Reviews

Neuropathology of Dystonia

Nutan Sharma[*]

Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Abstract

Background: Dystonia is characterized by sustained or intermittent muscle contractions resulting in abnormal, often repetitive, movements, postures, or both. Neuropathologic research has been essential in understanding the etiology and disease progression of other movement disorders, including Parkinson's disease and cerebellar ataxias. In the field of dystonia, however, research is stymied by the paucity of post-mortem tissue available and the phenotypic heterogeneity found in those with dystonia.

Methods: A PubMed search was conducted using the term "neuropathology of dystonia". The resulting list of references was limited to English-language human neuropathology articles. A total of 20 publications were retrieved and reviewed.

Results: Historically, based on study of acquired forms of dystonia, lesions of the putamen and globus pallidus have been identified as causing dystonia. After the identification of genetic causes of dystonia and the study of limited tissue available from those cases, as well as findings from cases of isolated focal and segmental dystonia, there is evidence that brainstem cholinergic neurons and specific cell populations within the cerebellum also play a role in the pathophysiology of dystonia.

Discussion: Based on limited available brain tissue, there is evidence that the pathophysiology of dystonia may involve a combination of dysfunction within neurons of the brainstem, cerebellum, putamen, and globus pallidus. In order to gain a better understanding of the pathophysiology of dystonia, a prospective, quantitative study in well-phenotyped subjects with different types of genetic and isolated dystonia is required.

Introduction

Dystonia is a neurologic disorder that is characterized by sustained or intermittent muscle contractions resulting in abnormal, often repetitive, movements, postures, or both.[1] Dystonia may be classified according to its clinical characteristics and its presumed etiology. Clinical characteristics that are used in the current classification scheme include age of onset, bodily distribution, temporal pattern, and presence or absence of another movement disorder. In addition, cases of dystonia are referred to either as isolated, meaning that dystonia is the only motor feature with the exception of tremor, or combined, meaning that dystonia is combined with other movement disorders, such as Parkinsonism. Categories of presumed etiology include evidence of degeneration or a structural lesion and whether the dystonia is inherited, acquired, or idiopathic. Inherited dystonias include those

caused by autosomal dominant or recessive gene mutations, as well as those resulting from mutations on either the X chromosome or in mitochondrial genes. Acquired dystonias are those due to nervous system insult, such as infection, vascular insult, or brain injury. Lastly, many cases of adult-onset focal dystonia fall into the category of idiopathic.

Neuropathology has been essential in understanding the etiology and disease progression of many neurological disorders, including Alzheimer's disease, Parkinson's disease, and cerebellar ataxias. In Parkinson's disease, in particular, degeneration of dopaminergic neurons in the substantia nigra pars compacta leads to clinical features of the disease. In the field of dystonia, however, neuropathologic studies have had minimal impact on our understanding of the underlying disease mechanisms. The majority of the published work

has involved non-quantitative neuropathologic analysis, in which the loss of up to 40% of a particular cell type will not be apparent. Research is stymied by the paucity of post-mortem tissue available for study, the lack of systematic quantitative assessment of the existing tissue, and the phenotypic heterogeneity found in those with dystonia. The purpose of this review is to summarize the state of knowledge regarding neuropathologic abnormalities that may contribute to the pathogenesis of genetic and isolated dystonias. One hypothesis of the pathogenesis of dystonia is that multiple intracellular defects may result in a similar abnormality at the level of brain circuitry, thus producing a similar phenotype. This review summarizes neuropathologic analyses of brains from both isolated and combined dystonias in which the genetic mutation is known and from cases of isolated dystonia in which no genetic etiology is suspected or known, in order to determine the extent to which evidence exists that supports the hypothesis of "multiple defects, similar phenotype".

Methods

A PubMed search was conducted on March 11, 2018, using the term "neuropathology of dystonia". Because of the scarcity of neuropathology reports in dystonia, no date limit was applied to the search. A total of 127 articles were identified. The reference list was further limited to articles written in English that analyzed human brain tissue and focused on either isolated dystonia or combined dystonia in which the underlying gene mutation was identified and there was no known symptomatology outside the nervous system (thus excluding diseases such as Wilson's and mitochondrial disorders). Publications in which there was limited clinical information that made it difficult to reliably classify the type of dystonia were also excluded.[2,3] In addition, movement disorders in which dystonia occurs as the disease progresses, rather than being a primary and early feature of the disease, such as Huntington's and Parkinson's, were excluded, as the goal in this review was to focus on disorders in which dystonia is part of the primary pathology. Additional criteria to exclude reports of paroxysmal dystonia and cases associated with developmental delay or regression were applied. Commentary and review articles were also excluded. During the writing of this article, an additional report of secondary dystonia cases was included,[2] in order to provide readers with a more comprehensive background. In total, 20 neuropathology reports were retrieved and reviewed.

Results

Acquired dystonia

Prior to the identification of dystonia-causing gene mutations, retrospective imaging analysis of acquired forms of dystonia revealed that lesions of the lentiform nucleus most commonly caused dystonia.[4] These data pointed to the putamen and globus pallidus as playing an essential role in motor control. However, acquired dystonias arise because of a variety of insults, resulting in a heterogeneous sample for study. The identification of dystonia-causing mutations allowed neuropathologic analysis of more homogeneous samples.

Genetic dystonias

DYT1. DYT1 is an isolated dystonia, as there are no other neurologic features with the exception of tremor. The *DYT1* gene mutation consists of a 3-bp (GAG) deletion in the coding region of the *TOR1A* gene that encodes the protein torsinA.[5] While the function of torsinA is not fully understood, the totality of evidence indicates that it is associated with the nuclear envelope and plays a role in intracellular trafficking and secretion of proteins.[6] Initial neuropathologic studies focused on identifying the localization of wild-type torsinA in control human brains. TorsinA mRNA was found to be enriched in the substantia nigra pars compacta, hippocampus, and cerebellum in control tissue.[7] Subsequent analyses of TorsinA protein expression in both control and DYT1 cases revealed varying results (summarized in Table 1). Two independent reports focused on torsinA expression in the substantia nigra, neostriatum, and cerebellum, and did not find any difference in the pattern of torsinA immunoreactivity between DYT1 and control brains.[8,9] The second report also analyzed the substantia nigra from three of the DYT1 brains and found a semiquantitative difference in the nigral dopaminergic neurons, which appeared to be larger and more closely spaced together in the DYT1 brains when than in the control tissue.[9] A combined total of seven unique DYT1 cases were used in these two publications. Neither report included an analysis of brainstem tissue. Subsequent research, which included studies of the brainstem tissue, reported intraneuronal inclusions within cholinergic neurons in the pedunculopontine nucleus, cuneiform nucleus, and periaqueductal gray matter.[10] These inclusions were immunoreactive for ubiquitin, the nuclear envelope marker lamin A/C, and torsinA. A total of four DYT1 cases were analyzed. A review of demographic data revealed that three of the cases had most likely been utilized previously by Rostasy et al.[9] and the fourth case had most likely been utilized previously by Walker et al.[8] However, the previous studies did not analyze brainstem tissue. The presence of inclusions in brainstem nuclei that are known to play a role in locomotor control raises the possibility that neuronal dysfunction in this region plays a role in the pathology of DYT1 dystonia.

Two additional studies[11,12] sought to reproduce the findings of brainstem, intraneuronal inclusions by McNaught et al.[10] Using a somewhat different panel of antibodies for immunohistochemistry, Paudel et al.[11] did not find evidence of protein aggregates within neurons of the midbrain. However, the anti-lamin A/C antibody was not utilized, which may have identified torsinA aggregates associated with the nuclear envelope. A more recent analysis of DYT1 brain tissue also failed to reveal intraneuronal inclusions.[12] The authors studied brain tissue from six genetically confirmed cases of DYT1, four of which had likely been analyzed previously by Paudel et al.[11] The authors used antibodies to torsinA, ubiquitin protein conjugate (UPC), and choline acetyl transferase (ChAT) to analyze tissue from the midbrain and striatum. No intraneuronal inclusions were identified and immunoreactivity for torsinA, ChAT, and UPC was similar between the DYT1 and control groups.

In a more recent study, a quantitative assessment was performed to determine average cell body, nuclear, and nucleolar volume of nigral

Table 1. Immunohistochemical Findings in Neuropathologic Studies of Genetic Forms of Dystonia

Author	Cases	Regions	Antibodies	Findings
Walker et al.[8]	1 DYT1 4 Control	motor ctx, hippocampus, caudate, putamen, SN, cerebellum	torsinA, PDI	No torsinA aggregates
Rostasy et al.[9]	6 DYT1 9 Control	hippocampus, neostriatum, SN, cerebellum	torsinA, GFAP, HLA-DR, β-amyloid, ubiquitin	No difference in staining pattern between cases and controls
McNaught et al.[10]	4 DYT1 4 Control	ctx, hippocampus, striatum, midbrain, pons	UPC, α-synuclein, lamin A/C, MAP2, ChAT, GFAP, β-amyloid, PDI, torsinA	Intraneuronal ubiquitin + and torsinA+ inclusions in midbrain, pons and periacqueductal gray
Paudel et al.[11]	7 DYT1	Frontal ctx, temporal ctx, striatum, globus pallidus, thalamus, STN, cerebellum, midbrain, pons, medulla	Ubiquitin, tau, GFAP, α-synuclein, p62, CD68, TDP-43	No intraneuronal inclusions
Pratt et al.[12]	6 DYT1 7 Control	striatum, motor ctx, sensory ctx, midbrain, pons	torsinA, UPC, β-amyloid, AT8, α-synuclein	No torsinA aggregates
Iacono et al.[13]	2 DYT1 manifesting 2 DYT1 non-manifesting 4 Control	SN	torsinA, ubiquitin, β-amyloid, α-synuclein, pTDP-43, laminin A + C, CD68	
Paudel et al.[18]	2 DYT6	Ctx, hippocampus, caudate, putamen, globus pallidus, thalamus, STN, SN, LC, pontine nuclei, dorsal motor nucleus of vagus, 12th nerve nucleus, inferior olive, cerebellum	Ubiquitin, tau, GFAP, Aβ, internexin, α-synuclein, p62, TDP-43	No neuronal loss, no gliosis, no Lewy bodies in cortex or brainstem
Waters et al.[25]	1 DYT3	Cerebral ctx, cerebellum, midbrain, pons, medulla	GFAP	Purkinje cell loss (not quantified), astrocytosis in white matter of cerebellum, astrocytosis in mosaic pattern in caudate and putamen
Goto et al.[26]	7 DYT3 7 Controls	Striatum, SN	Calcineurin, calbindin, TH, GFAP, ChAT	Preferential cell loss in striosome
Goto et al.[27]	4 DYT3	Striatum	Neuropeptide Y, Met-enkephalin, calcineurin	Reduced NPY staining in striosome, compared to matrix

Table 1. Continued

Author	Cases	Regions	Antibodies	Findings
Grotzsch et al.[16]	1 DYT5a 1 Control	Ctx, hippocampus, thalamus, caudate, putamen, globus pallidus, cerebellar ctx, medulla, mesencephalon, pons	GFAP, ubiquitin	Reduced melanin-containing neurons in SN
Oblak et al.[29]	4 DYT12	Globus pallidus, STN, red nucleus, inferior olivary nucleus, Cerebellar Purkinje and granular cell layers, dentate nucleus	Aβ, AT8, GFAP, α-synuclein, TDP-43, ubiquitin, syantophysin, calbindin	Neuronal loss in: globus pallidus, STN, Purkinje and granular cell layers of cerebellum, dentate nucleus, red nucleus, inferior olivary nucleus

CD68 is a marker of macrophages and is expressed in activated microglia; p62 is a marker of autophagy.
Abbreviations: AT8, Anti-phospho-Tau; ChAT, Choline Acetyl Transferase; ctx, Cortex; GFAP, Glial Fibrillary Acid Protein, a marker of reactive astrocytes; HLA-DR, Human Leukocyte Antigen DR isotype, a marker of reactive glia; laminin A + C, nuclear envelope marker; LC, Locus Coeruleus; MAP2, Microtubule-Associated Protein 2, a marker of neuronal dendrites and cell bodies; NPY, Neuropeptide Y; PDI, Protein Disulfide Isomerase, an endoplasmic reticulum marker; pTDP-43, Phosphorylated Transactive Response DNA binding protein 43 kDa; SN, Substantia Nigra; STN, Subthalamic Nucleus; TDP-43, Transactive Response DNA Binding Protein 43 kDa, a component of neuronal aggregates in some neurodegenerative diseases; TH, Tyrosine Hydrdoxylase; UPC, Ubiquitin Protein Conjugate.

neurons in two DYT1 brains from subjects who manifested signs of dystonia.[13] Compared with both the two DYT1 brains from subjects without dystonia and the two age-matched control subjects, the DYT1 manifesting subjects displayed a quantitative increase in volume of the cell body, nuclear, and nucleolar volume of nigral pigmented dopaminergic neurons. The authors also used antibodies to alpha-synuclein, tau, β-amyloid, ubiquitin, phosphorylated-TAR-DNA binding protein-43, torsinA, and lamin A/C to identify inclusions within the substantia nigra, and none were identified.

DYT5a. DYT5a, also known as Segawa syndrome, is an isolated dystonia caused by one of a variety of mutations in the Guanosine triphosphate (GTP) cyclohydrolase 1 gene (*GCH1*).[14] Limited neuropathologic studies included biochemical analysis of two brains revealed a reduction in striatal levels of both biopterin and tyrosine hydroxylase when compared with age-matched control cases.[15] Additional neuroanatomic studies have revealed a reduction in melanin-containing neurons in the substania nigra pars compacta in a single brain compared with an age-matched control subject.[16]

DYT6. DYT6 is also classified as an isolated dystonia. Mutations in the transcription factor, thanatos-associated protein domain containing apoptosis-associated protein 1 (*THAP1*) result in DYT6 dystonia.[17] A single report on tissue from two subjects with DYT6 dystonia, each with a different DYT6 mutation, did not reveal any evidence of significant neuronal loss.[18] In addition, there was no evidence of ubiquitin immunoreactive inclusions in the midbrain.

DYT3. DYT3 is a combined dystonia, with affected individuals displaying features of Parkinsonism as well. The most frequently documented clinical phenotype consists of an initial focal dystonia that spreads to multiple body regions over time and combines with, or is replaced by, Parkinsonism.[19–23] Recently, the causal locus was identified as a hexameric repeat expansion within the Short Interspersed Nuclear Elements-Variable Number of Tandem Repeats-Alu (SINE-VNTR-Alu) intronic region of the *TAF-1* gene on the X chromosome.[24] Like other repeat expansion disorders, a larger repeat length correlated with an earlier age at onset of symptoms. Neuropathologic data from a limited number of DYT3 cases, consisting of elemental immunohistochemical staining, revealed preferential loss of medium spiny neurons in the striosomal component during the dystonic phase of the disease, with more widespread loss of striosomal and matrix component neurons, with evidence of astrocytosis, as the disease progresses and subjects display more parkinsonian signs.[25,26] Immunohistochemical analysis of striatal tissue from four X-linked Dystonia Parkinsonism (XDP) subjects revealed a decrease in neuropeptide Y-positive cells in the caudate and putamen compared with control tissue.[27]

DYT12. DYT12 is also a combined dystonia, as subjects display features of Parkinsonism and dystonia. The disorder is associated with mutations in the *ATP1A3* gene, which encodes the alpha subunit of the Na$^+$/K$^+$ ATPase that plays a critical role in maintaining

Table 2. Immunohistochemical Findings in Neuropathologic Studies of Isolated Dystonia, with no Known Genetic Cause

Author	Cases	Regions	Antibodies	Findings
Kulisevsky et al.[30]	1 Meige syndrome	Caudate, putamen, pallidum, SN, LC, dentate nucleus	None (conventional staining only)	LBs and mild to moderate neuronal loss in SN and LC, consistent with age
Gibb et al.[31]	4 Cranial Dystonia 3 Control	SN, LC	None (conventional staining only)	No morphologic abnormalities or cell loss evident, using semi-quantitative method
Holton et al.[32]	6 Isolated segmental Dystonia 4 Control	Periaqueductal gray, PPN, cuneiform nucleus, reticular formation, strisome, caudate nucleus, putamen, globus pallidus, hippocampus	torsinA, ubiquitin, lamin A + C, GFAP, Aβ, tau, α-synuclein,	No intraneuronal inclusions, no striatal neuronal loss
Prudente et al.[33]	6 Isolated cervical dystonia 16 control	Somatosensory ctx, caudate, putamen, globus pallidus, SN, red nucleus, cerebellar hemispheres and deep nuclei	Parvalbumin, calbindin, calretinin, ubiquitin, IC2, TDP-43, GFAP, HLA-DR	Ubiquitin inclusions in SN, Reduced Purkinje cell density in cerebellum
Mente et al.[34]	8 Isolated cervical dystonia 7 Control	PPN, frontal ctx, parietal ctx, hippocampus, cerebellum	ChAT	Reduced ChAT staining in PPN

CD68 is expressed in activated microglia; laminin A + C is a nuclear envelope marker.

Abbreviations: AT8, Anti-Phospho-Tau; ChAT, Choline Acetyl Transferase; ctx, Cortex; GFAP, Glial Fibrillary Acid Protein, a marker of reactive astrocytes; HLA-DR, Human Leukocyte Antigen DR isotype, a marker of reactive glia; IC2, anti-polyglutamine antibody; LB, Lewy Body; LC, Locus Coeruleus; NPY, Neuropeptide Y; PPN, Pedunculopontine Nucleus; SN, Substantia Nigra; TDP-43, Transactive Response DNA Binding Protein 43 kDa, a component of neuronal aggregates in some neurodegenerative diseases; TH, Tyrosine Hydroxylase.

sodium and potassium gradients across cell membranes.[28] A report of four family members who carried a DYT12 mutation, with three of them affected, revealed neuronal loss and gliosis in the globus pallidus and subthalamic nucleus in all the affected siblings when compared with 16 control cases.[29] The cerebellum and midbrain were available from two of the three affected siblings, and revealed mild to moderate neuronal loss and gliosis in the Purkinje and granule cell layers of the cerebellum, as well the dentate nucleus. Neuronal cell loss was also found in the periaqueductal gray matter, red nucleus, and inferior olivary nucleus. Tissue from the asymptomatic sibling did not reveal significant degeneration in those regions.

Isolated focal/segmental dystonia

In 1988, a single case report of neuropathologic findings in Meige syndrome, a combination of blepharospasm and lower facial dystonia, revealed mild abnormalities that may be consistent with normal aging.[30] No immunohistochemical staining or quantitative analysis was performed. Another report, of four patients with isolated focal or segmental dystonia of the face and jaw, also did not reveal any abnormalities.[31] However, as with the case report, no immunohistochemistry or quantitative analysis was performed. A more recent study, of six cases of adult onset, isolated focal, and segmental dystonia, did include immunohistochemical analysis.[32] There was no evidence of pathology similar to that seen in DYT1 dystonia, namely neuronal inclusions immunoreactive for torsinA or ubiquitin.[8] In addition, there was no evidence of neuronal loss in the striosome compartment of the striatum, as has been demonstrated in DYT3 dystonia.[26] Thus, the limited number of adult-onset isolated focal/segmental dystonias do not appear to demonstrate pathology similar to that seen in genetic forms of dystonia (summarized in Table 2).

Cervical dystonia

Additional neuropathologic analysis has been done on cases that share a single phenotype, namely focal cervical dystonia.[33] Prudente et al.[33] analyzed post-mortem brain tissue from six subjects with cervical dystonia and compared them with 16 control subjects. Using a two-stage approach, an experienced neuropathologist examined tissue from four of the cervical dystonia subjects for overt changes. This subjective assessment revealed ubiquitin-positive inclusions in nigral neurons and patchy loss of cerebellar Purkinje cells. In the second stage of the analysis, quantitative assessment for nigral inclusions and Purkinje cell number was performed. While there was no significant difference in the number of ubiquitin-positive inclusions in the nigra, there was a significantly lower density of Purkinje cells in the cerebellum from those with cervical dystonia.

Recently another case series, focusing on the cholinergic system, was conducted on eight cervical dystonia subjects and seven control subjects.[34] In the pedunculopontine nucleus (PPN), but not the putamen, of the cervical dystonia patients, there was markedly decreased or absent choline acetyltransferase staining, indicating the presence of a functional cholinergic deficit in cervical dystonia. However, stereologic quantification of the difference in staining in the PPN was not reported.

In addition, there was no evidence of an underlying neurodegenerative process, as assessed by lack of gliosis and lack of beta-amyloid, tau, and alpha-synuclein pathologies.

Conclusion

Traditionally, dystonia has been regarded as a disorder arising within the basal ganglia.[4] The availability of post-mortem tissue from a limited number of genetic and focal dystonia cases has allowed the existence of neuropathologic lesions throughout the brain to be explored. While the number of unique cases is limited, the largest body of evidence is from analysis of DYT1 and cervical dystonia cases. The DYT1 cases were not all analyzed in the same manner, because different groups analyzed varying brain regions and antibody combinations. In the few cases in which intraneuronal aggregates were found, they were located in the brainstem.[10] Similarly, brainstem abnormalities were identified in cases of isolated cervical dystonia, in the form of reduced cholinergic immunostaining.[34] Taken together, these data indicate that brainstem nuclei, and basal ganglia nuclei, may play a role in the pathophysiology of dystonia.

While the primary dystonias have not revealed consistent evidence of cell loss or neuronal pathology, the combined dystonias have shown evidence of degeneration. Cases of DYT12 dystonia displayed neuronal loss in multiple layers of the cerebellum.[28] Cases of DYT3 dystonia have shown selective loss of neurons within specific populations of the basal ganglia.[26] Subsequent analysis of four XDP brains indicates that neuropeptide Y may play a role in the preferential vulnerability of striatal neurons in DYT3.[27] However, the tissue was not subjected to rigorous, quantitative analysis.

Taken together, the available data from neuropathologic studies do not reveal solid evidence of marked neuronal loss within the striatum, cerebellum, and brainstem nuclei in different forms of dystonia. However, the number of cases examined is limited, and rigorous quantification of different cell types in each region has not been performed. A large, prospective and quantitative neuropathologic study in clinically well-characterized patients with genetic and focal dystonias is required to better understand the pathology of dystonia.

References

1. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013;28:863–873. doi: 10.1002/mds.25475

2. Iacono D, Geraci-Erck M, Peng H, Rabin ML, Kurlan R. Reduced number of pigmented neurons in the substantia nigra of dystonia patients? Findings from extensive neuropathologic, immunohistochemistry, and quantitative analyses. *Tremor Other Hyperkinet Mov* 2015;5. doi: 10.7916/D8T72G9G

3. Zweig RM, Hedreen JC, Jankel WR, Casanova MF, Whitehouse PJ, Price DL. Pathology in brainstem regions of individuals with primary dystonia. *Neurology* 1988;38:702–706. doi: 10.1212/WNL.38.5.702

4. Bhatia KP and Marsden CD. The behavioral and motor consequences of focal lesions of the basal ganglia in man. *Brain* 1994;117:859–76. doi: 10.1093/brain/117.4.859

5. Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. *Nat Genet* 1997;17:40–8. doi: 10.1038/ng0997-40

6. Cascalho A, Jacquemyn J, Goodchild RE. Membrane defects and genetic redundancy: are we at a turning point for DYT1 dystonia? *Mov Disord* 2017;32: 371–381. doi: 10.1002/mds.26880

7. Augood SJ, Penney JB, Friberg IK, Breakefield X0, Young AB, Ozelius LJ, et al. Expression of the early-onset torsion dystonia gene (DYT1) in human brain. *Ann Neurol* 1998;43:667–673. doi: 10.1002/ana.410430518

8. Walker RH, Brin MF, Sandu D, Good PF, Shashidharan P. Torsin A immunoreactivity in brains of patients with DYT1 and non-DYT1 dystonia. *Neurology* 2002;58:120–4. doi: 10.1212/WNL.58.1.120

9. Rostasy K, Augood SJ, Hewett JW, Leung JC, Sasaki H, Ozelius LJ. Torsin A protein and neuropathology in early onset generalized dystonia with GAG deletion. *Neurobiol Dis* 2003;12:11–24. doi: 10.1016/S0969-9961(02)00010-4

10. McNaught KS, Kapustin A, Jackson T, Jengelley T, Jnobaptiste R, Shashidharan P, et al. Brainstem pathology in DYT1 primary torsion dystonia. *Ann Neurol* 2004;56:540–547. doi: 10.1002/ana.20225

11. Paudel R, Kiely A, Li A, Lashley T, Bandopadhyay R, Hardy J, et al. Neuropathological features of genetically confirmed DYT1 dystonia: investigating disease-specific inclusions. *Acta Neuropathol Commun* 2014;2:159–166. doi: 10.1186/s40478-014-0159-x

12. Pratt D, Mente K, Rahimpour S, Edwards NA, Tinaz S, Berman BD, et al. Diminishing evidence for torsinA-positive neuronal inclusions in DYT1 dystonia. *Acta Neuropathol Commun* 2016;4:85–88. doi: 10.1186/s40478-016-0362-z

13. Iacono D, Geraci-Erck M, Peng H, Rabin ML, Kurlan R. Hypertrophy of nigral neurons in Torsin1A deletion (DYT1) carriers manifesting dystonia. *Parkinsonism Relat Disord* 2018.08.020. doi: 10.1016/j.parkreldis.2018.08.020

14. Segawa M. Hereditary progressive dystonia with marked diurnal fluctuation. *Brain Dev* 2011;33:195-201. doi: 10.1016/j.braindev.2010.10.015

15. Furukawa Y, Nygaard TG, Gutlich M, Rajput AH, Pifl C, DiStefano L, et al. Striatal biopterin and tyrosine hydroxylase protein reduction in dopa-responsive dystonia. *Neurology* 1999;53:1032–1041. doi: 10.1212/WNL.53.5.1032

16. Grotzsch H, Pizzolata GP, Ghika J, Schorderet D, Vingerhoets FJ, Landis T, et al. Neuropathology of a case of dopa-responsive dystonia associated with a new genetic locus, DYT14. *Neurology* 2002;58:1839–1842. doi: 10.1212/WNL.58.12.1839

17. Fuchs T, Gavarini S, Saunders-Pullman R, Raymond D, Ehrlich ME, Bressman SB. Mutations in the THAP1 gene are responsible for DYT6 primary torsion dystonia. *Nat Genet* 2009;41:286–288. doi: 10.1038/ng.304

18. Paudel R, Li A, Hardy J, Bhatia KP, Houlden H, Holton J. DYT6 Dystonia: A Neuropathological Study. *Neurodegener Dis* 2016;16:273–8. doi: 10.1159/000440863

19. Lee LV, Kupke KG, Caballar-Gonzaga F, Hebron-Ortiz M, Müller U. The phenotype of the X-linked dystonia-parkinsonism syndrome. An assessment of 42 cases in the Philippines. *Medicine (Baltimore)* 1991;70:179–187. doi: 10.1097/00005792-199105000-00002

20. Evidente VG, Advincula J, Esteban R, Pasco P, Alfon JA, Natividad FF, et al. Phenomenology of "Lubag" or X-linked dystonia-parkinsonism. *Mov Disord* 2002;17:1271–1277. doi: 10.1002/mds.10271

21. Evidente VG, Gwinn-Hardy K, Hardy J, Hernandez D, Singleton A. X-linked dystonia ("Lubag") presenting predominantly with parkinsonism: a more benign phenotype? *Mov Disord* 2002;17:200–202. doi: 10.1002/mds.1263

22. Lee LV, Maranon E, Demaisip C, Peralta O, Borres-Icasiano R, Arnacillo J, et al. The natural history of sex-linked recessive dystonia parkinsonism of Panay, Philippines (XDP). *Parkinsonism Relat Disord* 2002;9: 29–38. doi: 10.1016/S1353-8020(02)00042-1

23. Lee LV, Rivera C, Teleg RA, Dantes MB, Pasco PM, Jamora RD, et al. The unique phenomenology of sex-linked dystonia parkinsonism (XDP, DYT3, "Lubag"). *Int J Neurosci* 2011;121(Suppl. 1):3–11. doi: 10.3109/00207454.2010.526728

24. Bragg DC, Mangkalaphiban K, Vaine CA, Kulkarni NJ, Shin D, Yadav R, et al. Disease onset in X-linked dystonia-parkinsonism correlates with expansion of a hexameric repeat within an SVA retrotransposon in TAF1. *Proc Natl Acad Sci USA* 2017;114:E11010–E11028. doi: 10.1073/pnas.1712526114

25. Waters CH, Faust PL, Powers J, Vinters H, Moskowitz C, Nygaard T, et al. Neuropathology of Lubag (X-linked dystonia parkinsonism). *Mov Dis* 1993; 8:387–390. doi: 10.1002/mds.870080328

26. Goto S, Lee LV, Munoz EL, Tooyama I, Tamiya G, Makina S, et al. Functional anatomy of the basal ganglia in X-linked recessive dystonia-Parkinsonism. *Ann Neurol* 2005;58:7–17. doi: 10.1002/ana.20513

27. Goto S, Kawarai T, Morigaki R, Okita S, Koizumi H, Nagahiro S, et al. Defects in the striatal neuropeptide Y system in X-linked dystonia-parkinsonism. *Brain* 2013;136:1555–1567. doi: 10.1093/brain/awt084

28. De Carvalho Aguiar P, Sweadner KJ, Penniston JT, Zaremba J, Liu L, Caton M, et al. Mutations in the Na+.K+-ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. *Neuron* 2004;43:169–175. doi: 10.1016/j.neuron.2004.06.028

29. Oblak AL, Hagen MC, Sweadner KJ, Haq I, Whitlow CT, Maldjian JA, et al. Rapid-onset dystonia-parkinsonism associated with the I758S mutation of the ATP1A3 gene: a neuropathologic and neuroanatomical study of four siblings. *Acta Neuropathol* 2014;128:81–98. doi: 10.1007/s00401-014-1279-x

30. Kulisevsky J, Marti MJ, Ferrer I, Tolosa E. Meige syndrome: neuropathology of a case. *Mov Dis* 1988;3:170–175. doi: 10.1002/mds.870030209

31. Gibb WRG, Lees AJ, Marsden CD. Pathological report of four patients with cranial dystonias. *Mov Dis* 1988;3:211–221. doi: 10.1002/mds.870030305

32. Holton JL, Schneider SA, Ganesharajah T, Gandhi S, Strand C, Shashidharan P, et al. Neuropathology of primary adult-onset dystonia. *Neurology* 2008;70:695–699. doi: 10.1212/01.wnl.0000302175.76229.f0

33. Prudente CN, Pardo CA, Xiao J, Hanfelt J, Hess EJ, Ledoux MS, et al. Neuropathology of cervical dystonia. *Exp Neurol* 2013;241:95–104. doi: 10.1016/j.expneurol.2012.11.019

34. Mente K, Edwards NA, Urbano D, Ray-Chaudhury A, Iacono D, Alho ATDL, et al. Pedunculopontine nucleus cholinergic deficiency in cervical dystonia. *Mov Disord* 2018. doi: 10.1002/mds.27358