Milestones in Dystonia

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ABSTRACT: The last 25 years have seen remarkable advances in our understanding of the genetic etiologies of dystonia, new approaches into dissecting underlying pathophysiology, and independent progress in identifying effective treatments. In this review we highlight some of these advances, especially the genetic findings that have taken us from phenomenological to molecular-based diagnoses. Twenty DYT loci have been designated and 10 genes identified, all based on linkage analyses in families. Hand in hand with these genetic findings, neurophysiological and imaging techniques have been employed that have helped illuminate the similarities and differences among the various etiological dystonia subtypes. This knowledge is just beginning to yield new approaches to treatment including those based on DYT1 animal models. Despite the lag in identifying genetically based therapies, effective treatments, including impressive benefits from deep brain stimulation and botulinum toxin chemodenervation, have marked the last 25 years. The challenge ahead includes continued advancement into understanding dystonia’s many underlying causes and associated pathology and using this knowledge to advance treatment including preventing genetic disease expression.

The last 25 years have seen remarkable advances in our understanding of the genetic etiologies of dystonia, new approaches into dissecting underlying pathophysiology, and independent progress in identifying effective treatments. These advances take advantage of the many new techniques that have revolutionized medical scientific research. They also build on a critical base of clinical and pathological studies from prior decades, particularly the rich observations and classification schema proposed by David Marsden and Stanley Fahn through the 1970s and '80s. Twenty-five years ago, the Second International Dystonia Symposium was held in Harriman, New York. That fully international 3-day event allowed for state-of-knowledge presentations and lively discussion meant to generate ideas on pathophysiology, treatment, and future study. The content of that meeting is summarized in volume 50 of Advances of Neurology, a long book of almost 700 pages.1 In that volume are the intimations and foundations of the advances to come, including pilot family and genetic linkage studies, neurophysiological analyses, PET and MRI reports, and discussions of botulinum toxin for focal dystonias. This review will briefly discuss the advances made since that meeting in defining genetic etiologies and the ramifications of gene identification both in terms of clinical applications and basic investigation, neurophysiological and imaging studies that have helped tease apart underlying brain mechanisms in dystonia, and progress in treatment. Despite these advances, many questions remain. Indeed the progress of the last 25 years has served to raise many new questions and opened up new avenues of research. These will be mentioned as well; hopefully, they will help to

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engender interest and novel approaches, especially among those newly entering this most exciting field.

**Genetics**

Coupling the major advances in human genetics including linkage mapping of Mendelian traits, the advent of polymerase chain reaction for amplification of specific DNA regions, and the completion of the human genome sequence with careful phenotypic studies in families, 20 monogenic dystonia loci have been defined in the last 25 years. The DYT loci have been designated historically based on phenotype or chromosomal location and thus represent a clinically heterogeneous group of disorders including primary dystonia where dystonia is the only phenotype (DYT1, DYT2, DYT4, DYT6, DYT7, DYT13, DYT17, and DYT21), dystonia plus loci where other phenotypes in addition to dystonia such as parkinsonism or myoclonus are seen (DYT3, DYT5/14, DYT11, DYT12, DYT15, and DYT16), and paroxysmal forms of dystonia/dyskinesia (DYT8, DYT9, DYT10, DYT18, DYT19, and DYT20). Among these loci, 10 genes have been identified, all using the genetic technique of linkage analysis in families. See Table 1 for dystonia genetic highlights.

**Primary Torsion Dystonia (PTD)**

The phenotypic spectrum associated with PTD is broad, ranging from early-onset generalized to adult-onset focal. The prevalence of PTD has been estimated at between 330 and 15 per million, with focal cases constituting the majority. However, these studies are likely to underestimate the true frequency of PTD because a significant proportion of disease is not diagnosed. Among these loci, 10 genes have been identified, all using the genetic technique of linkage analysis in families. See Table 1 for dystonia genetic highlights.
for later-onset forms, but only 2 genes, DYT1 and DYT6, have been identified.

**Early-Onset PTD**

Two features of early-onset PTD were recognized early on: its occurrence was familial, and it was more frequent among Ashkenazi Jews (AJs). However, the mode of inheritance was thought to be dominant for non-Jewish (NJ) families and recessive in AJ families. Studies in the United States, Israel, and Britain showed that the disease was inherited as an autosomal dominant trait with reduced penetrance in both the AJ and NJ populations.

**DYT1.** Linkage analysis in a large NJ family with early-onset disease identified the first locus for early-onset PTD, DYT1, on chromosome 9q34, which was subsequently confirmed in other AJ and NJ families. Strong linkage disequilibrium was observed between the disease gene and a particular haplotype in the AJ population, indicative of a founder mutation. The haplotype was used to estimate that the mutation was introduced into the AJ population about 350 years ago and probably originated in Lithuania or Byelorussia and also to define the disease gene within a 150-kb region. Screening of the genes in this region resulted in the identification of a 3-bp deletion in the TOR1A gene causing the removal of a single in-frame amino acid in the encoded protein, torsinA, in both AJ and NJ cases. The deletion mutation in TOR1A has been found in patients with diverse ethnic origins and accounts for about 80% of early-onset PTD in the AJ population because of the founder mutation, suggesting a significant proportion of early-onset NJ PTD may be a result of other genes. Two other missense mutations in the TOR1A gene have been described, each in a single case. A third missense variant, D216H, found to have functional significance in cell culture studies, was subsequently shown to be associated with reduced penetrance and functionally confirmed by imaging studies that correlated altered metabolism in specific brain regions in DYT1-nonmanifesting carriers with the D216H SNP.

Although the clinical phenotype associated with DYT1 dystonia can vary from severe dystonic storm to mild writer’s cramp, a typical phenotype has been described across ethnic groups characterized by early (mean age at onset, 13 years; with the majority before 26 years) limb (arm or leg is affected first in 90% of cases) onset, progressing to generalized/multifocal (65%) involvement, with spread to cranial muscles less common (15%–20%). Genetic testing for the deletion mutation is readily available and relatively inexpensive and should be considered for any non-dopareresponsive case with onset before age 26 years.

TorsinA is a member of the AAA+ superfamily (ATPases associated with a variety of cellular activities) of molecular chaperones. It is widely distributed in the brain but restricted to neurons. Within the cell, most of the wild-type protein is in the endoplasmic reticulum (ER), whereas the mutant protein is more often associated with the nuclear envelope (NE). TorsinA disrupts ER/NE and cytoskeletal dynamics, which may be important for neurite extension during brain development and has also been implicated in synaptic vesicle recycling, including impaired dopamine release and alter tyrosine hydroxylase activity. Exactly how torsinA function is compromised to produce disease is unknown, but both animal and cellular studies indicate that mutant torsinA results in a loss of function.

**DYT6.** This locus was initially mapped to the centromere of chromosome 8 in 3 Amish–Mennonite families that shared a haplotype and were related via a common ancestor. In these families, the disease showed autosomal dominant inheritance with a penetrance of about 60%. Using the Amish–Mennonite families, a complex insertion/deletion mutation that results in a truncated protein was identified in the THAP1 (thanatos-associated protein domain-containing apoptosis-associated protein 1) gene. Unlike the TOR1A gene, where a single mutation accounts for most cases, more than 45 heterozygous mutations have been reported in THAP1, mainly in patients of European ancestry, but also in Chinese and Brazilian cases. Interestingly, 2 homozygous missense mutations have been reported. In addition, heterozygous synonymous amino acid substitutions as well as variants in the 5' untranslated region and within introns have been found in PTD cases but are of unknown significance. Finally, because almost every individual/family has a unique mutation, molecular diagnosis requires sequencing of the 3 exons of the THAP1 gene.

Comparing clinical symptoms in mutation carriers, a typical DYT6 phenotype emerges characterized by early onset (mean, 16 years; range, 5–62 years); onset most often in an arm (50%), followed by cranial muscles (about 25%) or the neck (about 25%) but in contrast with DYT1, rarely the leg (4%); with spread to a generalized or multifocal distribution in more than half and prominent speech involvement in more than two thirds of cases. However, about 10% of cases have only focal dystonia and in screens of adult-onset focal cases, low frequency (1%) of THAP1 mutations has been reported.

THAP1 is a transcription factor with a conserved DNA binding domain at its N-terminus, and a coiled-coil domain and nuclear localization signal (NLS) at its C-terminus. THAP1 function in the brain is
unknown, but it regulates endothelial cell proliferation by pRb/E2F cell-cycle target genes, is a proapoptotic factor, and through its C-terminus, interacts with prostate apoptosis response 4 protein (Par-4), an effector of cell death linked to prostate cancer and neurodegenerative diseases, including Parkinson’s diseases. Recently, Thap1 protein has been shown to bind to the TOR1A promoter and repress its expression. DNA binding is disrupted and repression decreased by pathogenic THAP1 mutations. These data link the molecular pathways underlying DYT1 and DYT6 dystonia and highlights transcriptional dysregulation as a cause of PTD. In addition, THAP1 has been shown to be physically linked to OGT, a gene that is next to TAF1 on Xq13.1 in the DYT3 critical region (see below).

At present, there are no genotype:phenotype correlations noted in THAP1. Most of the mutations occur in the DNA binding domain or around the NLS and are thought to eliminate the DNA binding function of the protein. A few mutations occur in the coiled-coil domain, a region important for dimerization that could indirectly disrupt DNA binding if, as proposed, THAP1 binds DNA as a homodimer.

DYT2 and DYT4. DYT2 and DYT4 are loci that have been assigned based on phenotype alone with no chromosomal location or gene identified to date. DYT2 is an autosomal recessive form of PTD reported in consanguineous families of Spanish gypsy (1988), Sephardic Jewish, and Arab descent. All the cases have a similar phenotype to DYT1 dystonia, with early limb onset followed by rapid generalization. DYT4 is an autosomal dominant form of PTD reported in a single large Australian family with prominent whispering dysphonia that begins in the second decade in most family members (range, 13–37 years). The THAP1 gene was excluded as a cause in this family.

DYT13 and DYT17. These 2 loci are each described in a single family that was used to map their chromosomal positions. Both show adolescent onset, but DYT13 is inherited as a dominant disorder with reduced penetrance, whereas DYT17 is inherited as an autosomal recessive trait. DYT13 was mapped to chromosome 1p36 in an Italian family with mainly segmental dystonia, prominent craniocervical involvement, but less speech than in DYT6 dystonia. A consanguineous Lebanese family with 3 siblings was used to map DYT17 to chromosome 20. Onset was in the neck in all sibs but progressed to segmental dystonia in 2 and to generalized dystonia in the third and featured severe dysphonia and dysarthria. It is possible that some of the families currently designated as DYT2 could be linked to the DYT17 gene region.

Late-Onset PTD

Late-onset PTD is more complex genetically than early-onset PTD, and the role of genes in the etiology of the various adult clinical subtypes (torticollis, writer’s cramp, blepharospasm, and spasmodic dysphonia) is not fully elucidated. However, the forms are thought to be related complex diseases that share common susceptibility genes as well as additional individual genetic and environmental risk factors that occur in different combinations resulting in specific disease. Segregation analyses concluded that focal dystonia is inherited as an autosomal dominant trait but with very low penetrance (about 12%–15% compared with 30% for early onset), alternatively, penetrance may be higher in a subset, with the remainder nongenetic. Descriptions of several large families with highly penetrant autosomal dominant late-onset PTD are consistent with this latter idea and have resulted in the mapping of 2 genes for late-onset PTD: DYT7 and DYT21.

DYT7 and DYT21. DYT7 and DYT21 are both autosomal dominant disorders each described in a single pedigree. DYT7 was assigned to chromosome 18p in a family from northwestern Germany with 7 affected members, all with adult-onset cervical dystonia (mean, 43 years; range, 28–70 years), although some also had brachial and cranial involvement. Several phenotypically similar families were excluded from this region, suggesting the existence of other late-onset loci. A family with 16 affected members from northern Sweden was linked to a region on chromosome 2q14.3–q21.3 and designated as DYT21. The phenotype in this family is characterized by later onset (mean, 27 years; range, 13–50 years) and mainly generalized/multifocal PTD, with onset in the cranial/cervical muscles in most and the hands in about 25%.

Because the majority of late-onset PTD cases do not have many affected relatives, linkage mapping is not an option, and instead, association studies using cases and controls have been employed to find genetic risk factors in candidate genes. A polymorphism in the dopamine D5 receptor (DRD5) gene is associated with torticollis and blepharospasm in 3 studies but could not be replicated in 2 other studies. Contradictory findings have been reported for the functional V66M SNP in brain-derived neurotrophic factor (BDNF), with 1 group finding no association among cranial and cervical PTD patients and a second team finding a twofold increase in the V66M heterozygotes among a small sample of cervical cases. Studies examining the involvement of the THAP1 and TOR1A genes in late-onset dystonia have also been performed. Several of these have suggested that variants in THAP1 might contribute to the risk of focal dystonia, but the associated variants were not consistent. Associations
with variations in TOR1A are also confusing. The D216H SNP has been associated with increased risk in patients with a positive family history, whereas SNPs in the 3’ untranslated region have been associated with risk in some sporadic cases, risk of spread of blepharospasm in other cohorts, and protection from risk, particularly in sporadic cervical cases. Finally, 2 studies failed to show any association with SNPs in the TOR1A gene.

The contradictory data reported for these candidate genes is a result of several factors including clinical heterogeneity (different subtypes of PTD, with and without family history, etc.), limited sample size, small number of SNPs tested, and different ethnic groups. To overcome these issues, the use of new genetic techniques including genome-wide association studies (GWASs) and next-generation exome or whole-genome sequencing approaches is critical for identifying the genetic risk factors contributing to late-onset PTD. However, especially for GWASs, a large number of uniformly phenotyped late-onset cases will be needed and can only be achieved through a worldwide collaborative effort.

**Dystonia Plus**

Within the dystonia plus classification there are 4 forms that include parkinsonism as part of their phenotype (DYT3, DYT5/14, DYT12, and DYT16), and 2 that have myoclonus in addition to dystonia (DYT11 and DYT15). Genes have been identified for all these forms except DYT15.

**DYT3**

DYT3 is the only form of dystonia that is inherited as an X-linked trait. The disease originated on the island of Panay in the Philippines due to a founder mutation and primarily affects males, although a few females have been reported with the disease. The DYT3 locus was mapped to Xq13.1 with further linkage and linkage disequilibrium analyses narrowing the locus to Xq13.1. Several disease-specific changes were identified in a 300-kb region including a 48-bp deletion in an exon of a novel transcript, 3 single base-pair changes in the TATA-binding protein-associated factor (TAF1) gene, and a retrotransposon insertion in an intron of TAF1. Although the region is complex and contains multiple transcripts, the retrotransposon insertion appears to reduce neuron-specific expression of TAF1 and the dopamine receptor D2 gene in the caudate nucleus, suggesting this gene plays a role in the disease. In addition, a physical association between the OGT gene, adjacent to TAF1 and within the 300-kb DYT3 multiple transcript region, and THAP1/DYT6 has been identified.

Disease onset of DYT3 dystonia typically occurs in the mid-thirties (range, 12–52 years), with complete penetrance by the end of the fifth decade. The symptoms start as focal dystonia in almost any part of the body and progress to multifocal or generalized dystonia within 5 years in most cases. Parkinsonism evolves later in the disease in about 50% of the patients and can become the predominant symptom. DYT3 dystonia is unique among the DYT loci in that neuronal degeneration has been noted on postmortem analysis. Neuronal loss and astrogliosis have been reported in the caudate and lateral putamen in 2 patients’ brains with dramatic depletion of striatonsomes and relative sparing of the matrix, suggesting that imbalance between the striosomal and matrix-based pathways could contribute to the neurologic symptoms.

**DYT5**

The disease that would eventually be designated as the DYT5 locus was initially described by Segawa in 1976 under the name hereditary progressive dystonia with marked diurnal fluctuation (HSP) and later by Nygaard and colleagues as dopa-responsive dystonia (DRD) because of the dramatic and sustained response to low-dose levodopa seen in patients. The disease is inherited as an autosomal dominant trait with reduced penetrance that appears to be sex dependent, with females expressing symptoms more frequently. In 3 DRD families, the gene was mapped to chromosome 14q13 and subsequently confirmed in an HSP family. At about the same time, the gene for GTP cyclohydrolase 1 (GCH1) was mapped into the DRD/HSP-linked region of chromosome 14. GTP cyclohydrolase 1 is the rate limiting enzyme in the synthesis of tetrahydrobiopterin, an essential cofactor for tyrosine hydroxylase, which, in turn, is needed to synthesize dopamine. This gene was immediately tested as a positional candidate and mutations identified in HSP patients. More than 100 mutations of all types (non-sense, missense, splicing, promoter region, and large genomic deletions) have been described in the GCH1 gene (for a complete listing, go to http://www.hb4.org), with most arising as new mutations. Comprehensive screening (including exon deletions) of the GCH1 gene identifies about 80% of mutations in “typical” DRD patients, and comprehensive molecular testing is available.

The typical phenotype associated with GCH1 mutations includes childhood (average, 6 years) limb-onset dystonia with worsening symptoms as the day progresses, improvement after sleep, and dramatic response to L-dopa therapy. Additional features can include arm and axial dystonia, hyperreflexia, and parkinsonism (bradykinesia, hypomimia, postural instability), and occasionally cranial muscles (upper
face, oromandibular, laryngeal) may be affected.\textsuperscript{141} With the identification of the disease gene, the clinical spectrum of DRD has expanded to include oromandibular dystonia.\textsuperscript{142} Spasticity with developmental delay mimicking cerebral palsy,\textsuperscript{143} scoliosis,\textsuperscript{144} psychiatric abnormalities,\textsuperscript{145} and generalized hypotonia with proximal weakness.\textsuperscript{146}

In a minority of cases, DRD can also be inherited as an autosomal recessive disorder with mutations in other enzymes involved in dopamine synthesis including tyrosine hydroxylase,\textsuperscript{147-150} 6-pyruvoyltetrahydropterin synthase,\textsuperscript{151} and sepiapterin reductase.\textsuperscript{159,152,153} Because these conditions include deficiencies of serotonin and norepinephrine as well as dopamine, the clinical manifestations are often more severe and can include mental retardation, oculogyria, hypotonia, severe bradykinesia, drooling, ptosis, and seizures. However, in 1 family a heterozygous mutation in sepiapterin reductase underlies a typical DRD phenotype.\textsuperscript{153}

**Formerly DYT14**

Genetic heterogeneity was suggested when a single Swiss family with autosomal dominant DRD was mapped to a distinct nearby region on chromosome 14q13 and designated DYT14.\textsuperscript{154} Subsequently, an exonic deletion was found in GCH1 and the mistaken linkage result explained by the finding that 1 of the affected members was actually a phenocopy.\textsuperscript{155} The DYT14 designation has been withdrawn by the human genome nomenclature committee.

**DYT12**

The DYT12 locus was mapped to chromosome 19q13 in 2 families\textsuperscript{156} and confirmed in 2 others.\textsuperscript{157,158} In these families, the disease is inherited as an autosomal dominant trait with reduced penetrance. Using positional cloning, 6 heterozygous missense mutations were identified in the Na\textsuperscript{+},K\textsuperscript{+}-ATPase alpha 3 subunit gene (ATP1A3), and all were shown to impair cell viability in cell culture experiments.\textsuperscript{159} Currently, a total of 10 novel mutations (8 missense mutations, a 3-bp in-frame deletion, and a 3-bp in-frame insertion) have been reported in 17 families, including 8 de novo cases.\textsuperscript{38,159-166} ATP1A3 encodes the catalytic subunit of the sodium pump that uses ATP hydrolysis to exchange Na\textsuperscript{+} and K\textsuperscript{+} across the cell membrane to maintain ionic gradients. Functional biochemical studies with several pathogenic mutations all showed reduced Na\textsuperscript{+} affinity, suggesting that defects in the handling of Na\textsuperscript{+} may be a general feature of the disease.\textsuperscript{164,167,168}

The disease phenotype was first described in 1993\textsuperscript{169} and designated rapid-onset dystonia–parkinsonism because of key clinical features including abrupt onset of dystonia, within hours to weeks, with signs of parkinsonism (bradykinesia and postural instability) usually triggered by physical or emotion stress (fever, child birth, running, alcohol binging). The dystonia typically follows a rostrocaudal gradient (face > arm > leg) with prominent bulbar involvement.\textsuperscript{160} The age of onset varies from 4 to 58 years but typically presents in the teens or early twenties. Patients with the typical phenotype can undergo commercially available genetic testing; however, because of the number of de novo mutations that have been identified, a positive family history is not a prerequisite. One family with a rapid-onset dystonia–parkinsonism (RDP)-like phenotype but with more cranio-cervical involvement is not linked to chromosome 19q and does not have a mutation in the ATP1A3 gene, thus implicating a second locus for RDP.\textsuperscript{170}

**DYT16**

An autosomal recessive form of dystonia-parkinsonism, DYT16, was assigned to chromosome 2q31 using homozygososity mapping in 2 consanguineous families and a sporadic case, all from Brazil. The same homozygous missense mutation (P222L) was identified in the protein kinase, interferon-inducible double-stranded RNA-dependent activator (PRKRA) gene in the 6 affected family members as well as in the 1 sporadic case.\textsuperscript{171} The phenotype in these patients is characterized by early (2–18 years) limb onset (6 of the 7 cases) with progression to generalized dystonia including prominent bulbar involvement with spasmodic dysphonia, dysarthria, and even dysphagia. Four of the affected members in the 2 families also have parkinsonism limited to bradykinesia. A heterozygous frameshift mutation leading to a protein truncation was identified in a sporadic German case with early-onset dystonia.\textsuperscript{172} Further screening of early-onset cases will be needed to determine the overall contribution of this gene to early-onset dystonia and to understand the significance of heterozygous mutations in this gene. The PRKRA gene is involved in cellular stress response, but exactly how this may lead to disease is unknown. Possible mechanisms of action were reviewed by Bragg et al (2011).\textsuperscript{173}

**DYT11**

The DYT11 locus was mapped to chromosome 7q21 in a large North American family with 10 affected members\textsuperscript{174} and subsequently confirmed and narrowed in several other myoclonus dystonia (M-D) families.\textsuperscript{175-177} Using classical positional cloning, 5 heterozygous mutations were identified in the epsilon sarcoglycan (SGCE) gene in 6 M-D families from Germany.\textsuperscript{178} Worldwide, more than 50 mutations of all types have been found in the SGCE gene in more than 100 probands (reviewed in Kinugawa et al, 2009\textsuperscript{179}). Genotype/phenotype studies have not shown any difference in phenotype associated with the different types of mutations in SGCE, which is
most likely because all the mutations are thought to result in loss of function of the protein. Most mutations are localized to the extracellular domain of the protein, suggesting functional importance. Several nonsense and small-deletion mutations have been reported independently and thus appear to be recurrent mutations. In addition, exonic deletion mutations and other larger deletions have also been reported. These latter deletions do correlate with phenotype, as they also remove other nearby genes and result in more complex manifestations including skeletal abnormalities, facial dysmorphism, developmental delay, or cavernous cerebral malformations. Finally, maternal uniparental disomy can also cause M-D because of imprinting (inactivation) of both maternal genes.

M-D linked to the DYT11 locus is inherited as an autosomal dominant trait with reduced penetrance related to maternal imprinting. Imprinting is an epigenetic phenomenon that results in the selective silencing of 1 of the 2 parental alleles, in the case of SGCE, by promoter methylation. Consequently, disease expression is dependent on the sex of the transmitting parent, with almost all individuals who inherit an SGCE mutation from their father showing symptoms. Imprinting of SGCE is supported by RNA expression studies that revealed expression of only the mutant allele in affected individuals and expression of the normal allele in unaffected mutation carriers. Maternal imprinting has also been reported for the mouse Sgce gene, whereas in heterozygous Sgce-knockout mice, exclusive expression of the paternal allele was found in mouse brains. However, up to 5% of M-D cases inherit their mutated allele from their mothers and presumably also express the wild-type allele from their fathers. The reason for reversal of the maternal imprint in these cases is not known.

SGCE is a member of a gene family that also includes alpha, beta, gamma, delta, and zeta sarcoglycans. Mutations in the genes encoding these other sarcoglycans, which are mainly expressed in muscle, cause autosomal recessive limb-girdle muscular dystrophies. The sarcoglycans encode transmembrane components of the dystrophin-glycoprotein complex that links the cytoskeleton to the extracellular matrix. SGCE is 68% homologous to alpha-sarcoglycan and can functionally replace it in skeletal muscle. It is widely expressed in embryonic and adult tissues including the brain and a brain-specific transcript results from an alternatively spliced message with a unique C-terminus. However, SGCE function in the brain is largely unknown. In the cell, the protein is located at the plasma membrane. Studies expressing pathogenic M-D missense mutations show impair trafficking of the mutant protein to the plasma membrane and degradation by the proteasome that is enhanced by an interaction with torsinA (the protein encoded by TOR1A/DYT1). M-D is characterized by a combination of brief lightning-like myoclonic jerks and dystonia that usually begins in childhood. Onset occurs earlier in girls than in boys regardless of mutation type. Myoclonus is usually the presenting symptom and most often affects the neck, trunk, and upper limbs, with legs affected less prominently. About two thirds of patients with M-D show dystonia, mostly cervical dystonia or writer’s cramp, which tends to remain mild. The myoclonic jerks typically show a dramatic response to alcohol in many patients. In addition, prominent psychiatric manifestations including depression, anxiety, panic attacks, and obsessive-compulsive disorder (OCD) have been reported, and in particular, OCD has been found in those not affected with motor signs suggesting it is related to the genetic defect. The proportion of M-D and clinically related phenotypes from SGCE mutations is debated and depends on the clinical criteria used to select subjects for screening as well as the screening method. Up to 50% of “typical” M-D cases will have a mutation in the SGCE gene; however, this percentage increases in familial cases with paternal inheritance. Therefore, these factors should be considered when deciding on which M-D patients to test.

**DYT15**

Although the SGCE gene appears to be a major locus for M-D, sporadic and familial cases without mutations in SGCE have been reported, suggesting genetic heterogeneity. One of these families, with autosomal dominant inheritance and reduced penetrance, was used to map a second locus for M-D to chromosome 18p. This Canadian family has 13 affected members, with average age at onset of 9.6 years (range, 7–15 years) and typical alcohol-responsive M-D. Fine-mapping studies in this family have refined the locus to a 3.2-Mb region; however, all the genes in this interval have been sequenced and no mutations identified.

**Paroxysmal Dystonia/Dyskinesia**

This is a heterogeneous group of disorders characterized by sudden transient attacks of involuntary movements. They are subdivided into kinesigenic (DYT10 and DYT19), nonkinesigenic (DYT8 and DYT20), and exercise-induced forms (DYT9 and DYT18). The genes for DYT8 and DYT18 have been identified.

**DYT8**

Paroxysmal nonkinesigenic dyskinesia (PNKD1) is inherited as an autosomal dominant trait with high penetrance. The DYT8 locus was localized to chromosome...
2q33–36 in 2 families, a 5-generation Italian family and a large Polish-American family; then subsequently, the region was narrowed in a third family. Two missense mutations (A7V and A9V) were identified in the myofibrillogenesis regulator (MR-1) gene. These 2 missense mutations have been found in 14 unrelated families on different haplotype backgrounds and appear to be mutation hot spots. A third missense mutation (A33P) was reported in this gene in a single family. The transcript is alternatively spliced, resulting in at least 3 isoforms, 1 of which is specifically expressed in the brain. The function of the MR-1 gene is unknown, but its sequence is closely related to hydroxyacylglutathione hydrolase, an enzyme known to detoxify methylglyoxal, which is produced as a by-product of oxidative stress and found in coffee and alcohol. Lee et al proposed that impaired function of MR-1 might block this pathway, resulting in the accumulation of methylglyoxal and explain how alcohol, stress, and caffeine might precipitate attacks. However, a recent study showed that several of the MR-1 isoforms are targeted to the mitochondria via an N-terminal mitochondrial targeting sequence (MTS) that is cleaved off the mature protein. All 3 PNKD-associated mutations are in the cleaved MTS peptide, suggesting a possible toxic gain-of-function mechanism.

PNKD is characterized by attacks of dystonia, chorea, ballismus, or athetosis, often provoked by alcohol or caffeine. The episodes last from minutes to hours, with a frequency from once per day to 2 per year. The age at onset is typically in childhood or adolescence but can be as late as 50 years. Comparison of MR-1 mutation–positive and –negative cases revealed that an earlier age at onset, precipitation of attacks with alcohol and caffeine but not exercise or fatigue, and lack of seizures distinguished the mutation–positive cases and that when these strict criteria were applied, the MR-1 patients were clinically similar to the original description by Mount and Reback (1940). Genetic testing for PNKD should be considered for patients who meet these strict criteria, with testing for the recurrent mutations done first. PNKD can be distinguished clinically from PKC (DYT10/19), in which attacks are shorter, more frequent, and triggered by sudden movement, and from PED (DYT9/18), which is precipitated by prolonged exercise.

**DYT9**

This locus was assigned to a 12-cM interval on chromosome 1p21–p13.3 in a large German family with 18 affected members and clear autosomal dominant inheritance. Age at onset ranged from 2 to 15 years, and symptoms included episodes of involuntary dystonia of the limbs, dysarthria, double vision, paroxysmal choreoathetosis, episodic ataxia, and dyskinesia. In addition, 5 members had constant spastic paraplegia. Episodes usually lasted approximately 20 minutes and occurred between twice a day and twice a year. Attacks are precipitated by physical exercise, emotional stress, fatigue, and alcohol. This disorder has been termed paroxysmal choreoathetosis/spasticity. Both the phenotype and the chromosomal location overlap with the DYT18 locus (see below), which has recently been identified and can now be tested in this family to determine if these are the same disorder.

**DYT10**

In 8 Japanese families showing autosomal dominant inheritance of paroxysmal kinesigenic dyskinesia (PKD), linkage analysis was used to map the DYT10 locus on chromosome 16p11.2–q12.1. This was confirmed in an African American family as well as in 4 new families, in which 157 genes within the critical region were sequenced, with no pathogenic mutations identified. The disease is characterized by short (seconds to minutes), frequent (up to 100 times per day) attacks of dystonic or choreiform movements precipitated by sudden unexpected movements. Age at onset is usually during childhood or adolescence, but symptoms can resolve in adulthood. A second locus for PKD, designated DYT19, maps to an overlapping region and thus may represent the same locus (see below). In addition, another PKD pedigree has been excluded from linkage to chromosome 16 and thus most likely represents a novel PKD locus.

**DYT18**

Paroxysmal exercise-induced dyskinesia (PED) shows an autosomal dominant inheritance pattern with slightly reduced penetrance. The locus was identified by candidate gene search in 1 case and by linkage analysis in a second. Based on several clinical clues including various CSF glucose parameters and the co-occurrence of hemolytic anemia with PED in 1 family, the SLC2A1 gene encoding glucose transporter 1 (GLUT1) was screened and a mutation identified in 3 families. Around the same time, linkage analysis in a 5-generation Belgian family with PED and epilepsy identified a region on chromosome 1p33–p31 that included the SLC2A1/GLUT1 gene. Mutations were identified in this and 3 other PED families. Mutations in SLC2A1 have also been found in sporadic cases of PED and in a family with dystonic tremor as the presenting feature. SLC2A1/GLUT1 is the main glucose transporter in the brain. PED is thought to be caused by reduced glucose transport into the brain, particularly when energy demand is high after prolonged exercise.

PED is characterized by exercise-induced attacks of dystonic, choreoathetotic, and ballistic movements affecting the exercised limbs that last from a few
minutes to an hour.\textsuperscript{234,235} The disease usually has its onset in childhood and can have other disease manifestations including epilepsy, migraine, developmental delay, and hemolytic anemia.\textsuperscript{230,231} The DYT9 critical region is in an overlapping interval of chromosome 1p, and the phenotype resembles that of DYT18; therefore, it is possible these are the same disease.

**DYT19**

DYT19 is the designation for the second locus for paroxysmal kinesigenic dyskinesia (PKD2). This locus was mapped to chromosome 16q13–q22.1 in an Indian family with 13 affected members.\textsuperscript{236} This region is in close proximity to the DYT10 locus and overlaps this locus in 1 family.\textsuperscript{227} The clinical features in this family mimic those of DYT10-associated PKD1, suggesting they may be the same locus; however, until a gene is found for either locus, this will remain uncertain. In the Indian family, the age at onset ranged from 7 to 13 years. Attacks could last up to 2 minutes, occurred with a frequency of 1–20 per day, and produced dystonic or choreic movements in response to sudden movements. Several affected members showed spontaneous remission by age 23.\textsuperscript{229}

**DYT20**

This locus designates a second form of paroxysmal nonkinesigenic dyskinesia (PNKD2), which was described in a single Canadian family with 10 affected members. Linkage analysis in this family assigned the locus to chromosome 2q31, just proximal to the DYT8/MR-1 gene.\textsuperscript{237} No mutations were detected in the MR-1 gene, and thus a new PNKD locus was designated. The clinical symptoms in this family are very similar to those described in the DYT8/MR-1 families. Detection of mutations in a different gene than MR-1 will be required to confirm the existence of this second form of PNKD.

**Genetics Summary**

The genes involved in monogenic forms of dystonia reflect the clinical heterogeneity of the dystonias. Although the genes identified to date are diverse and at present, the underlying functions of most of these genes and how they lead to dystonia remain elusive, their identification has fostered basic research (development of animal and cellular models) aimed at understanding the pathophysiology of dystonia.\textsuperscript{173,238,239} The recent discovery that Thap1 binds to the TOR1A promoter\textsuperscript{81,82} and the potential association of variants in TOR1A and THAP1 with susceptibility to focal/segmental PTD suggests that common pathways may be involved in dystonia, and thus novel therapeutics targeting these common pathways could be effective for the treatment of different forms of dystonia. The definition of genetic subtypes has also allowed clinical researchers to compare and contrast these subtypes to better understand the common and unique pathophysiology that should help direct therapies and define endophenotypes\textsuperscript{240,241} that can eventually be applied back to families with dystonia to help elucidate more genes. Finally, harnessing the new genetic technologies, including Chip-seq for genome-wide identification of transcription factor–binding sites (related to downstream targets of TAF1 and THAP1) and next-generation exomic and whole-genome sequencing, should accelerate gene discovery for dystonias that in turn should further elucidate the underlying pathways.

**Neurophysiology and Imaging**

Over the last 25 years important advances in our understanding of dystonia pathophysiology have come from work using neurophysiologic and imaging techniques; they have been applied to clinical and etiologic subtypes of dystonia, especially genetic PTD subtypes and focal dystonias. See Table 2 for highlights of dystonia physiology, imaging, and treatment.

**Neurophysiology**

Three interrelated neurophysiologic abnormalities have been identified: impaired inhibition including surround inhibition, increased plasticity, and sensory processing dysfunction.

Loss of inhibition was an early finding; both loss of reciprocal inhibition in patients with arm dystonia\textsuperscript{242,243} and abnormalities in blink reflex recovery in blepharospasm\textsuperscript{244} were discovered more than 20 years ago. These findings of inhibitory dysfunction were thought to help explain the cocontraction of antagonists that marks action-induced dystonia. Both these abnormalities were thought to be a result of dysfunction in supraspinal control, particularly corticostriato-thalamocortical circuitry and the ability to select a wanted movement and inhibit unwanted “overflow.” Thus, cortical inhibition was interrogated next, using techniques that employed transcranial magnetic stimulation (TMS). These studies demonstrated loss of short\textsuperscript{245,246} and long\textsuperscript{247} intracortical inhibition and a shortened silent period.\textsuperscript{247} Other work focused on demonstrating a lack of surround inhibition, assessing MEP amplitudes of antagonist hand muscles in subjects with writer’s cramp.\textsuperscript{248}

These studies all point to deficient inhibition as a correlate of having a dystonic movement. However, the meaning of these neurophysiologic findings vis-à-vis dystonia etiology and brain mechanisms producing dystonic movements is unclear. For example, DYT1 gene carriers not manifesting dystonia,\textsuperscript{249} and subjects...
with psychogenic dystonia also have abnormal intracortical inhibition and a shortened silent period.

Another feature of dystonia recognized in the past 25 years is increased plasticity. One of the first findings invoking enhanced plasticity was the Byl monkey model of task-specific hand dystonia. That model displays dedifferentiated hand representation in the primary somatosensory cortex. Similarly, a degraded homunculus with enlarged receptive fields was identified in subjects with focal hand dystonia. Both suggest that repeated afferent input from overtraining or overuse could lead to dystonia by driving improperly adjusted cortical plasticity. Subsequent support for abnormalities in plasticity has derived from studies of primary dystonia patients using indirect measures of long-term potentiation and depression, including paired associative stimulation (PAS) and TMS. Using theta bursts of TMS, both DYT1 mutation carriers with dystonia and torticollis subjects had prolonged responses compared with controls. Interestingly, in contrast, nonmanifsting carriers had no response, suggesting a hyperregulated state that may protect these individuals from developing dystonia. Several studies have assessed PAS in focal dystonia, finding enhanced effects consistent with increased plasticity but also loss of spatial specificity; the latter is consistent with loss of surround inhibition. Recurring questions are whether the presence of increased plasticity derives from impaired inhibition and whether measures of cortical inhibition and plasticity are necessary correlates of dystonia. To help address these questions, psychogenic and organic dystonia subjects were studied using tests of cortical inhibition and plasticity. Again, there was evidence of impaired intracortical inhibition in both groups of patients, but abnormal plasticity as measured by PAS was observed only in those with organic dystonia.

A third focus of neurophysiologic investigation has been the study of sensory function. Although clinically overt sensory abnormalities are not a feature of dystonia, several lines of evidence stimulated this focus of research including the efficacy of sensory tricks, the presence of dystonia after trauma or in cases of chronic regional pain, and sensory abnormalities.

### TABLE 2. Highlights in Dystonia Physiology, Imaging, and Treatment

<table>
<thead>
<tr>
<th>Period</th>
<th>Highlights</th>
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<tr>
<td>1995–1999</td>
<td>Monkey model of task specific dystonia displaying enlarged sensory receptive fields is described, supporting theory of increased plasticity. Abnormal somatosensory cortical representation identified in focal hand dystonia. Rodent model of blepharospasm created by partial dopamine depletion and partial weakening of orbicularis oculi. PET studies demonstrate a hypermetabolic pattern involving lentiform, cerebellum, and supplementary motor area in DYT1 gene carriers whether or not they have dystonia. Intra-operative neuronal activity recorded from GP and thalamus of dystonia patients identifies abnormalities in firing patterns. Striatal dopamine receptor binding abnormalities detected by PET in focal dystonia. Pallidotomy begins to replace thalamotomy as preferred surgical treatment for generalized dystonia. First report of GPi DBS for treatment of generalized dystonia.</td>
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<tr>
<td>2000–2004</td>
<td>Multiple reports of defects in sensory processing, especially temporal processing. Failure of surround inhibition identified using paired associative stimulation (PAS). Animal models of DYT1 dystonia developed.</td>
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<tr>
<td>2005–2010</td>
<td>Abnormal motor cortex plasticity in different dystonia subtypes. Basal ganglia interactions are demonstrated in cerebellar animal models of dystonia. DTI MRI demonstrates that connectivity of cerebellothalamic and thalamocortical pathways regulates penetrance in genetic PTD. Studies of DYT1 transgenic mice support D2 receptor dysfunction. Two double-blind controlled trials of bilateral GPi DBS for treatment of primary generalized dystonia demonstrate significant reduction of dystonia symptoms and functional disability. Reports of good outcomes after GPi DBS for various forms of secondary dystonia (PKAN, Lubag, tardive dystonia) and dystonic storm.</td>
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identified in the monkey model. And, indeed, subtle but significant abnormalities in spatial and temporal discrimination have been uncovered,\textsuperscript{257} as have SEP abnormalities.\textsuperscript{251} The sensory findings appear to be a dystonia endophenotype, in that the dysfunction is not directly dependent on the presence of dystonic movements per se. For example, temporal discrimination is abnormal in DYT1 gene carriers that do not manifest dystonia,\textsuperscript{258} and it is also abnormal in the unaffected limbs of patients with focal dystonia.\textsuperscript{259}

How these neurophysiological findings come together mechanistically to explain dystonia remains conjectural; indeed, because dystonia is so etiologically and clinically heterogeneous, it may be best to only consider data and hypotheses restricted to one etiology or phenotype. Nevertheless, one proposed overarching explanation\textsuperscript{240} draws from pathological studies of secondary dystonias as well as deep brain stimulation (DBS) experience in primary dystonia patients\textsuperscript{260} and DYT1 animal findings.\textsuperscript{261} These point to dysfunction in GPi that may in some etiologies be related to abnormal striatal dopaminergic signaling and increased cholinergic tone\textsuperscript{262,263}; this dysfunction leads to abnormal synchronization of the basal ganglia output to the thalamus and sensory feedback misprocessing. Together they have the effect of increasing striatal, brain stem, and cortical plasticity and over time producing neural reorganization and overt dystonia. The various etiologies may feed into this cycle of events in different and multiple ways, including the presence of trauma or overuse that may be more or less important in driving neural reorganization.

**Imaging**

Imaging studies have extended the findings of the neurophysiological studies by delineating cerebral metabolic and microstructural abnormalities in dystonia patients and gene carriers that point to disturbed connectivity in both the cortico-striato-pallido-thalamo-cortical and cerebello-thalamocortical pathways. In early studies using FDG-PET imaging, Eidelberg and colleagues applied a principal-components analysis to identify disease-specific patterns of covarying metabolic activity, first in patients with sporadic dystonia and then in both manifesting and nonmanifesting DYT1 gene carriers.\textsuperscript{264} These patients expressed an abnormal metabolic brain network characterized by relative increases in the posterior putamen/globus pallidus, cerebellum, and supplementary motor area (SMA). These changes are often referred to as trait or genotype specific.\textsuperscript{264}

Nonmanifesting DYT6 gene carriers were found to have a somewhat different pattern of abnormalities, with regional hypometabolism in the putamen, cerebellum, and upper brainstem and hypermetabolism in the temporal cortex.\textsuperscript{39,265} Although the trait-related metabolic abnormalities differed across genotypes, all DYT1 and DYT6 patients with dystonia showed relative metabolic increases in the pre-SMA and parietal association regions regardless of genotype or heterogeneous clinical manifestations.\textsuperscript{265} More recent studies have identified a distinct metabolic pattern related to clinical penetrance (termed state- or phenotype-associated changes as opposed to trait or genotype), characterized by relative increases in the pre-SMA and parietal association cortices and also relative reductions in the cerebellum, brain stem, and ventral thalamus.\textsuperscript{39} This pattern distinguished manifesting from nonmanifesting carriers across genotypes. These findings are consistent with an important role of sensorimotor processing dysfunction in the clinical penetrance of dystonia.\textsuperscript{39}

Further support for maladaptive sensorimotor processing has been provided by oxygen-labeled H\textsubscript{2}O PET studies of DYT1 gene carriers tested in 2 scenarios; one assessed brain activation during a simple motor task and the other tested activation in a nonmotor audiovisual setting.\textsuperscript{266} Not surprisingly differences were noted between manifesting and nonmanifesting carriers. Both had a pattern of increased activation in the nonmotor setting involving the sensorimotor cortex, dorsal premotor cortex, supplementary motor area, and cerebellum. When performing a motor task, however, only the manifesting carriers had increased activation. This dissociation between motor and nonmotor patterns suggests an underlying genotype-processing abnormality in the sensory integration of audiovisual input and then additional motor-activated dysfunction.

The pathoanatomic basis for penetrance, the difference between manifesting and not-manifesting dystonia in susceptible individuals, may relate to developmental structural defects in the cerebello-thalamo-cortical pathway. Evidence for microstructural abnormalities have been identified in diffusion tensor imaging (DTI) studies of focal and genetic forms of dystonia.\textsuperscript{267–270} The most recent studies of both manifesting and nonmanifesting DYT1 and DYT6 gene carriers point to critical abnormalities involving cerebellothalamic tracts; nonmanifesting mutation carriers, however, appear to have additional fiber tract disruption, situated distally along the thalamocortical segment of the pathway (in tandem with the proximal cerebellar outflow abnormality). In individual gene carriers, clinical penetrance appears to be dependent on the difference in connectivity for these 2 tracts.\textsuperscript{39,266,271} The cerebellum has been suggested to have a prominent role in modulating cortical plasticity,\textsuperscript{272–274} so that basal abnormalities in the cerebellum and its outflow pathways may give rise to alterations in cortical activation responses during movement and learning, leading to the functional changes seen in dystonia.
Hand in hand with findings pointing to the import of the cerebellum and thalamus and their outflow is the more traditional focus on the basal ganglia and dopaminergic mechanisms. Dopaminergic deficits are known to be etiologic in secondary dystonias such as dystonia in Parkinson’s disease and dopa-responsive dystonia and also in primary inherited dystonia, where DYT1 animal models displayed D2 receptor dysfunction. In this setting, early PET and SPECT studies in primary dystonia subjects tested striatal D2 receptor binding, and moderate reductions were identified. More recently, reduced D2 receptor availability has been identified in DYT1 and DYT6 mutation carriers regardless of whether dystonic signs were manifest. These findings of dopaminergic dysfunction are consistent with neurophysiologic and animal studies in supporting abnormalities in dopamine signaling and consequent GPi firing. How they relate to the microstructural abnormalities of cerebellothalamic and thalamocortical tracts detected by MRI DTI in the same cohort of DYT1 and DYT6 mutation carriers still needs to be worked out. Determining the temporal-causal relationships of microstructural neurodevelopmental defects verses functional and possibly secondary/downstream changes remains a challenge for future studies of PTD.

**Therapy**

The landscape of treatment options for dystonia has dramatically changed over the last 25 years, first with the introduction of botulinum toxin injections for the treatment of focal dystonias and then with the advent of DBS surgery for generalized dystonia. For decades, treatment for many forms of dystonia relied on oral medications, which were often only modestly effective and frequently caused significant adverse effects. However, with the widespread application of these 2 therapeutic options over the last 2 decades, the armamentarium for clinicians treating patients with dystonia has been radically expanded and improved.

**Oral Medications**

The efficacy of high-dose trihexyphenidyl for treatment of primary generalized dystonia was established in a double-blind prospective trial by Burke and colleagues in 1986. Since then, there has been little in the way of major progress in identifying oral medical therapies for primary dystonia, although medical treatments for the nonprimary dystonias have advanced; these latter include levodopa for DRD, tetrabenazine and clozapine for tardive syndromes, and therapies for metabolic syndromes such as glutaric acidemia. In current practice, options for oral medications for primary dystonia remain essentially the same as in prior decades and consist of anticholinergics (particularly trihexyphenidyl), baclofen, benzodiazepines, and levodopa.

Although trihexyphenidyl is an established first-line oral medication for primary generalized dystonia, it can also be used for symptomatic treatment of secondary dystonia, although there is a paucity of data regarding this use. Two recent small studies have addressed the question of the efficacy of trihexyphenidyl for treatment of children with dystonic cerebral palsy, with inconclusive results. Data are similarly lacking regarding the question of efficacy of levodopa for treatment of non-DRD forms of dystonia. Levodopa has been reported to provide benefit in some patients with DYT1 dystonia, and isolated case reports have described good responses to levodopa in various forms of secondary dystonia; its use in these forms of dystonia thus warrants further investigation.

**Intrathecal and Intraventricular Baclofen**

Intrathecal baclofen infusion has also been used for treatment of generalized dystonia refractory to oral medications, but it has been found to be most beneficial for patients with secondary dystonia, when dystonia occurs in association with spasticity or pain, such as in patients with dystonia from cerebral palsy. More recently, the use of intraventricular baclofen, with intraventricular catheters placed endoscopically in the third ventricle, has been explored for the treatment of severe secondary generalized dystonia refractory to oral medications. Results of a small study showed good response in 8 of 10 patients.

**Botulinum Toxin**

Treatment of various forms of focal dystonia, previously limited to oral medications that had limited efficacy and frequent systemic side effects, has been transformed by the introduction of botulinum toxin (BoNT) treatment. BoNT is a highly effective local treatment that causes minimal side effects. The toxin blocks the vesicular release of acetylcholine into the neuromuscular junction, causing temporary local chemonervation and resultant muscle weakness, reducing the excessive activity of dystonic muscles. Blepharospasm was one of the first studied indications for BoNT treatment, and Botox received FDA approval for blepharospasm or cranial nerve VII disorders in 1989. Since the early reports and studies in the 1980s and '90s, BoNT injections have become a crucial treatment option for various forms of focal dystonia. BoNT is currently the first-line treatment for blepharospasm, cervical dystonia, laryngeal dystonia (spasmodic dysphonia), and focal upper extremity dystonia and is also frequently used for hemifacial spasm, oromandibular dystonia, and focal lower limb dystonia.
Cervical dystonia (CD) is a frequent dystonia, with a prevalence of approximately 20–200 per million and is typically a lifelong disorder causing significant disability because of dystonic posture and pain. Treatment options prior to the introduction of BoNT consisted primarily of oral medications that had limited overall efficacy at tolerated dosages and selective peripheral denervation. The first study evaluating BoNT-A for CD was published in 1985 and was a single-blind study of 12 patients with cervical dystonia and showed improvement in head posture and pain in 92%, with the only adverse event being transient neck weakness in 3 patients. Since that time there have been approximately 80 studies evaluating BoNT for CD, including 8 prospective, double-blind, randomized, controlled clinical trials meeting the criteria for class I evidence.

Prior to BoNT, treatment options for patients with spasmodic dysphonia (SD) were limited to speech therapy and psychotherapy, both with poor results. Other forms of denervation procedures of the recurrent laryngeal nerve were also explored that had initially good results but many long-term failures. Blitzer et al gave the first laryngeal injection of BoNT for SD in 1984, and experience in 1300 patients over subsequent years has shown BoNT to be a safe and effective treatment for laryngeal dystonia.

BoNT is also currently the treatment of choice for focal upper extremity dystonia, including task-specific dystonias such as writer’s cramp and musician’s dystonia. Oral medications for treatment of these forms of dystonia can provide some benefit but only in some patients, and their use is often limited by side effects.

**DBS Surgery for Dystonia**

In the mid-20th century, surgical treatment for generalized dystonia consisted of lesional surgeries, classically targeting the thalamus. Although bilateral thalamotomy provided significant benefit to dystonic symptoms in some patients, it also frequently caused permanent, disabling neurological side effects, particularly dysarthria. Subsequently, the observation that pallidotomy in patients with Parkinson’s disease alleviated off-dystonia symptoms led to interest in the globus pallidus as the optimal surgical target in treatment of dystonia. After the introduction of DBS for the treatment of essential tremor and Parkinson’s disease in the mid-1990s established DBS as an alternative to ablative procedures for treatment of movement disorders, bilateral pallidal stimulation began to be used for treatment of generalized dystonia.

The first report of DBS for dystonia was by Munday in 1977, who reported benefit of unilateral, intermittent, low-frequency thalamic stimulation in 7 patients with cervical dystonia. Reports of DBS for dystonia next appeared in 1999 and the early 2000s and suggested that the GPi was the preferred target. Further, in some patients with primary generalized dystonia, especially those with DYT1 dystonia, the response was dramatic. Two double-blind, controlled trials of bilateral GPi DBS for treatment of primary generalized dystonia were reported, and both found significant reduction in dystonic symptoms and functional disability. Subsequently, bilateral GPi DBS has become a crucial treatment option for patients with medically refractory primary generalized dystonia. With DBS, patients who in the past would have been restricted to a life of severe motor disability from a young age can now lead lives with only minimal symptoms. In addition, studies of long-term follow-up of DBS in dystonia patients have found sustained clinical improvement in patients followed for up to 8 and 10 years.

However, important questions remain regarding the use of DBS for dystonia. Although some dystonia patients respond dramatically to DBS, there has been significant variability in the response across all the published reports, pointing to the crucial question of patient selection and factors predictive of response to DBS. Although no predictive factors have been definitively established, several studies including meta-analyses point to lower preoperative severity score, younger age at surgery, positive DYT1 mutation status, shorter duration of disease, and the lack of fixed skeletal deformity as possible predictive factors. The question of whether DBS is as effective for treatment of non-DYT1 forms of primary generalized dystonia remains unclear. Recent reports of DBS in a small number of patients with DYT6 dystonia have shown less robust results than in DYT1 patients.

Further, although the use of DBS for the treatment of primary generalized dystonia, and especially DYT1 dystonia, has become widely accepted, the question of whether DBS may be effective in various forms of secondary dystonia remains unresolved. Data regarding the efficacy of DBS for secondary dystonia consists, with one recent exception, of individual case reports or small case series with heterogeneous forms of secondary dystonia, with results ranging from no benefit to dramatic improvement. In 2009, Vidailhet et al reported a multicenter prospective pilot study of bilateral pallidal DBS in 13 adults with dystonia-choreothetotic cerebral palsy. The response in these patients was again heterogeneous; therefore, the question of DBS for secondary generalized dystonia from cerebral palsy requires further investigation. Case reports of good outcomes of DBS in patients with certain forms of secondary dystonia, such as dystonia due to the heredo-degenerative diseases PKAN (pantothenate kinase deficiency) and Lubag syndrome (X-linked dystonia parkinsonism), suggest a potential role for DBS. In addition, recent reports of small series...
of patients with DBS for treatment of severe tardive dystonia have also been promising.\textsuperscript{314–316} Patients with myoclonus-dystonia have also been found to have good responses to DBS.\textsuperscript{317–319} Bilateral GPi DBS has also been reported to be effective as a treatment for status dystonicus because of various underlying causes and should therefore be considered in the acute management of this life-threatening condition.\textsuperscript{320–322}

**Future Directions in Treatment**

Although the last 25 years have seen dramatic advances in treatment options for dystonia, there have been no significant advances in oral medications for primary dystonia, and all existing treatments including BoNT and DBS remain essentially symptomatic. Targeted treatments aimed at etiologic mechanisms of dystonia remain the ultimate goal of treatment.

Possibilities for potential novel therapies for dystonia have emerged out of recent basic science advances related to underlying molecular and neurochemical pathophysiologic mechanisms of dystonia. A study by Napolitano and colleagues investigating dopamine D2 receptor (D2R) transmission in a transgenic mouse model of DYT1 dystonia demonstrated a link between the torsinA mutation and D2R dysfunction and found that pharmacological blockade of adenosine A2A receptors restored the abnormal plasticity seen in the DYT1 mice. This suggests that antagonism of A2A receptors can counteract the abnormal D2 receptor–mediated transmission in the mutant mice and, as the authors note, opens new perspectives for treatment of DYT1 dystonia.\textsuperscript{263}

Along another line of inquiry related to DYT1 dystonia, Cao et al reported results of the first screen for candidate small-molecule therapeutics for dystonia in which they searched for compounds that could enhance wild-type torsinA activity. They found 2 classes of antibiotics, quinolones and aminopenicillins, that enhance wild-type torsinA activity and further found that a behavioral defect associated with a DYT1 mouse knock-in model was rescued following administration of ampicillin.\textsuperscript{323}

Ultimately, continued further investigation into the genetic, molecular, neurochemical, and functional–anatomical mechanisms of dystonia will lead to better, more rational targeted therapies for all forms of dystonia.

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