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Editorial

A new twist on the anatomy of dystonia

The basal ganglia and the cerebellum?

H.A. Jinnah, MD, PhD; and Ellen J. Hess, PhD

The dystonias encompass a heterogeneous collection of disorders that share characteristic involuntary twisting movements or odd postures. They can be classified according to the body part affected. The focal dystonias affect an isolated body region such as the neck (cervical dystonia), eyes (blepharospasm), hand (writer's cramp), or larynx (spasmodic dysphonia). Involvement of two continuous regions is segmental dystonia, and generalized dystonia has broader involvement including one or both legs.

In this issue of *Neurology*, Le Ber et al.[1] report a new syndrome based on 12 patients from 8 different families with slowly progressive ataxia and focal or segmental dystonia. Most displayed dystonia of the upper limbs, often with spasmodic dysphonia. Some also had cervical or facial dystonia. These patients are similar to those described in at least two prior reports. Fletcher et al.[2] described 8 patients with ataxia and a variety of focal dystonias including writer's cramp, cervical dystonia, or spasmodic dysphonia. Kuoppamaki et al.[3] described 5 patients with ataxia and cervical dystonia. Because these patients did not have any known metabolic or degenerative causes, they collectively may justify the recognition of a new heritable syndrome combining a slowly progressive ataxia with focal or segmental dystonia.

A provocative suggestion by Le Ber et al. is that dystonia, at least in their patients, arises from dysfunction of the cerebellum. This suggestion challenges traditional views of the anatomy of dystonia, which focus predominantly on the basal ganglia. The link between the basal ganglia and dystonia is supported by indisputable evidence. CT and MRI studies have repeatedly linked dystonia with focal lesions of the basal ganglia,[4] and PET and other functional imaging techniques reveal abnormal basal ganglia function even when focal lesions are not apparent.[5,6]

A major reason Le Ber et al. propose a link between dystonia and the cerebellum is that brain MRI revealed prominent atrophy of the cerebellum, without obvious abnormalities of the basal ganglia. They acknowledge that the cerebellar atrophy may be unrelated to dystonia, and that additional basal ganglia defects may have escaped detection. On the other hand, they also summarize some of the emerging evidence for a primary role of the cerebellum in the genesis of dystonia. Autopsy studies established a link between cervical dystonia and tumors of the cerebellum decades ago, and in some cases it improves or disappears after tumor removal.[7,8] More recent neuroimaging studies have shown the most frequent abnormalities among patients with cervical dystonia are in the cerebellum or its afferents.[9] Thalamic lesions can cause limb dystonia, and the responsible lesions occur most frequently in subnuclei linked to the cerebellum, not the basal ganglia.[10,11] An effective surgical target for deep brain stimulation in dystonia also involves the thalamic regions connected with the cerebellum. Dystonia can be a prominent feature in the degenerative spinocerebellar ataxias, including some where the known neuropathology is limited to the cerebellum.[12]

In nearly all of the functional imaging studies showing abnormal basal ganglia function in dystonia, there is parallel evidence for abnormal cerebellar function.[5] Though the cerebellar abnormalities are often interpreted as compensations for primary defects arising elsewhere, the nature of the studies makes it impossible to distinguish compensation from causation. The types of studies required to establish causation frequently can be done only in animals. Indeed, animal studies have shown that cerebellar abnormalities cause dystonia. In a genetic rat model, generalized dystonia was replaced by

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ataxia after surgical ablation of an abnormally functioning cerebellum.[13] In a genetic mouse model, paroxysmal dystonia was replaced by ataxia after selective elimination of abnormal cerebellar Purkinje neurons.[14] Dystonia can even be induced in normal mice by local application of excitatory drugs such as kainic acid to the cerebellar cortex.[15]

How could lesions of the cerebellum cause ataxia, dystonia, or both? The answer may lie in the nature of the lesion. A simple analogy involves the motor cortex. Whereas some lesions (such as stroke) lead to loss of function expressed as paralysis, other lesions (such as those responsible for epilepsy) produce aberrant function expressed as excessive motor output and convulsions. Similarly, lesions leading to loss of cerebellar function may result in ataxia, but lesions leading to abnormal output could cause dystonia. This suggestion is supported by the animal studies showing that ablation of the cerebellum causes ataxia while pharmacologic excitation causes dystonia.[15] How could dystonia result from lesions in distinct motor systems? One possibility is that the superficial similarities among the dystonias belie a much more heterogenous pathophysiology than currently conceived. Another possibility is that dystonia results from defective interactions among different nodes in a motor network, rather than a defect in one motor pathway. This suggestion is supported by recent studies revealing an anatomic link between the cerebellum and the basal ganglia.[16]

The evaluation of a neurologic problem traditionally proceeds by two basic steps. The first is to localize the lesion. The second is to generate a differential diagnosis of pathologic processes that could affect the region in question. The issue of anatomy is not purely academic, as it has an enormous impact on how we think about pathophysiology and new treatment strategies. For dystonia, a role for the basal ganglia is undisputed, yet evidence similar to what was used to establish the link between the basal ganglia and dystonia is accumulating for the cerebellum. The deep-seated focus on localization in neurology makes it unsettling that we are reconsidering a core bit of our knowledge concerning the anatomy of dystonia, but recent observations compel us to begin to look beyond the basal ganglia. If we do not look, we will not see.

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