Clinical Spectrum of Dopamine Transporter Deficiency Syndrome

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Contributor: Joanne Ng, Serena Barral, Simon N. Waddington, Manju A. Kurian

The clinical spectrum of dopamine-related conditions is broad, encompassing movement disorders and neuropsychiatric diseases such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), addiction, and bipolar disorder. Dopamine transporter deficiency syndrome (DTDS) is a primary neurotransmitter disorder due to defective dopamine reuptake. Infantile parkinsonism-dystonia due to dopamine transporter deficiency syndrome (DTDS) is an ultrarare childhood movement disorder caused by biallelic loss-of-function mutations in the *SLC6A3* gene.

Keywords: dopamine transporter deficiency syndrome ; spectrum

1. Introduction

The clinical spectrum of dopamine-related conditions is broad, encompassing movement disorders and neuropsychiatric diseases such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), addiction, and bipolar disorder [1]. The dopaminergic system is involved in controlling the initiation of motion, reinforcement, and motivation, as well as contributing to emotion and cognitive functions (learning, attention, and memory) [1].

Within clinical neurology, symptoms indicative of dopamine dysregulation include bradykinesia, tremor, hypomimia and dystonia, neuropsychiatric features (apathy, anxiety, and impulse control disorders), and cognitive impairment, as observed in Parkinson's disease [2]. Parkinsonism may also present in infancy, often in combination with dystonia; in contrast to adult patients, many affected children are found to have an underlying genetic aetiology, leading either to dopaminergic neurodegeneration or the impairment of dopamine synthesis, breakdown, or transport [3]. Several primary dopamine synthesis disorders are also reported, including tyrosine hydroxylase deficiency, aromatic L-amino acid dopa-decarboxylase (AADC) deficiency, pterin defects (GTPCH, SR, and PTPS), vesicular monoamine transporter (VMAT2) deficiency, and *DNAJC12* deficiency. These primary neurotransmitter disorders are associated with low cerebrospinal fluid dopamine metabolites [4]. Childhood disorders of dopaminergic deficiency may result from striatonigral neurodegeneration, as is evident in *DNAJC6*-related disease—one of many juvenile-onset forms of genetic parkinsonism—as well as numerous metabolic disorders, including the mitochondriocytopathies [5][6].

Dopamine transporter deficiency syndrome (DTDS) is a primary neurotransmitter disorder due to defective dopamine reuptake. Prior to gene discovery, the initial clinical description from 2004 reported three children presenting with infantile parkinsonism-dystonia and, paradoxically, raised cerebrospinal fluid (CSF) homovanillic acid (HVA) [7]. In 2009, with the identification of new patients—two cousins from consanguineous kindred and a separate singleton from another consanguineous family—further genetic analysis was possible. Through autozygosity mapping, the genetic interrogation of regions of homozygosity identified homozygous missense variants in *SLC6A3*, which encodes the dopamine transporter (DAT), in these two kindreds [8][9]. Since 2009, fifty-one patients have been identified worldwide with DTDS, with confirmed disease-causing biallelic variants in *SLC6A3*, which encodes DAT (Kurian personal communication).

DAT regulates dopamine homeostasis by transporting extracellular DA into the intracellular space that controls the synaptic levels of DA in the mesolimbic and nigrostriatal pathways [2]. In vitro modelling of DTDS-related *SLC6A3* variants revealed impaired dopamine transporter function due to reduced transporter activity, with impaired dopamine binding, reduced cell-surface expression, and aberrant posttranslational modification with impaired glycosylation [8]. The effects of failed dopamine reuptake result in persistent synaptic dopamine and raised HVA, with subsequent intraneuronal dopamine reduction and downregulation of TH activity through aberrant feedback to presynaptic D2 receptors, as observed in the DAT knockout mouse model [10]. DAT is the principal regulator of synaptic DA transmission, and genetic variants in *SLC6A3* alter expression, membrane localisation, hDAT density, dopamine reuptake activity, and dopamine neurotransmission dynamics, contributing to a pathophysiological spectrum from infantile to adult-onset parkinsonism-

dystonia, termed DTDS. In addition, *SLC6A3* variants are associated with neuropsychiatric diagnoses, including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and bipolar disorder [11][12][13][14].

2. Clinical Spectrum of DTDS

DTDS is a primary neurotransmitter disorder that presents with infantile parkinsonism-dystonia due to biallelic loss-of-function mutations in the *SLC6A3* gene (OMIM # 613135). The detailed clinical characterisation of eleven children with DTDS established the classical features and progression of DTDS over time. Since 2011, there have been thirty-one DTDS patients reported in the literature [8][9][15][16][17][18][19][20][21][22][23][24], and a further unpublished twenty patients reported to the centre (Kurian personal communication).

2.1. Classical Early Onset DTDS

The classical DTDS phenotype typically manifests during early infancy with irritability, feeding difficulties, hypotonia, and delayed motor development [8][9][15][25]. A hyperkinetic movement disorder develops with features of chorea, dystonia, ballismus, and orolingual dyskinesia [8][9][15][25]. Over time, the condition evolves to parkinsonism-dystonia with the development of dystonic posturing, bradykinesia, distal tremor, rigidity, and hypomimia. The movement disorder progresses to akinesia in late childhood/early adolescence [8][9][15][25]. Some children also experience episodic status dystonicus and eye movement disorders with oculogyric crisis, ocular flutter, eyelid myoclonus, and saccade initiation failure [8][9][15][25]. Although the children present with a severe movement disorder with motor and speech delays, many individuals are reported to have relative preservation of intellect and good cognitive development [9][25]. Cognition in children with severe motor impairment, as seen in DTDS, is difficult to assess, but children with DTDS are thought to remain relatively cognitively intact, showing good working memory, communication with eye-gaze devices, accurate recognition of familiar information, and empathy and social awareness [9]. Secondary orthopaedic complications such as scoliosis and joint contractures are also described. Reported classical early onset DTDS individuals have a distinct CSF neurotransmitter analysis profile, with raised HVA (a stable metabolite of dopamine) and normal hydroxyindoleacetic acid levels (5-HIAA, a stable metabolite of serotonin). The HVA:HIAA ratio is raised at 5.0–13.0 (normal range: 1.0–4.0) [8][9][15]. MRI brain imaging can be normal or show subtle nonspecific abnormalities, such as mild delayed myelination, white matter abnormalities (such as periventricular leukomalacia), and prominence of external frontotemporal spaces. Single-photon emission computerised tomography (SPECT) with 123Ioflupane (DaTScan) imaging shows either absent or significantly reduced tracer uptake in the basal nuclei [9].

With over a decade of experience in treating early onset DTDS patients, it is evident that there is limited response to standard pharmacotherapies [9][15]. Palliative treatment endeavours to control symptoms; this includes the use of tetrabenazine and benzodiazepines to treat chorea and dyskinesia early in the disease, and dopamine agonists such as pramipexole and ropinirole [9][15][25]. There is limited or no response to levodopa treatment. Gabapentin has been useful in easing stiffness and reducing hyperkinesia in some cases (Kurian personal communication). Focal treatment with botulinum toxin injections for dystonia and orthopaedic intervention for severe contractures have been tried in some patients [9][15][25]. Episodes of status dystonicus can be life-threatening, with associated rhabdomyolysis requiring emergency intensive care management. Neurosurgical interventions such as deep brain stimulation and intrathecal baclofen have been used in older patients, with limited therapeutic benefit [9]. The associated bulbar dysfunction and feeding difficulties contribute to poor weight gain, and most patients require gastrostomy feeding. Affected patients are at significant risk of respiratory problems, such as chest infections and aspiration pneumonia; eight children have died from cardiorespiratory complications. Although the long-term outcome of DTDS remains to be fully characterised, it is clearly associated with a significant risk of morbidity and premature mortality, with a mean age of death of 10.4 years old (range: 3–16.2) [9][15] Kurian personal communication). The oldest surviving early onset DTDS patients are now in their fourth decade of life [11][21].

2.2. Atypical Later-Onset DTDS

Since the first description of early onset classical DTDS, there has been an expansion of the clinical phenotype, with the identification of patients with a milder, more slowly progressive condition associated with biallelic missense variants in *SLC6A3*. Such patients with later-onset atypical DTDS usually have a history of normal early neurodevelopment in infancy and early childhood (achieving independent ambulation and spoken language), presenting later in the second decade of life with tremor, progressive bradykinesia, dystonic posturing, and variable tone [15]. The first reported atypical DTDS kindred identified three brothers who presented at 10–11 years old with head tremor. The brothers were diagnosed at 16, 26, and 28 years old, respectively, with the older brothers developing progressive symptoms in their 20s with tremor affecting the head, arms, cervical dystonia and hypomimia, and speech deterioration [15]. All three individuals harboured

homozygous missense variant Ala314Val, that on in vitro analysis retained 8% dopamine uptake activity, relatively higher than missense variants identified in classical infantile onset DTDS [15]. Another adult with atypical later-onset DTDS was reported; he initially presented with childhood failure to thrive as well as learning and behavioural problems in school. He presented with insidious right-sided tremor at 28 years old, which progressed to severe coarse tremor in all limbs and the trunk, with rigidity and bradykinesia, and was diagnosed with early onset PD at 35 years of age [16]. Molecular genetic investigation identified compound heterozygous missense variants Ile312Phe and Asp421Asn [16]. In vitro modelling of these variants showed both DAT variants exhibited markedly reduced dopamine uptake capacity (33% of the wildtype transporter) but preserved membrane targeting, consistent with impaired catalytic activity [16]. For DAT-Asp421Asn, substrate efflux experiments revealed a constitutive, anomalous efflux of dopamine, and electrophysiological analyses identified a large cation leak that might further perturb dopaminergic neurotransmission [16]. The long-term outcome of these individuals with atypical later-onset DTDS parkinsonism-dystonia is currently unknown.

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