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Commentary

Pathologic changes in the brain in cervical dystonia pre- and post-mortem — a commentary with a special focus on the cerebellum

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ABSTRACT

In a recent issue of Experimental Neurology, Prudente et al. (2012) investigated the neuropathology of cervical dystonia in six patients. Their most important finding was a patchy loss of cerebellar Purkinje cells in the cerebellum. In this article we discuss their findings in the context of a review including primary and secondary cervical dystonia. An update is given of the current knowledge on structural and functional brain abnormalities in idiopathic cervical dystonia with a special focus on the cerebellum.

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Cervical dystonia

Cervical dystonia (CD) is a disorder characterized by involuntary muscle contractions, leading to twisting movements and abnormal postures of the head and neck. CD is the most common form of focal dystonia (dystonia in one body part). The complaints usually debut between 30 and 50 years and slowly progress during the first 5 years (Dauer et al., 1998). In primary CD, patients have no brain abnormalities on conventional imaging with CT or MRI, while in secondary CD lesions such as lacunar infarcts, iron depositions or hemorrhage can be detected (Strader et al., 2011). The underlying pathophysiologic mechanisms of primary CD are still largely unknown. Attempts have been made to further unravel these mechanisms using post-mortem neuropathological techniques, genetic and animal studies, neuroimaging, and clinical neurophysiology. The study recently published by Prudente and co-workers (2012) in this magazine described post-mortem findings in six patients with CD and compared them to age-matched controls. Two brain regions showed changes. Firstly, ubiquitin-positive intranuclear inclusions (Marinesco bodies) were identified in the substantia nigra. This was of interest, but there was no significant increase of Marinesco bodies in CD patient's brains compared to controls. The most consistent finding included patchy loss of Purkinje cells, areas of focal gliosis and torpedo bodies in the cerebellum (Prudente et al., 2012). Before we further discuss this study, we will give an update of the current knowledge on structural and functional brain abnormalities in idiopathic CD with a special focus on the cerebellum.

Secondary dystonia

Anatomical or functional lesions in the brain leading to CD in patients can give good insight in the pathophysiology of CD. The only patient with CD in a cohort of 58 secondary dystonia patients had an ischemic lesion in the thalamus (Strader et al., 2011). In another study in nine patients with secondary dystonia (six with craniofacial dystonia and three with CD) lesions of the brainstem were more common compared to lesions in the basal ganglia (Obeso and Gimenez-Roldan, 1988). This finding was replicated in a larger cohort of 25 secondary CD patients, in which 11 had a lesion in the brainstem or cerebellum, six in the basal ganglia, and six in the spinal cord (LeDoux and Brady, 2003). Pontomesencephalic lesions have been described more often, but the dystonia is usually more widespread than the neck region (e.g. hemidystonia or craniofacial dystonia) (Loher and Krauss, 2009). Lesions in the basal ganglia are rare in secondary CD and suggest an indirect role of the basal ganglia in the pathophysiology.

In animal models different brain areas have been lesioned in an attempt to induce dystonia. Mesencephalic lesions were shown to be able to cause CD in monkeys (Foltz et al., 1959). Lesions in the interstitial nucleus of Cajal can also cause CD in monkeys and cats (Malouin and Bedard, 1982). In rats, lesions in the midbrain correlated with CD (Andy, 1989). Unfortunately, in most cases the electrophysiological effects of these lesions on other brain regions were not studied. It is striking to see that the basal ganglia are hardly mentioned in

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these animal studies. Most studies point to different regions, most notably the cerebellum or midbrain/brainstem (Neychev et al., 2011).

Even though lesions to the brainstem and cerebellum appear to be more common than basal ganglia lesions in patients with secondary CD and in animal models, the mechanism by which they cause dystonia is unclear. A direct destructive effect is unlikely since dystonia usually occurs with a delay of weeks to even years after stroke or trauma in patients. This indicates that maladaptive re-organization might play a more important role in the pathophysiology of secondary CD compared to direct damage to the cerebellum, brainstem, basal ganglia or other brain regions (Neychev et al., 2011).

Genetics of cervical dystonia

In generalized dystonia several causative gene defects have been found, but in CD in most cases no autosomal dominant inheritance pattern can be recognized. However, 30% of patients with CD have a positive family history. It therefore, seems likely that genetic polymorphisms play a role in the pathophysiology of CD. Recently two genes for CD were discovered. The first gene was CIZ1 which encodes Cip1-interacting zinc finger protein 1, a protein involved in DNA synthesis and cell-cycle control (Xiao et al., 2012). Of interest, THAP1, the gene associated with DYT6 dystonia, and TAF1, associated with DYT3 dystonia-parkinsonism, are also involved in cell proliferation regulation and cell-cycle progression (Campagne et al., 2010; Li et al., 2004). The expression of CIZ1 was highest in the cerebellum, but also high in the cerebral cortex, substantia nigra, and putamen. The mutated form of CIZ1 might be associated with aberrant DNA synthesis and/or transcription, leading to cell cycle dysregulation and via a yet unknown mechanism to dystonia (Xiao et al., 2012). A second recently discovered gene is the ANO3 gene causing autosomal-dominant craniocervical dystonia. ANO3 encodes a predicted Ca^{2+}-gated chloride channel highly expressed in the basal ganglia. Mutations in ANO3 might therefore lead to abnormal striatal-neuron excitability manifesting itself as dystonia (Charlesworth et al., 2012). These two recently discovered genes were not screened in the discussed neuropathological study by Prudente and co-workers (2012). Subjects were screened for mutations in the two most common dystonia genes: TorsinA and THAP1. Surprisingly, the authors found that five of the six CD patients and two of the 16 controls showed a sequence variant in the THAP1 gene, correlating with a lower Purkinje cell density irrespective of disease status (Prudente et al., 2012). Further studies towards these polymorphisms are required. In conclusion, the discovery of new genes and functional studies in the near future will increase our knowledge of dystonia.

Neuroimaging

We recently published an extensive review on structural, functional and molecular imaging of the brain in all forms of primary focal dystonia (Zoons et al., 2011). We will summarize the structural abnormalities found in CD here in short.

Using voxel-based morphometry (VBM) regional brain volumes can be compared between two groups on T1-weighted magnetic resonance imaging (MRI) scans. Five VBM studies have been published including patients with CD, but the results have been highly inconsistent. Two studies found decreased volume of the putamen (Obermann et al., 2007; Pantano et al., 2011), but an increase of putaminal volume has also been found (Bradley et al., 2009). Other replicated findings include increased volume of the globus pallidus pars interna (GPi) (Draganski et al., 2003; Egger et al., 2007) and the cerebellum (Draganski et al., 2003; Obermann et al., 2007). A number of other brain regions were found to be enlarged or decreased in different studies, but these findings have not been replicated in other studies. Overall, areas that have been most consistently implicated in VBM studies in patients with CD are the basal ganglia and the cerebellum.

Diffusion tensor imaging is a technique that measures macroscopic axonal organization in nervous system tissues by measuring water diffusion (Mori and Zhang, 2006). In total five DTI studies have been performed in patients with CD. A decreased fractional anisotropy (FA) was found in the corpus callosum, as well as decreased mean diffusivity (MD) in the left pallidum, left putamen and caudate nucleus bilaterally in patients with CD when compared to healthy controls. An increased FA was found bilaterally in the putamen (Colosimo et al., 2005; Fabbrini et al., 2008). MD was increased in the prefrontal cortex bilaterally and the left supplementary motor area (Fabbrini et al., 2008). These findings are consistent with increased fiber coherence and more ordered tissue, possibly indicating increased cellularity in the basal ganglia, including the putamen, and neuronal loss in the prefrontal cortex, supplementary motor area and the corpus callosum. In contrast to this, another study found an increase in FA in the thalamus, basal ganglia and adjacent white matter and significant decreased FA in the frontal projections in seven patients suffering mainly from CD (Bonilha et al., 2007). In a later study, the same group found disrupted thalamic–prefrontal pathways in seven patients with mainly CD compared to controls (Bonilha et al., 2009). One study found unilateral increased FA, consistent with subcortical white matter abnormalities in the ansa lenticularis in patients with CD, compared to controls, that disappeared 4 weeks after treatment with botulinum neurotoxin (Blood et al., 2006). Concluding, most found DTI abnormalities in patients with CD were located in the basal ganglia, the thalamus and in white matter structures connecting these two regions. Cerebellar abnormalities were not found using DTI in patients with CD.

In both VBM and DTI studies it is unclear whether the found abnormalities are cause or consequence of the dystonia. Especially, since it is known that repeated movements or other tasks often increase the size of certain brain areas (Groussard et al., 2010; Jancke et al., 2009). Another limitation of both VBM and DTI studies is that in most studies predefined regions of interest (ROIs) are being studied. As the basal ganglia have been implicated in the pathophysiology of dystonia for a long period they are usually also defined as ROI, while the cerebellum has only sparsely been investigated with VBM and DTI.

Post-mortem studies

In the beginning of the 20th century, neurosurgeons noted that approximately half the patients with a tumor in the posterior fossa, mostly affecting the cerebellum, showed a rotation of the head and/or head tilt with the ear approximating the shoulder (Batten, 1903; Brain, 1926; Grey, 1916). It is likely that these patients had CD even though focal forms of dystonia were not described as such until decades later. More recently, it has also been described that CD can remit by removing the mass from the posterior fossa (Krauss et al., 1997; Tranchant et al., 1991; Turgut et al., 1995).

More recent studies describe small case series of neuropathological findings in patients with primary CD. Prudente and co-workers (2012) reviewed the published cases and divided them based on the probability that it was truly a case of primary CD. In all but one of the cases with a high probability of primary CD there were no abnormalities found at brain autopsy (Garcia-Albea et al., 1981; Gibb et al., 1988; Jankovic et al., 1987; Tarlov, 1970; Zweig et al., 1988). One study found diffuse gliosis in the globus pallidus and patchy gliosis in the caudate nucleus and putamen in a patient with a high probability as well as two patients with a moderate probability of primary CD (Holton et al., 2008). One of the patients with a moderate probability also showed signs of Alzheimer's disease and Lewy bodies in the basal ganglia, while the other patient showed evidence of small vessel disease in the basal ganglia (Holton et al., 2008). As the authors correctly point out these studies have several limitations: all but one were performed before immunohistological staining was available and none of the studies used quantifiable measures for their findings. Furthermore, in all studies a limited number of predefined ROIs were investigated.

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