF, Land JM, Heales SJ (2009) A new perspective on the treatment of aromatic L-amino acid decarboxylase deficiency. Mol Genet Metab 97(1):6–14

Blackstone C (2009) Infantile parkinsonism-dystonia: a dopamine "transportopathy". J Clin Invest 119:1455–1458

Blackstone C (2011) Infantile parkinsonism-dystonia due to dopamine transporter gene mutations: another genetic twist. Lancet Neurol 10(1):24–25

Bonafé L, Thőny B, Penzien JM, Czarnecki B, Blau N (2001a) Mutations in the sepiapterin reductase gene cause a novel tetrahydrobiopterin-dependent monoamine-neurotransmitter deficiency without hyperphenylalaninemia. Am J Hum Genet 69:269–277

Bonafé L, Thöny B, Leimbacher W, Kierat L, Blau N (2001b) Diagnosis of dopa-responsive dystonia and other tetrahydrobiopterin disorders by the study of biopterin metabolism in fibroblasts. Clin Chem 47(3):477–485

Brasil S, Viecelli HM, Meili D et al (2011) Pseudoexom exclusion by antisense therapy in 6-Pyruvoyl –tetrahydrobiopterin synthase deficiency. Hum Mutat 32:1019–1027

Brun L, Ngu LH, Keng WT (2010) Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology 75(1):64–71

Cawello W, Kim SR, Braun M, Elshoff JP, Ikeda J, Funaki T (2013) Pharmacokinetics, safety and tolerability of rotigotine transdermal patch in healthy Japanese and Caucasian subjects. Clin Drug Investig. doi:10.1007/s40261-013-0150-5

Chambers SM, Fasano CA, Papapetrou EP, Tomishima M, Sadelain M, Studer L (2009) Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling. Nat Biotechnol 27(3):275–280

Chang Y, Sharma R, Marsh J et al (2004) Levodopa-responsive aromatic L–amino acid decarboxylase deficiency. Ann Neurol 55(3):435–438

Chi CS, Lee HF, Tsai CR (2012) Tyrosine hydroxylase deficiency in Taiwanese infants. Pediatr Neurol 46(2):77–82

De Grandis E, Serrano M, Pérez-Dueñas B et al (2010) Cerebrospinal fluid alterations of the serotonin product, 5-hydroxyindolacetic acid, in neurological disorders. J Inherit Metab Dis 33(6):803–809

Eberling JL, Jaqust WJ, Christine CW et al (2008) Results from phase 1 safety trial of hAADC gene therapy for Parkinson disease. Neurology 80:1980–1983

Espay AJ, Chen R (2013) Myoclonus. Continuum (Minneap Minn) 19 (5 Movement Disorders):1264–86

Fernandez-Alvarez E (2009) Movement disorders in children: recent advances in management. Indian J Pediatr 76:531–536

Friedman J, Hyland K, Blau N, MacCollin M (2006) Dopa-responsive hypersomnia and mixed movement disorder due to sepiapterin reductase deficiency. Neurology 67:2032–2035

Friedman J, Roze E, Abdenau JE et al (2012) Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy. Ann Neurol 71:520–530

Garcia-Cazorla A, Duarte S, Serrano M et al (2008) Mitochondrial diseases mimicking neurotransmitter defects. Mitochondrion 8(3): 273–278

Giovanniello T, Leuzzi V, Carducci C et al (2007) Tyrosine hydroxylase deficiency presenting with a biphasic clinical course. Neuropediatrics 38(4):213–215

Henriksen FH, Yasmeen S, Skjørringe T et al. (2012) Atypical dopamine transporter deficiency syndrome in two adult males with molecular characterisation of new transporter variants. New Orleans, LA: Soc Neurosci Meet Plann 2012, Poster 042

Hwu WL, Muramatsu S, Tseng SH et al (2012) Gene therapy for aromatic L-amino acid decarboxylase deficiency. Sci Transl Med 4(134): 134ra61

Hyland K, Surtess RAH, Rodeck C, Clayton PT (1992) Aromatic l-amino acid decarboxylase deficiency: clinical features, diagnosis and treatment of a new inborn error of neurotransmitter amine synthesis. Neurology 42:1980–1988

Kurian MA (2013) What is the role of dopamine in childhood neurological disorders? Dev Med Child Neurol 55:490–496

Kurian M, Gissen P, Smith M, Heales S, Clayton P (2011a) The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. Lancet Neurol 10:721–733

Kurian MA, Li Y, Zhen J et al (2011b) Clinical and molecular characterisation of hereditary dopamine transporter deficiency syndrome: an observational cohort and experimental study. Lancet Neurol 10(1):54–62

Kurian MA, Zhen J, Cheng SY et al (2009) Homozygous loss-of-function mutations in the gene encoding the dopamine transporter are associated with infantile parkinsonism-dystonia. J Clin Invest 119(6): 1595–1603

Lee HF, Tsai CR, Chi CS, Chang TM, Lee HJ (2009) Aromatic L-amino acid decarboxylase deficiency in Taiwan. Eur J Paediatr Neurol 13(2):135–140

Leuzzi V, Carducci C, Tolve M, Giannini MT, Angeloni A, Carducci C (2013) Very early pattern of movement disorders in sepiapterin reductase deficiency. Neurology 81(24):2141–2142

Lohmann E, Koroglu Ç, Hanagasi H, Dursun B, Tasan E, Tolun A (2012) A homozygous frameshift mutation of sepiapterin reductase gene causing parkinsonism with onset in childhood. Parkinsonism Relat Disord 18(2):191–193

Mastrangelo M, Caputi C, Galosi S, Giannini MT, Leuzzi V (2013) Transdermal rotigotine in the treatment of aromatic L-amino acid decarboxylase deficiency. Mov Disord 28(4):556–557

Molero-Luis M, Serrano M, Ormazábal A et al (2013) Homovanillic acid in cerebrospinal fluid of 1388 children with neurological disorders. Dev Med Child Neurol 55(6):559–566

Moran MM, Allen NM, Treacy EP, King MD (2011) "Stiff neonate" with mitochondrial DNA depletion and secondary neurotransmitter defects. Pediatr Neurol 45(6):403–405

Neville BG, Parascandalo R, Farrugia R, Felice A (2005) Sepiapterin reductase deficiency: a congenital dopa-responsive motor and cognitive disorder. Brain 128(10):2291–2296

Ng J, Tuschl K, Kinali et al (2013) TH gene-negative infantile onset severe dopamine deficiency syndrome: a novel neurotransmitter disorder? Dev Med Child Neurol 5(S1):15

Ng J, Zhen J, Meyer E et al. (2014) Dopamine transporter deficiency syndrome: phenotypic spectrum from infancy to adulthood. Brain. doi:10.1093/brain/awu022

Pons R, Ford B, Chiriboga CA et al (2004) Aromatic amino acid decarboxylase deficiency: clinical features, treatment, prognosis. Neurology 62:1058–1065

Pons R, Syrengelas D, Youroukos S et al (2013) Levodopa-induced dyskinesias in tyrosine hydroxylase deficiency. Mov Disord 28(8):1058–1063

Rilstone J, Alkhater R, Minassian B (2013) Brain dopamine–serotonin vesicular transport disease and its treatment. N Engl J Med 368:543–550

Stamelou M, Mencacci NE, Cordivari C et al (2012) Myoclonus-dystonia syndrome due to tyrosine hydroxylase deficiency. Neurology 79(5): 435–441

Swoboda K, Furukawa Y (2008) Tyrosine hydroxylase deficiency. GeneReviewsTM. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK1437/ in December 2013

Tay SK, Poh KS, Hyland K et al (2007) Unusually mild phenotype of AADC deficiency in 2 siblings. Mol Genet Metab 91(4):374–378

Tormenti MJ, Tomycz ND, Coffman KA, Kondziolka D, Crammond DJ, Tyler-Kabara EC (2011) Bilateral subthalamic nucleus deep brain stimulation for dopa-responsive dystonia in a 6-year-old child. J Neurosurg Pediatr 7(6):650–653

Verbeek MM, Willemsen MA, Wevers RA et al (2008) Two Greek siblings with sepiapterin reductase deficiency. Mol Genet Metab 94(4):403–409

Willemsen MA, Verbeek MM, Kamsteeg EJ et al (2010) Tyrosine hydroxylase deficiency: a treatable disorder of brain catecholamine biosynthesis. Brain 133(6):1810–1822

Yeung WL, Wong VC, Chan KY et al (2011) Expanding phenotype and clinical analysis of tyrosine hydroxylase deficiency. J Child Neurol 26(2):179–187

Zorzi G, Redweik U, Trippe H, Penzien JM, Thöny B, Blau N (2002) Detection of sepiapterin in CSF of patients with sepiapterin reductase deficiency. Mol Genet Metab 75:174–177