Motor and non-motor symptoms in cervical dystonia

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CHAPTER 5

5

Serotonergic perturbations in dystonia disorders – a systematic review

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ABSTRACT

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions. Emerging data describe high prevalence's of non-motor symptoms, including psychiatric co-morbidity, as part of the phenotype of dystonia. Basal ganglia serotonin and serotonin-dopamine interactions gain attention, as imbalances are known to be involved in extrapyramidal movement and psychiatric disorders.

We systematically reviewed the literature for human and animal studies relating to serotonin and its role in dystonia. An association between dystonia and the serotonergic system was reported with decreased levels of 5-hydroxyindolacetic acid, the main metabolite of serotonin. A relation between dystonia and drugs affecting the serotonergic system was described in 89 cases in 49 papers. Psychiatric co-morbidity was frequently described, but likely underestimated as it was not systematically examined.

Currently, there are no good (pharmaco)therapeutic options for most forms of dystonia or associated non-motor symptoms. Further research using selective serotonergic drugs in appropriate models of dystonia is required to establish the role of the serotonergic system in dystonia and to guide us to new therapeutic strategies.

Abbreviations

5-HIAA, 5-hydroxyindolacetic acid;
5-HT, 5-hydroxytryptamine;
5-HTP, 5-hydroxytryptophan;
AADC, aromatic L-amino acid decarboxylase;
ADR, acute dystonic reaction;
BH_4, tetrahydrobiopterin;
CSF, cerebrospinal fluid;
DRD, dopa-responsive dystonia;
dRN, dorsal raphe nucleus;
DTG, di-o-tolyguanidine;
DYT, dystonia;
GCH1, GTP cyclohydrolase deficiency 1;
GP, globus pallidus;
GPi, globus pallidus pars interna;
GPe, globus pallidus pars externa;
HVA, homovanillic acid;
PKAN, panthothenate kinase associated neurodegeneration;
RDP, rapid-onset dystonia-parkinsonism;
SERT, serotonin transporter;
SGCE, ε-sarcoglycan gene;
SNr, substantia nigra pars reticulata;
SPR, sepiapterin reductase;
SSRI, selective serotonin reuptake inhibitor;
VMAT2, vesicular monoamine transporter 2.

INTRODUCTION

Dystonia is defined as a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous [1]. Growing evidence suggests that the phenotype of dystonia also includes an important non-motor component, with psychiatric co-morbidity being most prevalent [2,3].

The pathophysiological basis of dystonia is still not fully unraveled. The basal ganglia are known to play a pivotal role in dystonia, and thus basal ganglia neurotransmitter systems are likely involved. Dopamine, as one of these neurotransmitters, plays a significant role in motor control, both via the direct and indirect motor pathway [4]. However, besides dopamine, serotonin is increasingly recognized for its potential role in dystonia. Postmortem studies show that the dorsal raphe nucleus (dRN) with its serotonergic neurons is connected with the basal ganglia and sensorimotor cortices [5]. The serotonin (5-hydroxytryptamine, 5-HT) axon bundle from the dRN travels through the median forebrain bundle located dorsolateral to the substantia nigra and subthalamic nucleus and innervates all basal ganglia nuclei, most densely to the output nuclei globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNr) [5]. This serotonergic circuit is likely to play a role within the hypothesized dysfunctional basal ganglia network involved in dystonia [6,7]. The role of the GPi is established in this circuit as it is the major target for dystonia deep brain stimulation [8]. Furthermore, within the substantia nigra, serotonergic neurons exert complex, mainly inhibitory effects on the dopaminergic system [9,10]. This interaction, associated with complex interactions of noradrenergic and cholinergic inputs [11], could contribute to the dystonia pathophysiology. The specific role of serotonergic action in these circuits needs to be further elucidated with respect to their influence on movement disorders.

Serotonin is synthesized in a two step synthesis pathway from the essential aminoacid tryptophan. Peripheral and central nervous system serotonin synthesis is differentially regulated through the enzymes tryptophan hydroxylase 1 (periphery) and tryptophan hydroxylase 2 (central nervous system) [12]. Serotonergic signaling is mediated by at least 18 different pre- and post-synaptic serotonin receptor subtypes, either activating or repressing serotonergic activity. An important regulator of the serotonergic system is the serotonin transporter (SERT), which reuptakes serotonin from the synaptic cleft back into the presynaptic neuron. After reuptake, the breakdown of serotonin is primarily mediated by monoamino oxidase A [12].

Since the 1980s, several studies have examined the role of serotonin in different forms of dystonia, both in animal models and in humans. The recognition of psychiatric co-morbidity as integral part of the clinical phenotype of dystonia [3], representing a shared neurobiology, highlights a likely role of the serotonergic system in the pathophysiology

of dystonia. For many years, psychiatric disorders have been linked to serotonergic disturbances and psychoactive drugs often influence the serotonergic system [13,14]. Moreover, serotonergic neurons are highly represented in the limbic system, which is an important modulator of mood and behavior [15].

Taken all together, there are several indications that disturbances of the serotonergic system are part of the pathophysiology of dystonia. At this moment, no good (pharmaco-) therapeutic options are available for most forms of dystonia. Zooming in on the aberrations of serotonergic metabolism may provide new insights in the pathophysiology of dystonia and therefore may well lead to a new potential target(s) for therapeutical interventions.
In this paper we systematically reviewed the involvement of serotonin in different types of dystonia and discuss the possible role of serotonin in the pathophysiology of dystonia.

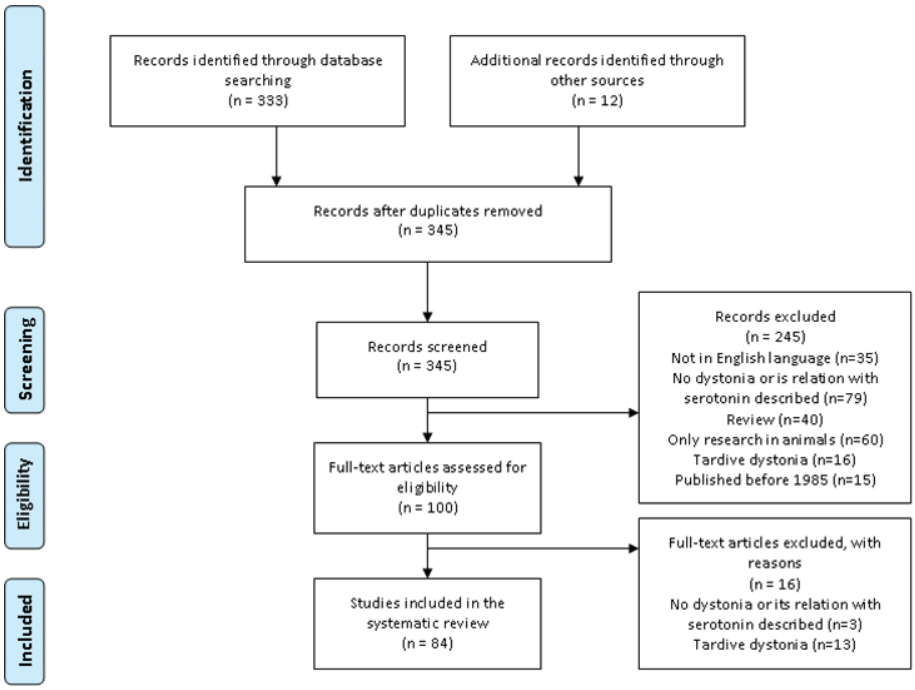
METHODS

A systematic literature search was performed according to PRISMA guidelines [16] to identify all papers describing the characterization, disturbances or influence of serotonin or its metabolites in dystonia patients and animal models of dystonia. Articles were selected from PubMed from January 1985 until December 2014, with a combination of the following MeSH terms and free text words: “dystonia”, “dystonic disorders”, “dysphonia”, “blepharospasm”, “torticollis”, “writer’s cramp”, “DYT” AND “serotonin”, “serotonergic”, “serotonin plasma membrane transport proteins”, “serotonin agents”, “serotonin receptors”, “5-HT”, “5-HTP”, “5-hydroxyindole acetic acid”, “5-HIAA”, “serotonin transporter”, “SERT”, “SLC6A4”. Additional articles were identified in the reference lists. Only articles in English language were reviewed. Articles concerning dystonia as part of tardive dyskinesia, resulting from prolonged treatment (> 6 months) with psychotropic agents, were excluded. Furthermore, only disorders comprising at least two cases are described in further detail in this review. Reported psychiatric co-morbidity in patients with dystonia in these papers was also evaluated.

RESULTS

The literature search retrieved papers describing a relation between serotonin and a heterogeneous group of dystonias. This included levels of serotonin or its metabolites in blood platelets, cerebrospinal fluid (CSF) or brain tissue, but also drugs affecting the serotonergic system. First, we will describe the dopa-responsive dystonias, in which gene mutations directly affect serotonin synthesis. These dopa-responsive dystonias provide a good model to interpret the results observed in other dystonias, such as inherited-, idiopathic- and acquired dystonias on which we will report thereafter. Finally, serotonergic perturbations in several animal models of dystonia are discussed.

Supplementary figure 1
Flowchart



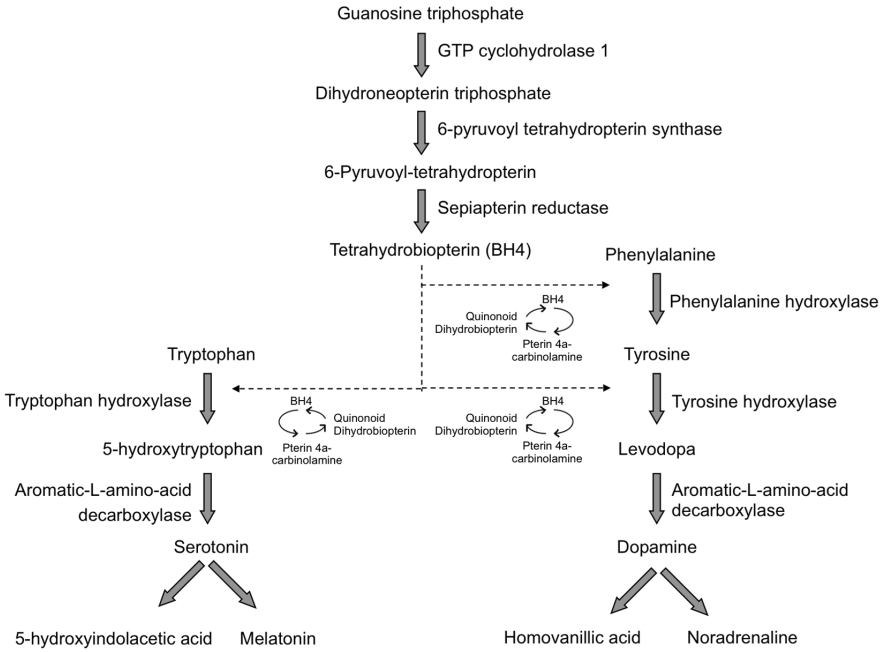
Dopa-responsive dystonias

Dopa-responsive dystonias included the autosomal dominant inherited GTP cyclohydrolase 1 deficiency, the autosomal recessive inherited GTP cyclohydrolase 1 deficiency, sepiapterin reductase deficiency and aromatic L-amino acid decarboxylase deficiency. All four disorders affect both the biosynthesis of serotonin and dopamine (Supplementary figure 2).

Autosomal dominant inherited GTP cyclohydrolase I deficiency

Dopa responsive dystonia (DRD), or Segawa syndrome (OMIM: #128230) (DYT5), is caused by GTP cyclohydrolase 1 (GCH1) deficiency. This in turn is the consequence of heterozygous mutations in the *GCH1* gene (OMIM: *600225). GTP cyclohydrolase 1 is the first and rate limiting enzyme for the tetrahydrobiopterin (BH_4) synthesis, the cofactor needed for the combined biosynthesis of serotonin and dopamine. Dopa responsive dystonia due to GCH1 deficiency is diurnally fluctuating and L-dopa responsive. Symptoms usually start in childhood or adolescence typically with dystonia in one leg, with progression to generalized dystonia until around young adulthood. Possible accompanying non-motor symptoms include psychiatric co-morbidity like autistic features, depression or obsessive-compulsive disorder [17].

Supplementary figure 2
The metabolic pathway of serotonin and dopamine.



Three studies examined the level of 5-hydroxyindolacetic acid (5-HIAA, the breakdown product of serotonin) in CSF in patients (n=7) with mutations in this gene, with results varying from decreased to increased levels (Table 1) [18–20]. Levels of CSF homovanillic acid (HVA), the breakdown product of dopamine, were also determined prior to supplementation therapy, showing a median of 100 nmol/L (range 39 – 410 nmol/L). According to the reported reference values the level of HVA was decreased in four out of seven patients.

Ishida et al. treated two patients with GCH1 deficiency alternately with L-dopa/carbidopa, BH_4, or 5-hydroxytryptophan (5-HTP) [18]. 5-HTP is the direct precursor of serotonin and can be given as medication providing the substrate for a sufficient synthesis of serotonin. In one case, 5-HTP supplementation resulted in a remarkable improvement of hand dystonia, which did not respond to L-Dopa therapy only (Table 2). The effect of 5-HTP in addition to L-dopa in another case was reported to be doubtful. Fatigability and gait disturbance showed a variable response. Acute aggravation of dystonia following treatment with serotonin reuptake inhibitors (SSRIs) was reported in two patients with DRD due to GCH1 deficiency [21]. Both patients were asymptomatic on L-dopa treatment. Treatment with SSRIs was started because of mood problems. After prescription of fluoxetine to one patient and venlafaxine to the other patient, dystonia reoccurred to the same extend as before L-dopa treatment.

Table 1
Cerebrospinal fluid concentrations of 5-HIAA in inherited dystonias.

Inheritance pattern	Affected gene/ OMIM	Characteristic features besides dystonia	Authors	Number of patients described	Median 5-HIAA (nmol/L) in CSF (range)	Interpretation*	
Autosomal Dominant	GCH1 *600225	Hypokinetic-rigid syndrome, diurnal fluctuation, psychiatric disorders	Van Hove et al., 2006 Zambrino et al., 1991 Ishida et al., 1988	7	66 (14-194)	Decreased: Normal: Increased:	3 3 1
	ATP1A3 *182350	Abrupt onset dystonia-parkinsonism, rostrocaudal gradient, bulbar symptoms	Brashear et al., 1998	10	114.6 (31.4-177.3)	Decreased: Normal:	1 9
Autosomal Recessive	GCH1 *600225	Diurnal fluctuation, swallowing difficulties, hypotonia, autonomic disturbances, mental retardation, developmental delay	Blau et al., 1995 Sato et al., 2014	2	103 (92-114)	Decreased:	2
	SPR *182125	Extrapyramidal disorders, diurnal fluctuation, axial hypotonia, autonomic disturbances, developmental delay, intellectual disability	Abeling et al., 2006 Arrabal et al., 2011 Blau et al., 1999 Blau et al., 1998 Dill et al., 2012 Echenne et al., 2006 Friedman et al., 2006 Friedman et al., 2012 Kusmierska et al., 2008 Leu-Semenescu et al., 2009 Steinberger et al., 2004 Verbeek et al., 2008 Wali et al., 2010	28	7.5 (1-100)	Decreased: Normal:	27 1
	AADC *107930	Hypotonia, severe extrapyramidal disorders, oculogyric crisis, epileptic seizures, autonomic disturbances, severe developmental delay	Manegold et al., 2009 Tay et al., 2007 Barth et al., 2012 Swoboda et al., 1999 Fiumara et al., 2002 Abdenur et al., 2006 Maller et al., 1997 Abeling et al., 1998 Gucuyener et al., 2014 Helman et al. 2014 Hyland et al., 1992	23	10 (1-53))	Decreased:	23

Autosomal Recessive	SLC18A2 *193001	Extrapyramidal disorders, mood disturbances, autonomic disturbances, developmental delay	Rilstone et al., 2013	1	169	Normal:	1
X-Linked	HPRT *308000	Auto-mutilation, behavioral problems, mental retardation, poor cognitive and speech development, spastic cerebral palsy, choreoathetosis, uric acid urinary stones	Jankovic et al., 1988 Silverstein et al., 1985	9	183.1 (104.6-355.7)	Normal: Unknown:	6 3

Cerebrospinal fluid concentrations of 5-HIAA in patients with dystonia (median, range).
A complete overview of all the individual 5-HIAA concentrations and corresponding reference ranges is provided in the supplementary material, table 1. * The interpretation is according to the provided reference ranges in the papers. 5-HIAA = 5-Hydroxyindolacetic Acid. CSF = Cerebrospinal Fluid.

Besides motor symptoms, non-motor symptoms were examined in another study in 16 patients with DRD [19]. In total, eight of 16 patients fulfilled the criteria of at least one psychiatric disorder including major depressive disorder (n=8), recurrent major depressive disorder (n=5), obsessive compulsive disease (n=4) or anxiety (n=4), either solitary or combined. Moreover, several patients developed psychiatric co-morbidity before the onset of motor symptoms. This finding suggests a shared neurobiology and a potential important role for serotonin, possibly in association with other neurotransmitters.

Autosomal recessive inherited GTP cyclohydrolase I Deficiency

Three case studies examined neurotransmitter metabolites in CSF in pediatric patients with the more severe autosomal recessive form of GCH1 deficiency (OMIM: #233910) [22–24]. Clinical characteristics included dystonia, hypotonia, clonic movements and developmental delay. In all three patients a decreased level of 5-HIAA was found, of which only in two patients were quantified (Table 1) [23,24]. The level of HVA was 20.9 nmol/L and 50 nmol/L respectively. All children received treatment with 5-HTP combined with L-Dopa/carbidopa and BH_4. In two cases, the biochemical effect of 5-HTP was described, which led to normalization of the level of 5-HIAA in CSF [23,24]. The clinical effect was variable and only reported at months or years after the start of supplementation therapy.

Sepiapterin Reductase Deficiency

Dopa-responsive dystonia (OMIM: #612716) could also be the consequence of sepiapterin reductase (SPR) deficiency, caused by mutations in the sepiapterin reductase (*SPR)* gene (OMIM: *182125), another autosomal recessive form of DRD. The last step in the tetrahydrobiopterin biosynthesis pathway is catalyzed by sepiapterin reductase and a deficiency again leads to an impaired dopamine and serotonin synthesis.

Forty-three patients with SPR deficiency are described in literature, reviewed by Friedman et al. [25–44]. Of 43 patients, 30 patients were affected by dystonia and 21 patients experienced psychiatric or behavioral symptoms. In 29 patients biochemical analysis of the CSF was performed, the level of 5-HIAA was determined in 28 cases. The median level of 5-HIAA in CSF was decreased: 7.5 nmol/L (Table 1). Nineteen patients were treated with 5-HTP in addition to L-dopa/carbidopa, which led to further improvement of motor and sleep symptoms in 16 of these patients. One patient was treated with only 5-HTP/carbidopa, which induced marked improvement in both motor and sleep problems. Sertraline, an SSRI, was initiated in one patient, with modest benefit in motor symptoms. Furthermore, assessment of cognitive skills revealed improvement in 13 of 38 patients assessed. Eleven of them received both L-dopa/carbidopa and 5-HTP. In eight patients 5-HTP was started a short time after start of L-dopa, so the additional effect remains unclear. However, three of these patients improved in school performance or had resolution of mild dysexecutive syndrome after adding 5-HTP at least 8 years after the start of L-Dopa.

Table 2
Effect of drugs specifically affecting the serotonergic system.

Dystonia	Affected gene	Author	Type of drug	Action on serotonergic system	Effect	
Inherited	GCH1	Ishida et al., 1988 Blau et al., 1995 Sato et al., 2014	5-HTP	Precursor serotonin	Improvement Variable	1 4
		Mathen et al., 1999	SSRI	SERT	Aggravation	2
	SPR	Friedman et al., 2012	5-HTP	Precursor serotonin	Improvement No effect	16 4
		Friedman et al., 2006	SSRI	SERT	Improvement	1
	AADC	Manegold et al., 2009 Swoboda et al., 1999	SSRI	SERT	Aggravation	2
		Fiumara et al., 2002 Swoboda et al., 1999	5-HTP	Precursor serotonin	Side effects	2
		Swoboda et al., 1999	Ergotamine tartrate	Serotonergic receptors	Side effects	1
Idiopathic		Piyasena et al., 2014	Mosapride	5-HT_4	Improvement	1
		Schreiber et al., 1995 Isaacs et al., 2008	SSRI	SERT	Improvement	3
Acquired		Arnone et al., 2002 Bates et al., 1998 Bilen et al., 2008 Boyle et al., 1999 Black et al., 1992 Coulter et al., 1995 Chong et al., 1995 Dave et al., 1994 George et al., 1993 Hoaken et al., 1995 Jones-Fearing et al., 1996 Lenti et al., 1999 Lewis et al., 1997 Moosavi et al., 2014 Najjar et al., 2004 Patel et al., 2006 Petitpain et al., 2005 Poyurovsky et al., 1997 Reccoppa et al., 1990 Shihabuddin et al, 1994 Tikka et al., 2013 Walker et al., 2002	SSRI	SERT	ADR	35
		Lopez-Alemany et al., 1997 Oterino et al., 1998	Sumatriptan	5-HT_1 agonist	ADR	2
		Patel et al., 2011	Ondansetron	5-HT_3 antagonist	ADR	1

SSSRI = Selective Serotonin Reuptake Inhibitor. SERT = Serotonin Transporter. ADR= Acute Dystonic Reaction.

Observed psychiatric and behavioral signs in these patients included inattention (n=14), irritability (n=11), anxiety (n=7), hyperactivity (n=5), aggression (n=4), obsessive or compulsive features (n=3), depression (n=2), impulsivity/disinhibition (n=2), panic (n=1) and psychosis (n=1).

Improvement of both motor and non-motor symptoms with 5-HTP treatment again suggests a role of serotonin in the phenotype of SPR deficiency. Furthermore, these studies illustrate that systematic searching for psychiatric and behavioral signs increases the awareness of non-motor symptoms being present in SPR deficiency and dystonia.

Aromatic L-amino acid Decarboxylase Deficiency

Mutations affecting the Dopa Decarboxylase (*DDC*) gene (OMIM: *107930) cause aromatic L-amino acid decarboxylase (AADC) deficiency, resulting in combined deficiencies of serotonin, dopamine and other catecholamines. The phenotype consists of severe extrapyramidal disorders, epileptic seizures, autonomic features and pronounced developmental delay (OMIM: #608643). The severity of the disorder in the majority of patients with this disorder usually precludes the scoring of psychiatric co-morbidity.

Eleven studies quantified the level of 5-HIAA in CSF in 23 patients with AADC deficiency and dystonia (Table 1) [45–55]. Four patients were treated with agents specifically acting on the serotonergic system, with different responses. One 17-year-old patient received a therapeutic trial with paroxetine, an SSRI. Unfortunately, oculogyric crises occurred and the trial was stopped [53]. In addition to L-dopa and vitamin B_6 supplementation, treatment with 5-HTP was initiated in a child [48], but had to be stopped due to severe abdominal pain. This therapy trial was initiated without a peripheral decarboxylase inhibitor. Swoboda et al. described different treatment trials in two children in an attempt to correct serotonergic deficits. A treatment trial with 5-HTP in one patient was stopped because it induced lethargy and worsened axial hypotonia. The use of a peripheral decarboxylase inhibitor is not described. Buspirone, a partial $5HT_{1A}$ agonist and weak dopaminergic (D_2) antagonist, reduced limb rigidity and irritability in both children, but had to be stopped because of tardive dyskinesia. Sertraline, an SSRI, led to impairment of dystonia. Ergotamine tartrate, a direct serotonin receptor agonist, was stopped because it induced lethargy and hypotonia [54].

Irritability and/or dysphoria were described in ten out of 23 cases [45,48–51,53,54]. Manegold et al. described patients with AADC deficiency in seven different families. A high incidence of psychiatric disorders was found in six out of seven investigated families in first or second degree relatives, including depression, psychosis and suicide [53].

In summary, in dopa-responsive dystonias a role of the serotonin system in the pathogenesis of the disorders is well established. Several gene defects affect the synthesis of serotonin, leading to significantly reduced levels of 5-HIAA in CSF. Alterations of motor

symptoms following serotonergic medication suggest new therapeutic possibilities for dystonia. A high prevalence of non-motor symptoms also suggests a possible role of the serotonergic system in the non-motor features associated with dystonia, likely in association with other neurotransmitter systems.

Inherited-, idiopathic- and acquired dystonias

Inherited dystonias form a heterogeneous group of dystonias with different genetic origins and include autosomal dominant, autosomal recessive, X-linked recessive and mitochondrial inheritance patterns. Acquired dystonias are dystonias due to a known specific cause, without evidence of a genetic origin. Finally, the idiopathic dystonias consists of a group of dystonias with an unknown cause and comprises many focal or segmental isolated dystonias. This is by far the largest group of dystonias as the focal adult onset dystonias are part of this group.

Inherited dystonias: Autosomal dominant disorders

The autosomal dominant inherited dystonias in which a relation with serotonin is reported included early-onset primary dystonia and rapid-onset dystonia-parkinsonism.

Early-Onset Primary Dystonia

Early-onset primary dystonia (OMIM: #128100), also known as DYT1 dystonia, is due to a defect in the ATP-binding protein torsin-A. Molecular analysis reveals a trinucleotide (GAG) deletion in the coding region of the *TOR1A* gene (OMIM: *605204). Early-onset primary dystonia usually starts as a focal dystonia during childhood or adolescence. Typically, there is a progressive course resulting in generalized dystonia.

Hornykiewicz et al. histologically and biochemically examined the postmortem brains of two patients with dystonia musculorum deformans [56,57]. Dystonia musculorum deformans is now classified as early-onset primary dystonia, but at that time genetic confirmation was not available. Both patients showed a decreased level of serotonin in the dorsal raphe nucleus and increased levels in the globus pallidus. In the first patient, 5-HT levels were also increased in the locus ceruleus and subthalamic nucleus. Increased levels of 5-HIAA, the main metabolite of serotonin, were found in both patients in the raphe nucleus obscurus and globus pallidus. Both patients were long-term treated with neuroleptics and underwent bilateral thalamotomy, which might have influenced the measurements of the serotonergic system.

Korczyn et al. examined platelets of 11 patients with dystonia musculorum deformans, showing similar concentrations of serotonin compared with matched healthy controls. Furthermore, an equal number of presumed binding sites was found. Though, a significant lower affinity of serotonin to its receptors was detected [58]. Only patients free of any medical treatment for at least several weeks were included, so the lower affinity could not be explained by medication use. Despite the normal concentrations of serotonin, they

proposed that the lower affinity of serotonin to its receptors may have led to hyposerotonergic function and thereby possibly contributed to the development of dystonia.

Rapid-Onset Dystonia-Parkinsonism

Rapid-onset dystonia-parkinsonism (RDP) (OMIM: #128235), or DYT12, is caused by mutations in the *ATP1A3* gene (OMIM: *182350) encoding the alpha-3 subunit of the N,K-ATPase. RDP is clinically characterized by an abrupt onset of dystonia and parkinsonism in young adulthood, with typically a rostrocaudal gradient. Symptoms are usually triggered by fever, stress or binge drinking [59]. After this initial phase, symptoms often show little improvement and then stabilize. Occasionally a second episode may occur with consequently worsening of symptoms.

Brashear et al. described (repeated) neurotransmitter metabolite levels in CSF from ten individuals clinically affected by RDP [60]. Only in one individual a slightly decreased level of 5-HIAA in CSF was found: 31.4 nmol/L (reference range: 55.4 – 160.1 nmol/L). Six out of ten initial lumbar punctures were performed during treatment with different medications, which hampered the interpretation of results in this study.

Inherited dystonia: Autosomal recessive disorders

In two disorders a possible association between dystonia and serotonin was described, including panthothenate kinase associated neurodegeneration (PKAN) and dystonia as a result of a *SLC18A2* gene mutation (vesicular monoamine transporter 2).

Panthothenate Kinase Associated Neurodegeneration

Panthothenate kinase associated neurodegeneration (OMIM: #234200) is due to a defect in panthothenate kinase, an enzyme involved in the Coenzyme A synthesis. This defect is caused by mutations in the panthothenate kinase 2 (*PANK2*) gene (OMIM: *606157) and results in progressive iron accumulation in the basal ganglia and other brain regions. Clinically it is characterized by progressive extrapyramidal movement disorders, including dystonia. Psychiatric co-morbidity like depression, impulsivity, obsessive compulsive disorder and tics are described in several cases [61]. Onset is usually before ten years of age, although late onset is also described.

Assmann et al. described the level of 5-HIAA in CSF in four patients with Hallervorden-Spatz syndrome, now called PKAN. Diagnosis was made based on clinical characteristics, as genetic confirmation was not available at the time. In three out of four patients a decreased level of 5-HIAA was found compared with healthy controls (median SD -1.2, range -1.1 - -1.5), with one patient showing a normal level (SD 0.7) [62]. The authors suggested that serotonergic tract degeneration, as part of the neurodegenerative process, may have caused the lowered levels of 5-HIAA in CSF.

Dystonia as result of SLC18A2 gene mutation
Dystonia can result from defects in the vesicular monoamine transporter 2 (VMAT2), due to recessive mutations in the *SLC18A2* gene (OMIM: *193001). VMAT2 is responsible for the storage of monoamine neurotransmitters including serotonin, dopamine and noradrenaline into (pre)synaptic vesicles. The phenotype is constituted by the deficiency of these monoamine neurotransmitters.

Eight children of an extended consanguineous Saudi Arabian family suffered from a complex movement disorder including dystonia [63]. Analysis of 5-HIAA in CSF was described in only one of these patients: 169 nmol/L (ref. range 74 – 345 nmol/L) (Table 1). At least five of the parents showed symptoms of depression. Mood disturbances in the patients were mentioned briefly, but not systematically described. Based on the sparse descriptions, the role of impaired serotonergic synaptic transmission in the phenotype of these patients remains unclear. However, the presence of mood disorders could suggest possible serotonergic involvement.

Inherited dystonias: X-linked inheritance
A relation between serotonin and dystonia due to disorders with an X-linked inheritance pattern is only described in Lesch-Nyhan syndrome.

Lesch-Nyhan syndrome
Lesch-Nyhan syndrome (OMIM: #300322) is caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase 1, due to mutations in the hypoxanthine-guanine phosphoribosyl 1 (*HPRT1*) gene (OMIM: *308000). Clinically it is characterized by dystonia, non-motor symptoms including auto mutilation, behavioral problems, poor cognitive and speech development. Increased levels of uric acid can be found in routine biochemical testing.

Two studies described the level of 5-HIAA in patients with Lesch-Nyhan syndrome. Four boys with Lesch-Nyhan syndrome, dystonia and self-mutilation had normal 5-HIAA levels in CSF over a five year period (Table 1) [64]. In another study, two patients with Lesch-Nyhan syndrome, dystonia and self-mutilation showed a normal level of 5-HIAA in CSF, in three cases the reference range was not provided (Table 1) [65]. The patient with the mildest self-mutilation had the highest level of 5-HIAA in CSF (272 nmol/L).

Idiopathic dystonias
In 15 patients with idiopathic adult-onset focal dystonia, 5-HIAA analysis in CSF showed significantly reduced levels in patients (median 59.6 nmol/L, range 26.2 – 130.8 nmol/L) compared to controls (median 92.2 nmol/l, range 44.5 – 196.2 nmol/L)) ($p < 0.02$) [66]. Levels of HVA in CSF were also lower in the group of focal dystonia patients compared with the healthy controls, however this finding did not appear to be statistically significant in contrast to the serotonin concentrations.

Another paper described a 60-year-old female with blepharospasm. Mosapride, a 5-HT_4 agonist, was started because of gastro-esophageal reflux disease [67]. Three days after starting mosapride, the patient experienced a major improvement of her dystonia symptoms. After cessation of mosapride the blepharospasm reoccurred. Treatment with fluoxetine, an SSRI, also induced a beneficial effect in two patients with idiopathic blepharospasm, as described by Schreiber et al. [68]. One patient with blepharospasm and an adjustment disorder experienced an improvement of symptoms three weeks after treatment with fluoxetine. The other patient suffered from blepharospasm, an adjustment disorder and a depressed mood, all with good response to fluoxetine. This patient decided to stop with fluoxetine after 12 weeks, after which the symptoms reoccurred. A similar result is described in a patient with writer's cramp. Sertraline, an SSRI, was initiated by a psychiatrist because of recurrent headaches. According to the patient, treatment with sertraline achieved a 95 percent remission of his writer's cramp [69].

Besides serotonin transporter blockers and specific serotonin receptor agonists, also antagonists of 5-HT_2 receptors can positively influence dystonia. One trial was performed with cyproheptadine, an antagonist of mainly 5-HT_2 receptors and histamine receptors, on five patients with blepharospasm [70]. In all five patients the blepharospasm improved in a few days, however in one patient cyproheptadine was stopped because of side effects. Another trial tested risperidone, a neuroleptic agent blocking 5-HT_2 and D_2 receptors, in five patients with idiopathic segmental dystonia [71]. After four weeks of treatment, a clear beneficial effect was reached on both duration and amplitude of the dystonic movements. Furthermore, all patients were previously treated and scored during haloperidol monotherapy and after washout, at which time higher mean scores on the Tsui's Dystonia Score were found. Following this trial, Grassi et al. treated seven patients (two patients with idiopathic dystonia, five patients with unknown or symptomatic dystonia) with risperidone. All patients showed improvement following risperidone. The best response was seen in patients with idiopathic dystonia [72]. These findings suggest a positive additive effect of 5-HT_2 receptor blocking above merely D_2 receptor blocking, which usually induces or aggravates dystonia [73].

Different aspects of the serotonergic system in patients with idiopathic dystonia have been described. Lowered levels of 5-HIAA in CSF in patients with idiopathic dystonia may point to the involvement of the serotonergic system, as well as the positive effect of drugs interacting with the serotonergic system.

Acquired dystonias: Perinatal brain injury & Infections

Only a very limited number of papers reported serotonin concentrations in acquired forms of dystonia. Five patients with cerebral palsy or postnatal hypoxic-ischemic encephalopathy and clinically manifest dystonia were described by Assmann et al. [62]. Levels of 5-HIAA in CSF were normal to slightly decreased (median SD -1.0, range -0.9 - -1.6).

A single study of 25 patients with Japanese encephalitis and four patients with non-specific encephalitis reported the prevalence of dystonia and neurotransmitter concentrations in CSF [74]. Eight out of 29 (non-specified) patients suffered from dystonia what was observed during the acute stage of encephalitis. Significantly decreased levels of 5-HT (p=0.0001) and HVA (p=0.01) in CSF were found in patients with encephalitis compared to controls. The level of 5-HIAA was not determined.

In this category, the broad spectrum of underlying pathophysiology and its anatomical localization makes it hard to draw any conclusions about aberrations of the serotonergic system.

Acquired dystonias: Drugs with effect on the serotonergic system
Acute dystonic reactions (ADR) have been reported after the use of several types of medication that affect the serotonergic system. In this review we will restrict ourselves to ADRs following the use of medication with a predominantly serotonergic effect. Papers describing ADRs following medication that mainly affects other neurotransmitters will not be discussed in further detail, because in these cases the observations cannot merely be attributed to changes in the serotonergic system.

Thirty-five patients were described with acute dystonic reactions provoked by SSRIs [75–96]. Furthermore, dystonia is described after treatment with sumatriptan (n=2), a 5-HT_1 receptor agonist [97,98], and after ondansetron (n=1), a potent 5-HT_3 receptor antagonist [99]. The differential effects of SSRI's on different types of dystonia will be further argumented below in the discussion section.

Animal models of dystonia
Perturbations of the serotonergic system are described in several animal models of dystonia, including early onset primary dystonia, myoclonus-dystonia and focal dystonias.

Several animal models exist for torsion dystonia, now called early-onset primary dystonia. LeDoux et al. examined the levels of serotonin and norepinephrine in both normal and genetically modified dystonic rats. Although similar levels of serotonin were found in both groups at the end of the study, they did found a significant association of serotonin with age and phenotype of the dystonic rats [100].
Michela et al. examined the response to quipazine, a serotonin agonist, is both normal and genetically modified dystonic rats [101]. The DYT1 rats showed an enhanced sensitivity to the tremorogenic effects of quipazine. The dystonic rats also showed a sixfold increased sensitivity to develop dystonia following administration of a 5-HT_{1A} agonist compared with normal littermates [102].

In the DYT1 hamster model, increases in both serotonin and noradrenaline were found in several (motor cortex) regions. Except for the olfactory bulb, no alterations in dopamine

metabolism were found [103]. Furthermore, in this hamster model prodystonic effects have been reported with 5-HT drugs altering the function of 5-HT_{1A} or 5-$HT_{2A/2C}$ receptors [103,104].

Signs of potential involvement of serotonin in dystonia and co-morbid psychiatric features were also found in ε-sarcoglycan gene (SGCE) knockout mice. Mutations in the ε-sarcoglycan gene in humans result in myoclonus-dystonia (DYT 11). As shown in this animal model, mutations of the murine *SGCE* gene also result in dystonia, myoclonus, hyperactivity, anxiety and depression. Measurement of monoamine neurotransmitters in the murine striatum revealed that the level of 5-HIAA, and the ratio of 5-HIAA to serotonin, had a tendency to be higher in the knockout mice, suggestive of an altered turnover or synthesis of serotonin. Furthermore, Chan et al. studied the expression of ε-sarcoglycan mRNA in the mouse brain, which was highly expressed in serotonergic neurons of the dorsal raphe nucleus [105].

Several animal studies also described a relation between focal dystonias and serotonin. In 12 cats, a lesion in the left side of the ventromedial tegmentun was induced electrically in order to obtain a spasmodic torticollis-like posture. In six out of 12 cats, this effect was actually achieved. In the caudate nucleus of these animals, the extracullular level of 5-HIAA was decreased compared to the level of HVA. In the four cats with the longest disease duration, the change in 5-HIAA levels was most prominent [106].

Another study tested involvement of serotonin in the development of blepharospasm in both cats and monkeys. Injections with serotonin in the facial nucleus induced unilateral blepharospasm and hemifacial spasm. Pretreatment with ketanserin, a 5-HT_2 antagonist, reduced the severity of the blepharospasm and hemifacial spasm [107].

Faherty et al. investigated the underlying mechanism of altered motor function following administering SSRIs in rats. Direct injection of several SSRIs into the left red nucleus of the rat lead to acute dystonic movements/posturing following fluvoxamine and fluoxetine, but not after citalopram, sertraline and paroxetine [108]. Consequently, Faherty et al. examined the influence of sensitization of σ2 receptors following SSRIs on motor behavior. Chronic treatment with fluvoxamine or the selective σ receptor ligand di-o-tolyguanidine (DTG) followed by an intra-rubral injection of DTG elicited dystonia and indicated a sensitization of σ2 receptors. This effect was also not observed after sertraline, citalopram and paroxetine. The dystonic posturing correlated with an increase in the concentration of serotonin in the brainstem [109].

DISCUSSION

This paper systematically reviewed the role of serotonin in the clinically heterogeneous group of inherited, acquired and idiopathic dystonias and presents an overview of the findings of serotonin in dystonia animal models. Several aspects of serotonergic perturbations in dystonia were described in these papers, which will be discussed in more detail below.

Biochemical analysis of serotonin metabolites

One of the most consistent findings comprised a decreased level of 5-HIAA in CSF in patients with several types of dystonia, indicating either an altered serotonergic turnover or an altered serotonergic synthesis. A decreased level of 5-HIAA was most consistently shown in dopa-responsive dystonias, in which different gene defects directly affect the synthesis of serotonin, but decreased levels of serotonin were also reported in idiopathic focal dystonias. Interpretation of serotonin levels in other inherited dystonias was often not reliable, mainly because of associated medication used that can influence serotonin. The widely divergent genes involved, all leading to a phenotype with dystonia, makes interpretation even harder, as the exact pathogenic effects of these mutated genes are often not known.

Serotonin and it metabolites can be analyzed in various ways and by different methods. Measurement of serotonin in peripheral blood platelets is thought to reflect serotonin levels in the brain, but has several limitations [110]. Measurement of serotonin and its metabolites in CSF more specifically reflects turnover of serotonin in the brain. Measurement of 5-HIAA is preferred, because this metabolite is a very stable degradation product of serotonin [111].

Another factor that should be taken into account is that levels of 5-HIAA can be influenced by many factors, including medication, other co-morbidity, age, diet, diurnal fluctuation and physical exertion [112]. Also, the analysis of 5-HIAA in CSF obtained by lumbar puncture does not specifically reflect cerebral serotonin synthesis, but also synthesis of serotonin within the spinal cord (and plexus) [110]. Interlaboratory variations of analytical methods used to determine the level of 5-HIAA and variable reference values hamper firm conclusions. But, despite these limitations, the decreased levels of 5-HIAA in CSF reported in multiple papers support a role of serotonin in the pathophysiology of dystonia.

Influence of drugs interacting with the serotonergic system

Another remarkable finding comprised serotonergic acting drugs either eliciting or improving dystonia, depending on the specific target on the serotonergic system and dystonia etiology. For example, SSRIs usually aggravated dystonia in dopa-responsive dystonias, it improved dystonia in the idiopathic dystonias and induced acute dystonic reactions in 35 subjects in which SSRIs were prescribed for several other indications (Table 2).

Several factors might explain the differential effects of serotonergic acting drugs. First, serotonergic drugs have different points of engagement and effects on the motor circuits. As recently reviewed by Ohno et al., 5-HT_{1A}, 5-$HT_{2A/2C}$, 5-HT_3 and 5-HT_6 receptors all are involved in regulating extrapyramidal motor disorders. Treatment with a 5-HT_{1A} agonist inhibits firing of serotonergic neurons of the raphe nuclei, attenuates $HT_{2A/2C}$, 5-HT_3 and 5-HT_6 receptor function and influences GABAergig, glutaminergic, acetylcholinergic and dopaminergic activity. Blockage of 5-$HT_{2A/2C}$ receptors relieves 5-$HT_{2A/2C}$ receptor mediated inhibition of dopamine release and neural firing of dopaminergic and cholinergic neurons. Antagonism of the 5-HT_6 receptor with SB-258585 inhibits acetylcholinergic activity in the striatum, and thereby alleviating extrapyramidal movement disorders [11]. As shown in the dystonia patients, drugs with different points of engagement on the serotonergic system had differential clinical effects. Better understanding of the role of these receptors and reuptake mechanisms is important to gain insight into the pathophysiology of dystonia and might improve current treatment strategies.

Another factor that might explain the differential effects of dystonia treatment with serotonergic agents is suggested to be from developmental modifications in the serotonergic system [113]. One of the factors influencing serotonergic systems/circuits might be the varying availability of serotonin during gestation and development. In DRD, gene mutations directly affect the availability of serotonin, which might have caused modifications in serotonergic neural networks during development. Another factor that may influence the development of the serotonergic system is a polymorphism in the promotor region of the gene encoding the serotonin transporter, resulting in either a short (S) or a long (L_G or L_A) allele. This in turn modulates mRNA expression and the amount of 5-HTT protein that is transcribed [114,115]. The short allele is associated with an increased risk of developing depression, although several studies have shown that the short allele does not lead to altered serotonin transporter activity in the adult brain (reviewed by Sibille and Lewis, 2006 [113]). This contradiction could be explained by a different maturation of the serotonergic system during gestation, childhood or adolescence, whereby environmental factors later in life have a different effect on the eventual phenotype [116,117].

A third explanation of the differential effects of serotonergic acting drugs is the different age at initiation of treatment and the differences in treatment duration. In childhood, SERT is highly available, followed by slowly decreasing levels during adulthood. In the psychiatric literature, different effects of SSRIs are described in children compared with adults, especially with a higher risk of worsening of symptoms and even more suicide within the first few weeks of treatment [118]. The treatment duration is another factor as the time frame in which SSRIs caused acute dystonic reactions was usually within hours. Aggravation of dystonia in DRD was mostly seen in the first weeks of treatment, whereas improvement of dystonia in the idiopathic dystonias usually took several weeks. In depression, initiation of an SSRI is associated with higher levels of synaptic serotonin in projection areas, but this increase in serotonin also induces a decreased firing rate by

activation of inhibiting 5-HT_{1A} autoreceptors in the raphe nuclei. Only after weeks, when the 5-HT_{1A} autoreceptors in the raphe nuclei desensitizes and the firing rate increases, serotonin signaling in projection areas actually increases [119]. This might explain some of the observations in dystonia as well, related to the different effects of treatment duration and consistent with network plasticity in dystonia, as the clinical effects of deep brain stimulation of the GPi takes several weeks to months to evolve.

In conclusion, several theories of serotonergic modulation of basal ganglia networks are likely to be involved in dystonia. In such a complex network, interpretation of results of studies using different dystonia models is difficult, and warrants further research specifically into the role of serotonergic modulation of dystonia networks/circuits.

Psychiatric co-morbidity

Psychiatric co-morbidity or unclassified behavioral disorders were not systematically examined but have been described in 50 cases [18,19,21,26,27,30,37,39,45,48–51,53,54,60,64,65]. Most (n=48) of the patients suffered from the inherited forms of dystonia. In the majority of these patients the synthesis of serotonin was disturbed as they suffered from a form of DRD. Psychiatric disorders included (a combination of) depression, obsessive compulsive disease, anxiety disorders, eating disorders, attention disorders, aggressive behavior, autistic disorders and self-mutilation. However, it should be noticed that psychiatric co-morbidity was often not described and likely not systematically examined. The results from our review may thus be an underestimation. As clearly shown by the study in patients with sepiapterin reductase deficiency, systematic testing of non-motor functions may reveal much higher numbers of (serotonin related) co-morbidity [37].

Strikingly, psychiatric co-morbidity often preceded motor symptoms. This is in accordance with previous studies described in literature on mainly focal dystonia [2,3,120–124], suggesting psychiatric co-morbidity as an integral part of the phenotype of dystonia and a shared pathophysiology.

Disruption of serotonergic functions is known to be involved in many psychophysiologic processes and (early life) serotonergic dysregulation is associated with a wide spectrum of psychiatric disorders. Furthermore, during gestation serotonin is involved in the formation of cortical circuits and modulating plasticity, which is known to be involved in the pathophysiology of dystonia [7,125,126]. Several papers described poorer motor development in infants exposed to SSRIs in utero. Unfortunately, no follow up is described so possible development of specifically dystonia in these cases is unknown [127–130].

Conclusion

In conclusion, our systematic review reveals an association between serotonergic neurotransmission and (the phenotype of) dystonia. In dopa-responsive dystonias, gene

defects directly affect serotonergic functioning. However, in other inherited, acquired and idiopathic dystonias disturbances of the serotonergic neurotransmission are also reported to be present. The influence of serotonergic medication furthermore suggests a shared pathophysiological mechanism of both motor and non-motor symptoms in dystonia patients. Thus far, only serotonergic metabolism at the level of 5-HT or 5-HIAA has been studied in a limited number of predominantly genetic disorders. Our review shows that in the majority of these studies a dysfunction of the serotonergic system or an imbalance with the dopaminergic basal ganglia innervation is suggested.

Our review also reveals the drawbacks of the conventional methods of analyzing serotonin concentrations and its metabolites in platelets and CSF. New technologies may overcome these shortcomings and provide valuable insights into serotonergic neurotransmission. Positron emission tomography imaging for instance allows in vivo quantification of the serotonergic system in specific brain regions and may provide a useful tool for future research [110].

Ultimately, a better understanding of the pathophysiology of the different forms of dystonia and the involvement of the serotonergic system in motor as well as non-motor symptoms will guide us to more rational therapeutic strategies in dystonia.

Supplementary table 1
Complete overview of 5-HIAA levels in CSF in dystonia patients.

Affected gene	Authors/year	N	CSF 5-HIAA (nmol/L)	Reference range (nmol/L	Interpretation
Autosomal dominant					
GTP Cyclohydrolase 1	Ishida et al., 1988	2	14	21 – 58.8	Decreased
			29	21 – 58.8	Normal
	Zambrino et al., 1991	1	17.8	78.5 – 130.8	Decreased
	Van Hove et al., 2006	4	194	58 – 190	Increased
			67	58 – 190	Normal
			66	58 – 190	Normal
			81	109 – 214	Decreased
ATP1A3	Brashear et al., 1998	10	111.9	55.4 – 160	Normal
			156.9	55.4 – 160	Normal
			31.4	55.4 – 160	Decreased
			61.7	55.4 – 160	Normal
			105.7	56.5 – 195.6	Normal
			117.2	56.5 – 195.6	Normal
			123.4	55.4 – 160	Normal
			177.3	55.4 – 160	Normal
			145.9	55.4 – 160	Normal
			98.9	56.5 – 195.6	Normal
Autosomal Recessive					
GTP Cyclohydrolase 1	Sato et al., 2014	1	114	539 – 953	Decreased
	Blau et al., 1995	1	92	114 – 336	Decreased
Sepiapterin Reductase	Friedman et al., 2012	11	17.0	88 – 178	Decreased
			6.0	88 – 178	Decreased
			5.0	105 – 299	Decreased
			10.0	105 – 299	Decreased
			6.0	114 – 336	Decreased
			3.0	88 – 178	Decreased
			3.0	88 – 178	Decreased
			1.0	66 – 141	Decreased
			4.0	88 – 178	Decreased
			10	88 – 178	Decreased
			13	114 – 336	Decreased
	Arrabal et al., 2011	2	9	125 – 303	Decreased
			25	63 – 185	Decreased
	Blau et al., 1999	1	4	105 – 299	Decreased
	Blau et al., 1998	1	14	88 – 178	Decreased
	Echenne et al., 2006	2	5	87 – 247	Decreased
			8	87 – 247	Decreased
	Friedman et al., 2006	1	10	79 – 140	Decreased
	Abeling et al., 2006	1	5	68 – 115	Decreased
	Steinberger et al., 2004 Data from: Friedman et al, 2012	1	100	66 – 141	Normal
	Verbeek et al., 2008	2	5	109 – 214	Decreased
			4	100 – 245	Decreased
	Kusmierska et al., 2008	1	12.3	100 – 400	Decreased

	Dill et al., 2012	1	10.3	114 – 336	Decreased
	Leu-Semenescu et al., 2009	1	45	65 – 200	Decreased
	Wali et al., 2010	2	6	88 – 178	Decreased
			12	114 – 336	Decreased
Aromatic L-amino acid decarboxylase deficiency	Hyland et al., 1992	2	10	63 – 503	Decreased
			21	63 – 503	Decreased
	Manegold et al., 2008	8	4	302 – 1952	Decreased
			2	105 – 299	Decreased
			53	130 – 362	Decreased
			31	159 – 989	Decreased
			2	105 – 299	Decreased
			2	87 – 372	Decreased
			2	87 – 372	Decreased
			2	87 – 372	Decreased
	Abeling et al., 1998	1	27	120 – 400	Decreased
	Maller et al., 1997	1	31.9	181.5 – 232.8	Decreased
	Abdenur et al., 2005	1	5	152 – 462	Decreased
	Fiumara et al., 2002	1	21	110 – 265	Decreased
	Swoboda et al., 1999	2	20	63 – 503	Decreased
			9	63 – 503	Decreased
	Barth et al., 2011	1	12	87 – 366	Decreased
	Tay et al., 2007	1	13	67 – 189	Decreased
	Gucuyener et al., 2014	1	10	155 – 350	Decreased
	Helman et al., 2014	4	9	129 – 520	Decreased
			5	129 – 520	Decreased
			Undetectable	Not provided	Decreased
			22	> 66	Decreased
SLC18A2	Rilstone et al., 2013	1	169	74 – 345	Normal
X-Linked					
HPRT	Jankovic et al., 1988	5	266.8	107.5 – 307.1	Normal
			183.1	107.5 – 307.1	Normal
			272	Not provided	
			109.8	Not provided	
			183.1	Not provided	
	Silverstein et al., 1985	4	355.7	172.6 – 413.2	Normal
			219.7	104.6 – 240.6	Normal
			136	57.5 – 219.7	Normal
			104.6	36.6 – 151.7	Normal

Total overview of all 5-HIAA levels in CSF in inherited dystonias including the interpretation according to the provided reference ranges in the original article. 5-HIAA = 5-Hydroxyindolacetic Acid. CSF = Cerebrospinal Fluid.

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