PET and SPECT Imaging in Dystonia

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29

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Contents

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Abstract

Dystonia is a syndrome characterized by involuntary, sustained muscle contractions causing twisting movements and abnormal postures. It is a common movement disorder with different forms that can be classified based on different clinical characteristics. Idiopathic focal dystonia (dystonia in one body part with no known cause) is the most common form. The more generalized (throughout the body) forms of dystonia have a younger age of onset and usually an underlying genetic defect. The mode of inheritance is usually autosomal dominant. Of these, the most common are DYT-TOR1A and DYT-THAP1 dystonia. In combined dystonia syndromes, also autosomal dominantly inherited disorders, dystonia patients have additional neurological symptoms (e.g., parkinsonism or myoclonus). This group includes dopamine-responsive dystonia, myoclonus-dystonia, rapid-onset dystonia-parkinsonism, and paroxysmal dystonia. In this chapter, we describe results from positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies in the different forms of dystonia.

Three different kinds of PET and SPECT techniques have been used in patients with dystonia: glucose metabolism scans, regional cerebral blood flow studies, and receptor imaging. Increased glucose metabolism was found in the basal ganglia, thalamus, and cerebellum of patients with different forms of focal dystonia and in DYT1 dystonia. Patients with DYT6 dystonia showed decreased glucose metabolism in the putamen. Results from regional cerebral blood flow (rCBF)-activation studies differed extensively among different studies and different patient groups, mainly because of study design. Overall, the primary and secondary motor and sensory cortices were found to be abnormal in almost all forms of dystonia, although the direction of the abnormalities differed. Dopamine was found to play a role in dystonia reflected by decreased dopamine D2/3 receptor binding in the striatum of patients with almost all forms of dystonia. In recent years, it has been established that other neurotransmitter systems, such as serotonin and gamma aminobutyric acid (GABA) also play a role in dystonia. In conclusion, dystonia is likely to be a network disorder with abnormalities in a large number of cortical and subcortical areas. There might be a central role for the basal ganglia with abnormalities in dopamine receptor binding, as well as other neurotransmitter systems.

29.1 General Introduction

29.1.1 Historical Background

Dystonia was first described in 1911 by Hermann Oppenheim, a renowned German neurologist, as a disorder causing variable muscle tone and recurrent muscle spasm and was initially called "dystonia musculorum deformans." Two neurologists from Poland, Flatau and Sterling, objected to the term dystonia, since they did not consider the varying muscle tone to be the clinical hallmark. They proposed the term "progressive torsion spasm," as patients showed torsion spasms of unknown origin. The two terms were combined and the term "primary torsion dystonia" became widely accepted (Grundmann 2005; Tarsy and Simon 2006). The etiology has been a matter of debate over the years. Especially in the time of Sigmund Freud, several patients with dystonia were described and considered to suffer from hysteria. In 1959, the hereditary nature of primary torsion dystonia was demonstrated. Since then, dystonia is considered to be a neurologic condition, although case reports of psychogenic dystonia have been published over the years (Munts and Koehler 2010).

29.1.2 Epidemiology

Dystonia is the third most common movement disorder (annual incidence: 15–25 per 100,000; ESDE 2000; Le et al. 2003) after Parkinson's disease (PD; von Campenhausen et al. 2005) and tremor (Louis and Ferreira 2010). Idiopathic cervical dystonia (CD; dystonia of the neck) is the most common form of dystonia. The estimated prevalence of CD in the Netherlands (total population: 16.9 million) is 8000 patients, although less than half of these patients are regularly seen by a neurologist (ESDE 2000; Le et al. 2003).

29.1.3 Classification, Clinical Features, and Etiology

Dystonia is a syndrome characterized by involuntary, sustained muscle contractions causing twisting movements and abnormal postures (Tarsy and Simon 2006). Dystonia can be classified based on different characteristics. A frequently used classification is based on topographic distribution, including focal dystonia (one body region), segmental dystonia (two or more adjacent regions), multifocal dystonia (two or more nonadjacent regions), hemidystonia (ipsilateral arm and leg), and generalized dystonia (Tarsy and Simon 2006). Another important division is made in associated features: isolated dystonia, combined dystonia (dystonia with another movement disorder), and dystonia associated with other neurological and systemic manifestations. The third commonly used classification is based on etiology:

nervous system pathology (neurodegenerative disorders and structural lesions), inherited dystonia, acquired dystonia, and idiopathic dystonia. In idiopathic dystonia, there is no underlying disorder recognized causing the dystonia (Albanese et al. 2013). A small proportion of these patients has an inherited form of dystonia. Combined dystonia syndromes are genetic syndromes with dystonia and another movement disorder, for example myoclonus (jerks) or parkinsonism. Acquired dystonia can be caused by a large number of neurological and other conditions, medication, and intoxications. Imaging today has a small role in clinical practice and is mainly used to exclude acquired dystonia in young patients or patients with an atypical disease course (Tarsy and Simon 2006). For an overview and classification of the different forms of dystonia, see Table 29.1.

Idiopathic focal dystonia is dystonia of unknown origin in one body part. The most common form of focal dystonia is CD. Other forms are for example blepharospasm (BLS; dystonia of the eyelids), writer's cramp (WC) or focal hand dystonia, oromandibular dystonia (dystonia of the jaw), and spasmodic dysphonia (dystonia of the vocal cords). Most forms of focal dystonia debut around the age of 50 years. One of the most extraordinary features of focal dystonia is that it can be action specific, a feature that is often used in imaging studies. The most well-known form of action-specific dystonia is WC where patients get a dystonic posture of the hand while trying to write, but not in rest or during other hand movements. Action-specific dystonia has been described in other body parts than the hands as well, for example in the mouth in musicians playing a wind instrument (embouchure dystonia). There usually is no identifiable genetic cause in focal dystonia, although in 20–30% of patients the family history is positive for dystonia (Tarsy and Simon 2006; Lohmann and Klein 2017). Over the years, many loci have been linked to dystonia; however, the precise role of these genetic risk factors remains to be determined (Lohmann and Klein 2017).

Patients with generalized dystonia usually develop dystonia in childhood or during adolescence. These patients frequently have a genetic cause for dystonia and most of these familial syndromes have been allocated a DYT number based on clinical characteristics. The combined dystonia syndromes are included in the DYT numbering as well (Muller 2009). Over the years, it has become clear that several DYT syndromes were caused by one gene, while in other DYT syndromes multiple genes were responsible for one phenotype. Recently, the DYT classification has therefore been changed to a system where DYT is now followed by the causative gene. For example, DYT1 is now named DYT-TOR1A (Lohmann and Klein 2017).

Two forms of generalized dystonia that have been well studied are DYT-TOR1A (formerly DYT1) and DYT-THAP1 (formerly DYT6) dystonia. Onset of dystonia in DYT-TOR1A is usually in childhood and first symptoms are typically in the limbs. Dystonia generalizes over the course of a few years in most cases. DYT-TOR1A dystonia is caused by a mutation in the TorsinA gene. The penetrance of the mutation is 30% meaning that only 30% of gene carriers develop dystonia during their lifetime (Muller 2009).

DYT-THAP1 is the second most common genetic cause of inherited dystonia. Age at onset is more variable than in DYT-TOR1A dystonia, varying from onset in

Table 29.1 Classification of dystonia

Type of dystonia	Prominent symptoms	Etiology
Focal dystonia		
Cervical	Dystonia of the neck muscles	Mostly idiopathic, some cases due to DYT-ANO3
Blepharospasm	Dystonia of the eyelids	Unknown
Writer's cramp	Action-specific dystonia of the hands	Unknown
Focal hand dystonia	Nonaction-specific dystonia of the hands	Unknown
Oromandibular dystonia	Dystonia of the jaw and tongue	Unknown
Spasmodic dysphonia	Dystonia of the vocal cords	Unknown
Segmental dystonia		
Meige syndrome	Blepharospasm with dystonia of the jaw or lower face muscles	Unknown
Inherited form of adult-onset segmental dystonia	Craniocervical dystonia with or without dystonia of one arm	DYT-GNAL
Multifocal dystonia		
Hemidystonia		
Post-stroke dystonia	Dystonia of the arm and leg on one side of the body	Usually post-stroke
Generalized dystonia		
Acquired	Generalized dystonia	Usually post-anoxia, e.g., birth trauma
DYT-TOR1A	Generalized dystonia starting in the limbs	TorsinA gene mutation
DYT-THAP1	Focal or generalized dystonia starting in the cranial or cervical muscles	THAP1 gene mutation
Combined dystonia		
Dopamine-responsive dystonia	Generalized dystonia starting in one leg that responds to levodopa	GCH1 gene or SRG gene mutation
Myoclonus-dystonia	Myoclonus, dystonia, and psychiatric symptoms	SGCE gene mutation
Rapid-onset dystonia-parkinsonism	Acute-onset dystonia and parkinsonism	ATP1A3 gene mutation
Paroxysmal dystonia		
Paroxysmal kinesigenic dystonia	Attacks of generalized dystonia triggered by sudden movements	Most commonly PRRT2 gene mutation, however several other genes described
Paroxysmal non-kinesigenic dystonia (DYT8 and 20)	Spontaneous attacks of generalized dystonia	Most commonly PNKD1 gene mutation
Paroxysmal exercise-induced dystonia (DYT18)	Attacks of generalized dystonia triggered by prolonged exercise	GLUT1 gene mutation

childhood to adult onset. Dystonia typically starts in cranial or cervical muscles after which it slowly progresses. Dysphonia is a common symptom in DYT-THAP1 dystonia. DYT-THAP1 dystonia is caused by a mutation in the THAP1 gene. This mutation also has reduced penetrance: 60% of gene carriers develop dystonia (Muller 2009).

The combined dystonia dopamine-responsive dystonia (DRD, also known as Segawa syndrome) has been named DYT-GCH1 dystonia (formerly DYT5). DRD usually starts in childhood with dystonia of a leg. After this, dystonia usually progresses and patients also develop parkinsonian features. Typical features of DRD are worsening of symptoms after sustained action and reduction of symptoms after rest or sleep (Muller 2009). DRD is most commonly (~80% of cases) caused by a mutation in the GCH1 gene encoding GTP-cyclohydrolase-1, an enzyme necessary for the production of dopamine. This mutation is transmitted in an autosomal dominant fashion with a penetrance of ~30%. The second most commonly affected gene is the sepiapterine reductase gene (SRG), another enzyme used in the production of dopamine. Both mutations lead to reduced production of endogenous dopamine (Muller 2009).

Myoclonus-dystonia (MD; DYT-SCGE formerly DYT11) is a form of combined dystonia. Patients exhibit both dystonia and myoclonic jerks. Onset is usually in childhood or adolescence with myoclonic jerks, later followed by a relatively mild form of dystonia. Patients with MD often also exhibit psychiatric symptoms, mainly depression, anxiety, and obsessive-compulsive syndrome. Motor symptoms in MD are highly responsive to alcohol. MD is caused by a mutation in the epsilon-sarcoglycan gene (SGCE gene) and is transmitted in an autosomal dominant matter with reduced penetrance and maternal imprinting. The latter means that only gene carriers inheriting the gene from their father can get the disease. This is largely true, but a small percentage of patients inheriting the gene from their mother also has (mild) symptoms (Muller 2009).

Rapid-onset dystonia-parkinsonism (RDP; DYT-ATP1A3 formerly DYT12) is an autosomal dominant disease with abrupt onset of dystonia and parkinsonism over days to weeks, followed by little or no improvement. Permanent and disabling dystonia presents acutely after physical or psychological stress, fever, or alcohol excess. RDP is caused by mutations in the α3 subunit of the Na/K-ATPase, the ATP1A3 gene (Muller 2009).

Paroxysmal dystonia is a group of disorders that is characterized by attacks of dystonic movements and postures with sometimes chorea or myoclonus. The disorders that can be distinguished are paroxysmal kinesigenic dystonia (PKD; attacks of several seconds triggered by sudden movements), paroxysmal non-kinesigenic dystonia (PNKD; spontaneous attacks lasting minutes to several hours), and exercise-induced dystonia (PED; Muller 2009). The most common form, PKD, was shown to be caused by mutations in the *PRRT2* gene (Wang et al. 2011). Exercise-induced dystonia is found to be caused by a mutation in the *GLUT1* gene, encoding a glucose transporter in the blood-brain barrier. Due to the mutation in this gene, there is reduced glucose transport to the brain (Muller 2009). Recent studies suggest that the phenotypes of the different genes are overlapping and there are even nongenetic disorders that can present with paroxysmal dystonia (Erro and Bhatia 2019).

29.1.4 Pathophysiology

The pathophysiology of dystonia is still largely unknown even for the inherited forms of dystonia. In the last few years, evidence has been gathered that suggests that TorsinA is needed for neuronal cell membrane stability and architecture, nuclear export, and protein trafficking (Gonzalez-Alegre 2019). It is still unclear what the function of the THAP1, GCH, SRG, and SGCE gene is and what happens at a cellular level when these genes are mutated. For focal dystonia, a combination of genetic and environmental factors is hypothesized to play a role (Tarsy and Simon 2006). Imaging studies with positron emission tomography (PET) and single-photon emission computed tomography (SPECT), though also with varying magnetic resonance imaging (MRI) techniques, have been performed over the years to try to unravel the pathophysiology of dystonia. Dopamine is believed to play an important role in the pathophysiology of all forms of dystonia and has been one of the points of focus in PET and SPECT imaging. One argument for the role of dopamine is DRD, which can successfully be treated with levodopa (Naumann et al. 1997). Other important arguments are the coexistence of dystonia in patients with Parkinson's disease, especially in patients who develop PD at a young age and patients who have been treated with levodopa for longer periods (Wickremaratchi et al. 2009) and the possibility of developing dystonia after use of antipsychotics (dopamine $D_{2/3}$ receptor blockers; Haddad and Dursun 2008). We will collaborate more on results from PET and SPECT studies below.

29.1.5 Treatment

Treatment differs for the different types of dystonia. Most forms of focal dystonia are treated locally with intramuscular botulinum toxin (BTX) injections (Zoons et al. 2012). BTX can also be used in patients with generalized dystonia or MD in the body part that is most affected or causes most disability. Usually patients with generalized dystonia are treated with drugs, for example, trihexyphenidyl (Artane), benzodiazepines, or baclofen, or with deep brain stimulation (DBS). Patients with DRD are treated with small amounts of levodopa with dramatic treatment response. The treatment for paroxysmal dystonia consists of anti-epileptics, for example, carbamazepine (Tarsy and Simon 2006).

29.2 Imaging with PET and SPECT in Different Forms of Dystonia

PET and SPECT studies have been performed in patients with different forms of dystonia. The studies that have been performed can roughly be divided into three types: PET studies for glucose metabolism, PET studies for regional cerebral blood flow (rCBF-activation studies), and PET and SPECT studies for receptor imaging, mainly dopamine; however, the serotonin, gamma aminobutyric acid (GABA), and opioid systems have also been studied. The information in this chapter is divided by

forms of dystonia, starting with focal dystonia and followed by generalized dystonia and combined dystonia: DRD, MD, RDP, and paroxysmal dystonia. We will not discuss the results in acquired dystonia. As mentioned above, the causes for acquired dystonia are numerous and the abnormalities found with imaging are usually a result of the underlying condition and not of dystonia per se. A general overview of findings is presented in Table 29.2.

29.3 Focal Dystonia

Several PET and SPECT studies have been performed over the years trying to unravel the pathophysiology of focal dystonia (for a review, see Zoons et al. 2011)

29.3.1 Glucose Metabolism PET

Using [18F]-fluorodeoxyglucose (FDG) PET, increases and decreases in FDG uptake have been found in the basal ganglia, cerebellum, and sensorimotor cortex (SMC) of patients with focal dystonia. A bilateral increase in glucose metabolism in the basal ganglia, thalamus, lentiform nucleus, premotor-motor cortex, and cerebellum has been found in patients with CD compared to controls (Galardi et al. 1996; Magyar-Lehmann et al. 1997). There was an increase in glucose metabolism in the striatum and thalamus of patients with BLS and Meige syndrome (combined dystonia of the eyes and mouth/jaw) compared to controls (Esmaeli-Gutstein et al. 1999) and in the cerebellum and pons in patients with BLS compared to controls (Hutchinson et al. 2000). During induced sleep, patients with BLS showed glucose hypometabolism in the superior-medial aspect of Brodmann area 8 compared to controls. This region is associated with supranuclear control of eyelid opening (Hutchinson et al. 2000). The glucose hypermetabolism in the cerebellum and the pons has been replicated in a study that examined patients with BLS after treatment with BTX. A bilateral glucose hypermetabolism in the thalamus and the pons of patients with BLS was found compared to controls as well as a trend toward glucose hypermetabolism in the putamen bilaterally. Patients with incomplete suppression of BLS on BTX had glucose hypermetabolism in the cerebellum and the pons compared to patients with complete suppression (Suzuki et al. 2007). Furthermore, a complex network of cortical and subcortical regions with increased and decreased metabolism was found in patients with BLS compared to controls. There was increased metabolism in the inferior frontal gyri, right posterior cingulated gyrus, left middle occipital gyrus, fusiform gyrus of the right temporal lobe, left anterior cingulate gyrus, and the caudate nucleus. Decreased glucose metabolism was found in the inferior frontal gyri, left cerebellar hemisphere, and thalamus. Lateralization of activation of the frontal and temporal cortex to the right with contralateral deactivation of the left cerebellum suggests a connection mediated by the corticopontocerebellar pathway (Kerrison et al. 2003). One study compared untreated patients with various forms of isolated focal dystonia (mainly CD and WC) to patients with

Table 29.2 Results of PET and SPECT imaging in dystonia

Type of dystonia	Glucose metabolism	Regional cerebral blood flow	Receptor imaging
Focal			
Cervical	↑ Basal ganglia, thalamus, lentiform nucleus, premotor-motor cortex, cerebellum ↓ Caudate nucleus, thalamus, lentiform nucleus, and temporal, frontal, prefrontal, and parietal cortices	↓ SMA, precentral gyrus, SMC and ↑ ipsilateral parietal cortex, and bilateral occipital cortex (during sensory trick)	↓ Striatal D2/3R binding = DAT binding ↓ Striatal VAChT binding ↓ Midbrain SERT binding (SPECT) = SERT binding (PET) ↑ GABA right precentral gyrus, left parahippocampal gyrus
Blepharospasm	↑ Striatum, thalamus, cerebellum, pons ↓ Brodmann area 8 (supranuclear control of eyelid opening; during induced sleep) *Network*: ↑ inf frontal gyri, r post-cingulated gyrus, l mid-occipital gyrus, fusiform gyrus of the r temp lobe, l ant cingulated gyrus and caudate nucleus and ↓ inf frontal gyri, l cerebellar hemisphere and thalamus	↓ PMC (in response to facial vibration; patients with OMD were also included)	↓ D2/3R binding
Writer's cramp/ focal hand dystonia	↓ Caudate nucleus, thalamus, lentiform nucleus, and temporal, frontal, prefrontal, and parietal cortices	↓ PMC, ↑ frontal and parietal association areas, PSC, SMA (while writing) ↓ SMC and premotor structures (during tasks) ↑ Inferior prefrontal cortex (rest) ↑ Contralateral thalamus, SMC and premotor cortex, and ipsilateral cerebellum (while writing)	↓ D2/3R binding ↓ GABA right cerebellum, left sensorimotor cortex ↑ GABA inferior prefrontal cortex
Segmental dystonia			
Meige syndrome	↑ striatum, thalamus	ND	ND

(continued)

Table 29.2 (continued)

Type of dystonia	Glucose metabolism	Regional cerebral blood flow	Receptor imaging
Inherited generalized dystonia			
DYT-TOR1A	↑ Sup frontal gyrus (incl pre-SMA), precuneus, inf parietal cortex ↑ Putamen ↑ Cerebellum	↑ l premotor area, SMA, ant cingulate cortex, l DLPFC, cerebellum, putamen, gyrus frontalis medialis, sup frontal gyrus, fronto-orbital cortex, and thalamus (during right-hand movements)	↓ D2/3R binding ↓ GABAa receptor binding in PMC, premotor cortex, PSC, SSC, posterior insula, l ant cingulate gyrus = Opioid receptor binding
DYT-THAP1	↑ Sup frontal gyrus (incl pre-SMA), precuneus, inf parietal cortex ↓ Putamen = Cerebellum	ND	↓ D2/3R binding
Combined dystonia			
Dopamine-responsive dystonia	ND	ND	↑ D2/3R binding = DAT binding = D1R binding ↑ VMAT2 binding
Myoclonus-dystonia	ND	ND	↓ D2/3R binding (stabilizes after GPi DBS)
Rapid-onset dystonia-parkinsonism	ND	=	↑ DAT binding = DAT binding ↓ DAT binding
Paroxysmal dystonia			
Paroxysmal kinesigenic dystonia (DYT9 and 10)	ND	↓ Basal ganglia and thalamus	ND
Paroxysmal non-kinesigenic dystonia (DYT8 and 20)	ND	ND	= VMAT2 binding
Paroxysmal exercise-induced dystonia (DYT18)	ND	↓ Cerebellum	ND

↑ increase, ↓ decrease; = no abnormalities, *ant* anterior, *D2/3R* dopamine D2/3 receptors, *DAT* dopamine transporter, *DBS* deep brain stimulation, *DLPFC* dorsolateral prefrontal cortex, *GPi* globus pallidus interna, *incl* including, *inf* inferior, *l* left, *mid* middle, *ND* not done, *OMD* oromandibular dystonia, *PET* positron emission tomography, *PMC* primary motor cortex, *post* posterior, *PSC* primary sensory cortex, *r* right, *SMA* supplementary motor area, *SMC* sensorimotor cortex, *SPECT* single-photon emission computed tomography, *SSC* secondary sensory cortex, *sup* superior, *VAChT* vesicular acetylcholine transporter, *VMAT2* vesicular monoamine transporter type 2

essential tremor (ET) and found that both groups show hypometabolism in the caudate nucleus, thalamus, lentiform nucleus, and temporal, frontal, prefrontal, and parietal cortices. There was a significant difference in the extent of decrease in glucose metabolism between these two groups in the left thalamus, right lentiform nucleus, cingulate gyrus, and pons. The authors propose that quantification of glucose metabolism in these areas can be used to differentiate between the two disorders; however, these results have not been replicated yet (Belenky et al. 2018).

In summary, both patients with CD and BLS showed hypermetabolism in basal ganglia, thalamus, and cerebellum. A network of other cortical and subcortical areas could also be affected in patients with BLS. There could be a difference in glucose metabolism between isolated focal dystonia and ET.

29.3.2 Regional Cerebral Blood Flow PET

Where the above-described studies using [18F]-FDG found abnormalities in glucose metabolism mainly in the basal ganglia, the abnormalities in regional cerebral blood flow-activation studies (rCBF-activation studies) as measured with [15O]-H_2O are mainly cortically localized. [15O]-H_2O PET is often used in task-related studies on WC patients. Due to the short half-life of [15O] (2 min), repeated studies can be performed in a short time period. rCBF-activation PET is essentially the prelude of functional MRI (fMRI) and can still be used in research especially in patients in whom movement artifacts are a problem, for example, dystonia patients (Mishina 2008).

One study showed impaired activation of the primary motor cortex (PMC) and greater activation in frontal and parietal association areas in WC patients compared to controls while writing. BTX treatment failed to normalize the impaired activation of primary motor cortex, but did enhance activation of parietal cortex and accessory motor areas (Ceballos-Baumann et al. 1997). Patients with WC also showed reduced rCBF-activation in sensorimotor and premotor structures in different tasks compared to controls. Certain regions were significantly abnormal for specific tasks. Patients showed significantly less rCBF-activation in the contralateral versus ipsilateral primary sensorimotor cortex, during sustained flexion or extension of the wrist. There was a significant decrease in rCBF-activation in the left premotor cortex with writing, but there were no differences during tapping (Ibanez et al. 1999). A significant increase was found in rCBF-activation of the primary sensory cortex and decrease in rCBF-activation of the supplementary motor area (SMA) in patients with WC during writing and tapping compared to controls. Increased activation of the primary sensory cortex found in this study might reflect more intense processing of the sensory information or possibly expanded cortical representation of the hand area. The investigators also found increased activation of the right cerebellum of patients with WC compared to controls (Lerner et al. 2004). In patients with CD using a sensory trick, a significant decrease in motor cortical activation contralateral to the side toward which the head tends to rotate was found. This modulation includes the SMA (anterior part), part of the precentral gyrus, and the primary

sensorimotor cortex (SMC). In addition, the sensory trick leads to an increased activation of the parietal cortex ipsilateral to the direction of dystonic head rotation and bilateral occipital cortex (Naumann et al. 2000). A study of patients with facial dystonia (blepharospasm and oromandibular dystonia) showed a significantly reduced primary sensorimotor area (PSA) activation response to vibration of the lower face in patients with facial dystonia compared to healthy controls. The peak activations the authors observed in this study were centered in the precentral gyrus, adjacent to the central sulcus, consistent with the primary motor cortex (Feiwell et al. 1999). The only study using [15O]-butanol in patients with WC found increased blood flow in the contralateral thalamus and primary sensorimotor and premotor cortical areas, though also in the ipsilateral cerebellum as the patients with WC invoked progressively greater dysfunction by a longer duration of writing (Odergren et al. 1998). Concluding, abnormalities in rCBF-activation were less consistent than those in glucose metabolism. The most consistent findings included a decreased rCBF-activation in the PMC, SMC, SMA, and PSA and an increase in rCBF-activation in frontal and parietal association areas.

29.3.3 Dopamine Receptor Imaging with PET and SPECT

Two PET studies looked at $D_{2/3}$ receptor (D2/3R) availability in patients with focal dystonia. Leenders and coworkers found no difference in striatal [11C]-*N*-methylspiperone (NMSP) binding to D2-like receptors in patients with mainly CD when compared to healthy controls. A trend was observed regarding the side to side differences: specific binding of the tracer tended to be higher in the striatum contralateral to the side to which the head was turning to (Leenders et al. 1993). Another study showed decreased [18F]-spiperone (SP; another D2-like receptor tracer) binding in the putamen of patients with hand and facial dystonia. There was no significant difference between patients with hand and facial dystonia (Perlmutter et al. 1997).

In patients with CD, the average specific striatal binding to D2/3Rs, measured with [123I]-iodobenzamide ([123I]-IBZM) SPECT, was not significantly different from a group of healthy controls. However, patients exhibited a more asymmetric striatal binding compared to controls and 50% of the patient group did show a higher receptor binding in the striatum contralateral to the direction of head rotation. The difference in binding was statistically significant for this patient group (Hierholzer et al. 1994). This is in accordance with the increased dopamine receptor binding in the contralateral striatum found in the PET study in patients with CD mentioned above and has also been found in other SPECT studies (Leenders et al. 1993). For example, a tendency for a reduced iodobenzamide (IBZM) binding in the dorsal portion and an increase in the ventral parts of the striatum contralateral to the side of head rotation was found by Becker et al. (1997) in CD patients, but these results did not reach statistical significance, probably because of small study size (n = 10). The low IBZM binding contralateral to the side of head deviation may indicate a reduced postsynaptic D2/3R density within the lentiform nucleus. These

findings may point toward the medial lentiform nucleus or pallidothalamic pathway as the site of pathology in CD (Becker et al. 1997). Another study evaluated both the pre- and postsynaptic dopaminergic system in patients with CD, using [123I]-epidepride (a tracer for D2/3R) and [123I]-β-CIT (a tracer for the presynaptic dopamine transporter, DAT). Striatal D2/3R binding was bilaterally significantly reduced in patients compared to controls, but there was no difference in striatal DAT binding (Naumann et al. 1998). A similar design has been used in a more recent study using [123I]-IBZM and [123I]-FP-CIT (DAT tracer) in 27 patients with CD and 15 controls. This study found no difference in striatal DAT binding overall and only a trend toward lower striatal IBZM binding. However, both striatal DAT and D2/3R binding correlated significantly with depressive symptoms, which are common in CD. Both striatal DAT and D2/3R binding were significantly lower in depressed CD patients compared to nondepressed CD patients (Zoons et al. 2017a). Previous dopamine imaging studies in patients with CD and other forms of focal dystonia did not correct for depressive symptoms, which could have caused the difference in results.

In a study evaluating patients with WC, the striatal D2/3R binding was bilaterally decreased in patients compared to controls (Horstink et al. 1997). Another SPECT study evaluated patients with WC pre- and post-biofeedback-based sensorimotor training with [123I]-IBZM SPECT and also found decreased striatal binding. The training made patients more confident to write with a relaxed limb, writing improved, and striatal D2R-binding restored to nearly normal levels (Berger et al. 2007).

In summary, the findings in PET and SPECT studies implicate a role for the striatal dopaminergic system and the basal ganglia in the pathophysiology of focal dystonia. However, it can be debated whether dopamine plays a more important role in the pathophysiology of motor or non-motor symptoms in patients with focal dystonia.

29.3.4 Receptor Imaging of Other Neurotransmitter Systems with PET and SPECT

Recently, other neurotransmitter systems than the dopamine systems have received more attention. One study evaluated the integrity of cholinergic nerve terminals in patients with CD using [123I]-iodobenzavesamicol ([123I]-IBVM), a SPECT tracer that binds to the vesicular acetylcholine transporter (VAChT). They found a reduced IBVM binding in the putamen as well as in the whole striatum in patients with CD compared to controls (Albin et al. 2003).

One PET and one SPECT study have evaluated the presynaptic serotonin transporter (SERT) in patients with CD. In the SPECT study, the nonselective tracer [123I], FP-CIT (this tracer binds predominantly to the DAT in the striatum, and to the SERT in extrastriatal brain areas; Booij et al. 2007) was used and consequently only SERT binding in the diencephalon/midbrain area could be evaluated in patients with CD. A clear trend toward lower SERT binding in CD patients with psychiatric symptoms (mainly depression and anxiety) was found compared to controls.

Furthermore, in CD patients with head jerks or tremor, there was a significant positive correlation between extrastriatal SERT binding and striatal DAT binding that was absent in CD patients without head jerks or tremor (Zoons et al. 2017b). In the PET study, the selective SERT tracer [11C]-DASB was used that allowed a more extensive evaluation of SERT binding throughout the brain and more detailed imaging of small brain regions, which showed a completely different picture. No significant difference was found in SERT binding between CD patients and controls before or after correction for psychiatric symptoms. However, higher SERT binding in the dorsal raphe nucleus was statistically significantly correlated with motor symptom severity and to a lesser extent also to pain and sleep disturbances. There was also a significant relationship between SERT binding in the medial raphe nucleus and fatigue as well as a significant relationship between SERT binding in the caudate nucleus and sleep disturbances (Smit et al. 2018).

In two molecular imaging studies in patients with focal dystonia, the GABA system has been investigated. In a study in patients with CD, using the PET tracer [11C]-flumazenil (FMZ), increased $GABA_A$ availability was found in the right precentral gyrus and in the left parahippocampal gyrus. Furthermore, the side of head turning correlated to a specific pattern in $GABA_A$ availability in several motor regions. Disease severity positively correlated to $GABA_A$ availability in the cerebellar hemispheres and disease duration correlated negatively to several brain regions including cerebellum, thalamus, and basal ganglia (Berman et al. 2018). In a study in patients with focal hand dystonia using both [11C]-flumazenil and [15O]-H2O to measure perfusion, different results were found. In this study, a decreased GABA availability was found in the right cerebellum and left sensorimotor cortex. Increased GABA availability was found in the inferior prefrontal cortex, which also showed an increase in perfusion. These findings correlated negatively to disease duration (Gallea et al. 2018). Both PET studies hypothesize that the areas that show reduced GABA availability are a result of loss of inhibition.

Several studies have implicated a role for the acetylcholine, serotonin, and GABA systems. However, the number of studies is limited and the results vary too much to draw definitive conclusions about the precise role of these neurotransmitter systems.

29.4 Inherited Generalized Dystonia

The discovery of the DYT-TOR1A and DYT-THAP1 genes gave the opportunity to perform imaging studies in both manifesting gene carriers and non-manifesting gene carriers. It is believed that abnormalities found in non-manifesting gene carriers are related to genotype, whereas abnormalities found in patients but not in non-manifesting gene carriers are consistent with phenotype and are either caused by the dystonia or have been the trigger that caused dystonia. On the other hand, abnormalities that have only been found in non-manifesting gene carriers and not in patients or controls could be a physical protection system (Carbon et al. 2004a).

29.4.1 Glucose Metabolism and Regional Cerebral Blood Flow

Differences in glucose metabolism have been found between patients with DYT-TOR1A, DYT-THAP1, and controls. Both the DYT-TOR1A and the DYT-THAP1 patients showed a bilateral increase in glucose metabolism in the superior frontal gyrus, including the pre-SMA, precuneus, and the inferior parietal cortex compared to controls. This increase is a similarity between DYT-TOR1A and DYT-THAP1, but overall there are more differences between the two groups. When comparing DYT-TOR1A carriers, both manifesting and non-manifesting, to controls, there is an increased glucose metabolism in the putamen. In DYT-THAP1 carriers, there is a decreased glucose metabolism in the putamen compared to controls. This decrease is more pronounced in DYT-THAP1 patients than in non-manifesting carriers. Another difference between DYT-TOR1A and DYT-THAP1 is the activation of the cerebellum. In DYT-TOR1A carriers, there is an increased cerebellar glucose metabolism compared to controls; however, the metabolism in the cerebellum of DYT-THAP1 carriers is normal. These differences also become apparent when directly comparing DYT-TOR1A and DYT-THAP1 carriers. DYT-TOR1A carriers have a bilateral increased metabolism in the inferior cerebellum and putamen compared to DYT-THAP1 carriers. DYT-THAP1 carriers have an increased metabolism in the anterior cingulate cortex bilaterally including the subgenual region, the ventral prefrontal cortex, and the middle and superior temporal gyri compared to DYT-TOR1A carriers. Thus far, it is unclear why these patients have different activation patterns in the brain, while they have overlapping symptomatology (Carbon et al. 2004b). In an earlier FDG-PET study, there was no difference in global and regional metabolism between patients with idiopathic torsion dystonia with mainly right-sided symptoms (DYT-TOR1A phenotype) and controls. However, a brain network was identified consisting of increased metabolic activity in the lateral frontal and paracentral cortices, associated with relative covariate hypermetabolism of the contralateral lentiform nucleus, pons, and midbrain. The presence of this network was associated with severity of dystonia. These findings suggest that dystonia is a network disorder (Eidelberg et al. 1995).

In another PET study, rCBF-activation in patients with generalized torsion dystonia (mostly DYT-TOR1A) was compared to that of controls during rest and during a joystick task with their right hand. There was little or no dystonia during task execution. There were no differences in rCBF-activation during rest, but during right-hand movements patients showed more rCBF-activation in the left premotor area, SMA, anterior cingulate cortex, and left dorsolateral prefrontal cortex (DLPFC) compared to controls. Also, some subcortical areas were more active during the joystick task. There was an increase in rCBF-activation in cerebellum and putamen in patients compared to controls. There was a decrease in rCBF-activation in the sensorimotor cortex contralateral to the hand that was executing the task in patients compared to controls (Playford et al. 1998). The overactivation of the DLPFC has been replicated in patients with generalized dystonia and globus pallidus interna (GPi) DBS when they were OFF stimulation. In these patients, other

areas that were overactivated were the gyrus frontalis medialis, superior frontal gyrus, fronto-orbital cortex, and thalamus. Turning the DBS stimulators ON reduced the activation in these areas, as well as in the putamen, but not to the level of controls (Detante et al. 2004).

Most abnormalities that have been found in patients with DYT-TOR1A dystonia have also been found in non-manifesting DYT-TOR1A carriers. In non-manifesting DYT-TOR1A carriers, there was reduced rCBF-activation during a sequence learning task bilateral in DLPFC, in the left dorsal premotor cortex, left ventral prefrontal cortex, and lateral cerebellum. DYT-TOR1A carriers deactivated their left cingulate cortex and activated the right inferotemporal areas during the task. This was opposite to the activation pattern in controls. In controls, there was activation of the left cingulate cortex and deactivation of the right inferotemporal areas (Carbon et al. 2011, 2008; Ghilardi et al. 2003). During a motor task with the right hand, non-manifesting DYT-TOR1A carriers showed increased activation of the left premotor cortex and right SMA and decreased activation of the posterior medial cerebellum compared to controls (Carbon et al. 2011, 2008; Ghilardi et al. 2003). As with FDG-PET, rCBF-activation PET has also been used to assess brain networks in generalized dystonia. A motor-related activation pattern was identified both in controls and DYT-TOR1A gene carriers consisting of covarying neural activity in the sensorimotor cortex, dorsal premotor cortex, SMA, and cerebellum. This network was hyperactive in manifesting DYT-TOR1A gene carriers compared to controls during movement, but not in asymptomatic gene carriers. In rest, there was increased activation of this network both in manifesting and non-manifesting DYT-TOR1A gene carriers compared to controls with the non-manifesting gene carriers showing activation levels between those of the patients and controls (Carbon et al. 2010).

In summary, glucose metabolism differs between patients with DYT-TOR1A and DYT-THAP1 dystonia, with increased metabolism in putamen and cerebellum in DYT-TOR1A dystonia and decreased metabolism in putamen and normal cerebellar metabolism in DYT-THAP1 dystonia. Large numbers of brain areas show abnormal rCBF-activation in patients with DYT-TOR1A, but the significance of these findings is uncertain. Both FDG-PET and rCBF-activation studies have indicated that DYT-TOR1A dystonia is likely to be a network disorder.

29.4.2 Receptor Imaging with PET

Different neurotransmitter systems have been imaged with PET in patients with inherited generalized dystonia. With [11C]-raclopride (RAC; a D2/3 receptor tracer), both manifesting and non-manifesting DYT-TOR1A and DYT-THAP1 carriers have been compared to healthy controls. Both DYT-TOR1A and DYT-THAP1 carriers had reduced RAC binding in the caudate nucleus, putamen, and right ventrolateral thalamus compared to controls (Asanuma et al. 2005; Carbon et al. 2009). In DYT-THAP1 carriers, RAC binding was more reduced than in DYT-TOR1A carriers. This finding combined with the abnormalities in glucose metabolism may indicate that DYT-THAP1 dystonia is associated with striatal receptor loss, while

DYT-TOR1A dystonia is associated with high levels of endogenous dopamine. Thus far, there is no clear evidence for this hypothesis (Carbon and Eidelberg 2009). Although the hypothesis was that RAC binding in non-manifesting carriers was between that of patients and controls, there were no differences in RAC binding between manifesting and non-manifesting carriers in either genotype (Asanuma et al. 2005; Carbon et al. 2009).

Besides dopamine, other neurotransmitters have been studied including GABA, since one hypothesis is that dystonia is a condition of disturbed inhibition. Patients with generalized dystonia (DYT-TOR1A carriers and sporadic cases) showed reduced binding of [11C]-flumazenil (FMZ), a selective $GABA_A$ receptor PET ligand, bilateral in the primary motor and premotor cortex compared to controls. FMZ binding was also reduced in the primary and secondary somatosensory cortex, posterior insula, and in the motor component of the left anterior cingulate gyrus of patients with generalized dystonia compared to controls (Garibotto et al. 2011).

The opioid system has also been investigated in patients with DYT-TOR1A dystonia with [11C]-diprenorphine and PET, but no differences were found cortically or subcortically in DYT-TOR1A patients compared to controls (Whone et al. 2004).

In summary, dopamine is likely to play a role in the pathophysiology of both DYT-TOR1A and DYT-THAP1 dystonia, as GABA in DYT-TOR1A dystonia.

29.5 Dopamine-Responsive Dystonia

Because of the extraordinary treatment effect of levodopa on DRD, molecular imaging studies have focused on dopaminergic neurotransmission.

One of the most consistent findings in DRD is an increased tracer binding to D2/3R in caudate nucleus and putamen measured with RAC (Kishore et al. 1998; Kunig et al. 1998; Rinne et al. 2004). This could be consistent with reduced endogenous dopamine or altered receptor characteristics due to chronic dopamine depletion (Kunig et al. 1998). Increased RAC binding has also been found in asymptomatic DYT-GCH1 carriers and is therefore probably a genotypic and not a phenotypic feature (Kishore et al. 1998). There are no abnormalities in tracer binding to the dopamine transporter (DAT) or dopamine D1 receptors between patients with DRD and controls (Rinne et al. 2004). However, one study using SPECT and the DAT tracer [99mTc]-TRODAT found that striatal uptake correlated to clinical heterogeneity. More specifically, in one family the family members with a predominant parkinsonian phenotype had reduced uptake compared to the family members with a predominant dystonia phenotype (Lin et al. 2018). Abnormalities have been found in [11C]-dihydrotetrabenazine (DTBZ) binding in DRD patients. DTBZ is a tracer that binds to the vesicular monoamine transporter type 2 (VMAT2). In the striatum, VMAT2 is believed to mainly transport dopamine. Patients with DRD showed an increased DTBZ binding compared to controls. This could have been caused by reduced competition because of low concentrations of intravesicular dopamine or by upregulation of VMAT2 (De La Fuente-Fernandez et al. 2003). Finally, one report on a case with DRD and a

mutation in the SRG gene also showed no loss of striatal DAT and D2/3R (Abeling et al. 2006).

As expected from the levodopa response, dopamine plays an important role in the pathophysiology of DRD. This is characterized by increased tracer binding to D2R and VMAT2 and normal tracer binding to DAT and D1R.

29.6 Myoclonus-Dystonia

Imaging results in myoclonus-dystonia (MD) only consist of two SPECT studies with [123I]-iodobenzamide (IBZM), a selective D2/3R SPECT tracer. Both MD patients and asymptomatic DYT-SCGE carriers show reduced IBZM binding compared to controls. This is consistent with the theory that a high level of endogenous dopamine causes downregulation of D2 receptors and leads to more occupied receptors, limiting IBZM binding potential (Beukers et al. 2009). After globus pallidus interna (GPi) DBS, IBZM binding in MD patients remains stable over time, whereas in patients who did not receive DBS, IBZM binding decreased further over time. This may mean that DBS in the GPi stabilizes the dopaminergic system in these patients (Beukers et al. 2012).

29.7 Rapid-Onset Dystonia-Parkinsonism

Because of the relation between dystonia and parkinsonism in this rare form of combined dystonia, most studies evaluated the dopamine system, more specifically the DAT, and compared the results to normal controls and patients with idiopathic Parkinson's disease. Tracer binding to DAT in three reports in a total of five patients yielded different results. One study in three patients showed a slight increase in tracer binding to striatal DAT (Brashear et al. 1999), while two other case reports showed normal DAT binding (Svetel et al. 2010) and a slight reduction in DAT binding (Zanotti-Fregonara et al. 2008), respectively. A perfusion SPECT scan in one patient showed no abnormalities (Zanotti-Fregonara et al. 2008).

Overall, gross abnormalities in dopaminergic neurotransmission are unlikely in RDP.

29.8 Paroxysmal Dystonia

In PKD, interictal perfusion SPECT showed regional hypoperfusion of the basal ganglia and the thalamus (Tsai et al. 2005). In PNKD, no abnormalities were found in VMAT2 binding in the striatum (Bohnen et al. 1999). Patients with exercise-induced dystonia showed reduced perfusion to the frontal cortex and basal ganglia and increased perfusion to the cerebellum during an attack using [99mTc]-ethyl cysteinate dimer (ECD) and SPECT (Kluge et al. 1998).

29.9 Conclusion

PET and SPECT studies have been performed in different forms of dystonia. Surprisingly, found abnormalities are quite similar in patients with idiopathic focal dystonia and DYT-TOR1A inherited generalized dystonia. Both focal and DYT-TOR1A dystonia patients show increased glucose metabolism in the basal ganglia, the cerebellum, and premotor structures. The areas in which rCBF-activation is abnormal are also comparable in focal and DYT-TOR1A dystonia, with increased rCBF-activation in premotor structures, frontal areas including DLPFC and cerebellum, and decreased activation in sensorimotor cortex. The found abnormalities indicate that dystonia is a circuit disorder and that the underlying cause lies somewhere in the cortico-striato-thalamo-cortical loop. The dopamine system plays an important role in both focal and DYT-TOR1A dystonia, with decreased D2R binding in the striatum pointing toward a hyperdopaminergic system. The precise role of other neurotransmitter systems, such as acetylcholine, serotonin, and GABA, remains to be determined.

DYT-THAP1 dystonia seems to be a different condition, since the reported abnormalities are different from other forms of dystonia. Striking are the decreased rCBF-activation in the putamen and normal rCBF-activation in the cerebellum, in contrast to increased rCBF-activation in the putamen and cerebellum of patients with DYT-TOR1A dystonia. The only similarity between DYT-THAP1 dystonia and other forms of dystonia is the decreased D2/3R binding. Thus far, it is still unclear what causes the differences between DYT-THAP1 dystonia and other forms of dystonia.

D2/3R binding is also decreased in MD, but is increased in DRD. Patients with DRD have a problem with the synthesis of dopamine and are therefore hypodopaminergic. The studies in different forms of paroxysmal dystonia are too limited and diverse to draw any definite conclusions.

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