Neurobiology of Disease 42 (2011) 148–151

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Update on the pathology of dystonia

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ARTICLE INFO

Article history:
Received 16 August 2010
Revised 22 December 2010
Accepted 2 January 2011
Available online 8 January 2011

Keywords:
Dystonia
Dopamine
Basal ganglia
Brainstem
Cerebellum
DYT1
Postmortem

ABSTRACT

Dystonia is a clinical syndrome with sustained muscle contraction, twisting, and abnormal postures. A number of different genetic forms have been defined, but most cases are sporadic in nature and of uncertain cause. Relatively few cases of dystonia have been studied pathologically. In primary dystonias, where dystonia is the main symptom, most reports describe little or no detectable neuropathology, although changes in brainstem neurons have been described in some cases. Secondary dystonias are associated with degenerative or destructive diseases of the nervous system; the pathology may be located in the basal ganglia, but in some cases the primary pathological changes are found in the cerebellum or cerebellar outflow pathways, suggesting that both regions may be involved in the pathogenesis of dystonic symptoms. Overall the number of well-documented pathological cases available for study is few, and there is an urgent need for additional postmortem studies. This article is part of a Special Issue entitled "Advances in dystonia".

Contents

Introduction

Dystonia is a clinical syndrome, identified by its characteristic features: sustained muscle contractions, twisting, and abnormal postures (Fahn, 1984). Collectively, the dystonias are relatively common disorders. They produce substantial disability, and from a therapeutic perspective the available treatments are for the most part unsatisfactory. In view of the frequency and burdensome nature of dystonias, the amount of data available on the pathological features of dystonia is surprisingly limited. Even in genetically defined forms of the disorder there are at most a few cases which have been closely studied, and there is much still to be learned about the structural features of dystonia.

Primary and secondary dystonias

From an etiological perspective, the dystonias are often divided into *primary* and *secondary* forms (Friedman and Standaert, 2001).

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Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.nbd.2011.01.012

The meaning of these terms has evolved in recent years, as concepts of the etiology and pathophysiology of dystonia have changed. In much of the early literature, primary dystonia is used to describe dystonic symptoms where no cause could be identified, and was sometimes used interchangeably with the term "idiopathic" (Bressman et al., 1988; Marsden and Quinn, 1990; Marsden and Rothwell, 1987), while the term secondary was used to describe dystonia which was a symptom of another recognizable disorder. With the discovery of the genetic basis of several of the dystonic disorders, this formulation has become more problematic: a disorder with a genetic cause is not idiopathic, even if there are no obvious neuropathological features. More recent efforts at defining primary dystonia have emphasized the lack of apparent neuropathology, rather than the lack of identifiable etiology (Tanabe et al., 2010), but even this approach is challenged by technologic advances such as diffusion tensor magnetic resonance imaging, which are expanding the ability to detect structural changes (Carbon and Eidelberg, 2009).

The most recent attempts to define the class of "primary" dystonias have placed the emphasis on the clinical features, rather than the pathological changes, by defining "primary pure dystonia" as a disorder in which "torsion dystonia is the only clinical sign (apart from tremor), and there is no identifiable exogenous cause," and allowing for subcategories of "primary-plus" dystonia (with myoclonus or parkinsonism) and paroxysmal dystonias (Albanese et al., 2011). While this is helpful from a clinical perspective, it doesn't fully address the issues either; all dystonias have an etiology which is based in altered brain function, it is merely that in many cases our present ability to detect the changes is insufficient. Clearly this is an area which is still in evolution, and as the underlying structural and functional nature of dystonia is elucidated, the nomenclature will be improved. For the purposes of discussion the clinically-based approach will be used where possible, but it is important to keep in mind that the terminology used in older publications may differ.

Genetics and the etiology of dystonia

In recent years, a great deal has been learned about the genetics of dystonia, and a large number of genes which can give rise to this movement disorder have been identified (Breakefield et al., 2008). Concerted efforts to identify the functions of the dystonia genes (many of which are identified using a "DYT" nomenclature) have yielded substantial insights into the molecular and cellular processes involved (Breakefield et al., 2008). These cover a remarkable spectrum, including proteins which appear to function as chaperones (DYT1), transcription factors (DYT6), structural proteins (DYT11) and enzymes involved in dopamine biosynthesis (DYT5). An important gap in knowledge, however, is how these molecular and cellular changes give rise to the systems-level changes in brain function responsible for abnormal patterns of movements.

One of critical "missing links" in the effort to understand dystonia is the paucity of information regarding the neuropathology of human dystonia. In the case of primary dystonias there are clearly functional abnormalities of the brain and likely corresponding structural abnormalities, at least at the synaptic level, but there is little anatomical evidence for this. In the secondary dystonias there is, by definition, clear evidence of neuropathology but in many cases it is not clear which pathology, and which structures, are responsible for the dystonic features.

These are not novel observations. In 1970 Dr. Edward Tarlov published an article titled "On the problem of the pathology of spasmodic torticolis in man," in which he noted that the "pathophysiological basis … (of dystonia)… has never been convincingly demonstrated" (Tarlov, 1970). A conservative view would be that the same statement is still true today. This lack of information is a substantial barrier to progress, because our limited understanding of the neuropathology of the human disease makes it difficult to develop targeted therapeutic strategies. It also impairs our ability to assess the authenticity of animal models, a point noted by Tarlov (Tarlov, 1970).

Pathology of primary dystonias

The most common forms of primary dystonia are focal, affecting a single body part such as the neck, and come on during adult life. Most of these are sporadic, meaning that there is no clear family history and that they are not caused by any of the known dystonia genes. A minority of cases of primary focal dystonia will have a positive family history or early onset suggesting a genetic origin; among the genes presently known, the most frequent to present in this way would be DYT6, caused by mutations in the transcription factor THAP1 (Fuchs et al., 2009). Additional features which may distinguish DYT6 from sporadic focal dystonias are that the dystonia is more likely to begin in brachial, rather than cervical, muscles, to become generalized, and to include speech involvement (Bressman et al., 2009).

Generalized primary dystonia is less common than primary focal dystonia, and more likely to be genetic in origin. Among patients with young onset of generalized dystonia (before age 28) the most common cause is DYT1 dystonia, the result of a mutation in the TOR1A gene encoding the protein torsinA (Ozelius et al., 1997). This is the prototypical primary dystonia, sometimes called Oppenheim's dystonia or, in the older literature, dystonia musculorum deformans (DMD, a term which likely was applied to other kinds of generalized dystonia, as well).

Pathological studies in sporadic primary dystonia

The number of reported autopsy studies of primary dystonia is very limited, numbering no more than a dozen all together, and the evidence for detectable neuropathological changes is mixed and inconsistent. The gene for DYT1 dystonia was not identified until 1997, so reports published prior to this lack information on genetic status and cannot be distinguished from dystonia unrelated to DYT1 except by clinical phenotype. Zweig et al. (1988) reported postmortem studies in four patients with primary dystonia, and found numerous neurofibrillary tangles and mild neuronal loss within the locus ceruleus in one case (described as DMD) and moderate-to-severe neuronal loss in several brainstem nuclei, including the substantia nigra pars compacta, locus ceruleus, raphe nuclei, and pedunculopontine nucleus in another case described as Meige syndrome; the remaining two cases (another with DMD and one with spasmodic torticollis) appeared normal (Zweig et al., 1988). Gibb et al. (1988) reported four cases of "primary" dystonia, three with cranial dystonia (blepharospasm with oromandibular dystonia in two, blepharospasm alone in one), and one patient with oromandibular dystonia with retrocollis. They observed an angioma in the dorsal pons in the patient with isolated blepharospasm, while the other cases examined were normal (Gibb et al., 1988). Kulisevsky et al. (1988) examined a case of Meige syndrome, and found mild to moderate cell loss in the zona compacta of the substantia nigra, locus ceruleus, midbrain tectum, and dentate nucleus of the cerebellum and frequent Lewy bodies in pigmented nuclei of the brainstem (Kulisevsky et al., 1988). Similar findings of Lewy pathology in Meige syndrome were reported by Mark et al. (1994), but they also observed that there was evidence for decreased dopamine turnover and suggested that the underlying disorder was a form of Lewy Body disease rather than a primary dystonia (Mark et al., 1994).

Pathology of genetic dystonias: DYT1 and DYT6

While studies of genetically-identified dystonia might seem to offer less heterogeneity than studies of sporadic dystonia, there is little data of this kind available. In 2002, Walker et al. reported a study in which they examined the localization of torsinA in a single case of