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Review article

Using the shared genetics of dystonia and ataxia to unravel their pathogenesis

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ABSTRACT

In this review we explore the similarities between spinocerebellar ataxias and dystonias, and suggest potentially shared molecular pathways using a gene co-expression network approach. The spinocerebellar ataxias are a group of neurodegenerative disorders characterized by coordination problems caused mainly by atrophy of the cerebellum. The dystonias are another group of neurological movement disorders linked to basal ganglia dysfunction, although evidence is now pointing to cerebellar involvement as well. Our gene co-expression network approach identified 99 shared genes and showed the involvement of two major pathways: synaptic transmission and neurodevelopment. These pathways overlapped in the two disorders, with a large role for GABAergic signaling in both. The overlapping pathways may provide novel targets for disease therapies. We need to prioritize variants obtained by whole exome sequencing in the genes associated with these pathways in the search for new pathogenic variants, which can than be used to help in the genetic counseling of patients and their families.

Contents

Abbreviations: AMPAR, α-amino-3-hydroxyl-5methyl-4-isoxazole-proprionate Receptor; BDNF, brain derived neurotrophic factor; CB, cerebellum; DCN, deep cerebellar nuclei; EBCC, eye blink classical conditioning; GABA, gamma aminobutyric acid; NGS, next generation sequencing; NMDA, *N*-methyl-D-aspartate; PC, Purkinje Cell; SCA, spinocerebellar ataxia.

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1. Introduction

The cerebellar ataxias are a heterogeneous group of movement disorders characterized by degeneration of Purkinje cells (PCs) and atrophy of the cerebellum. Motor symptoms include loss of balance and coordination, unstable gait, dysarthria and abnormal eye movements. Cerebellar ataxias can be primary (genetic), congenital (brain malformations) or acquired (e.g. after stroke). The spinocerebellar ataxias (SCAs), the genetically dominant forms of cerebellar ataxia, have an estimated prevalence of 1–3 per 100,000 in Europe with onset usually occurring in adulthood (Durr, 2010). Dystonia is a neurological movement disorder characterized by involuntary muscle contractions that cause abnormal twisting movements and postures. It has many clinical manifestations, ranging from isolated and focal to generalized dystonia, or dystonia in combination with other neurological symptoms such as myoclonus or ataxia. The list of diseases that can cause or present with dystonia is extensive (Fung et al., 2013).

Many patients show a combination of cerebellar ataxia and dystonia. Dystonia is frequently seen in SCA2 (14%), SCA3 (24%) and SCA17 (53%), and regularly seen in SCA types 1, 6, 12, 14, 15/16 and 20, in ataxia telangiectasia, in Friedreich's ataxia, and in ataxia with oculomotor apraxia (Neychev et al., 2011; Prudente et al., 2014; van Gaalen et al., 2011). Kuoppamaki and Van de Warrenburg reported eleven patients in total who showed early onset, primarily cervical, dystonia in combination with slowly progressive cerebellar ataxia. All had tested negative for the most common SCA types, although some patients had a positive family history, and all the patients showed cerebellar atrophy (Kuoppamaki et al., 2003; van de Warrenburg et al., 2007).

Taken into account the clinical and etiological heterogeneity, the exact pathophysiological mechanisms of SCA and dystonia are not exactly clear. For SCA, several etiological roles have been identified that lead to neurotransmission deficits and result in PC death, including transcriptional dysregulation, autophagy, mitochondrial defects and alterations in calcium homeostasis (Matilla-Dueñas et al., 2014). In dystonia, the basal ganglia have classically been attributed a key role. However, recent theories support a pathophysiological model in which dystonia is seen as a network disorder involving several brain regions, including the sensorimotor cortex, brainstem, thalamus and cerebellum (Neychev et al., 2011; Prudente et al., 2014). Nevertheless, it remains uncertain whether dysfunction of a single brain area, combined dysfunction of multiple areas, or abnormal communication between several brain areas leads to dystonia. Dystonia is regarded as a disorder of motor control (Hallett, 2011) involving the cerebellum (Shadmehr and Krakauer, 2008) and the basal ganglia, which are interconnected (Fig. 1). The cerebellum also plays a role in cerebellar ataxias. In this review, we therefore focus on the potentially shared pathophysiology of the cerebellum in SCA and dystonia.

2. Evidence for overlap in pathology between ataxia and dystonia

2.1. Evidence from clinical studies

Evidence of cerebellar involvement in dystonia comes from several lines of research. By the beginning of the 20th century it had already been recognized that tumors in the posterior fossa could result in the abnormal postures of the head that we would now classify as dystonia (Batten, 1903; Extremera et al., 2008; Grey, 1916; Krauss et al., 1997). These clinical findings were replicated in a larger cohort of 25 cervical dystonia patients, in which almost half of the patients had a lesion in the brainstem or cerebellum, whereas lesions in the basal ganglia were seen in only a quarter of them (LeDoux and Brady, 2003). Batla et al. showed cerebellar abnormalities in 26 out of 188 (14%) cervical dystonia patients (Batla et al., 2015). For secondary blepharospasm, a focal form of dystonia, lesions were found mostly in the thalamus, with the remainder equally split between basal ganglia and cerebellum (Khooshnoodi et al., 2013). Other cases reported oromandibular dystonia and blepharospasm after cerebellar infarction (Akin et al., 2014; O'Rourke et al., 2006; Rumbach et al., 1995), hemidystonia caused by vertebral artery occlusion (Waln and LeDoux, 2010), and focal limb dystonia after isolated cerebellar tuberculoma (Alarcón et al., 2001).

Only small case series have been reported for neuropathological changes in dystonia, specifically in isolated cervical dystonia. A recent review showed that no pathological abnormalities were found in almost all reported cases that had a high probability of suffering from cervical dystonia (Prudente et al., 2013). These case studies have, however, several shortcomings. The major limitation is that most were focused on specific brain regions that did not include the cerebellum or the brainstem. The authors also found that the cerebellums of the cervical dystonia patients had significantly lower PC density compared to healthy controls (Prudente et al., 2013; Zoons and Tijssen, 2013). This implies a role for the cerebellum in dystonia, and it is further worth noting that loss of PCs is also associated with other neurodegenerative disorders, such as SCA.

2.2. Evidence from imaging studies

In addition to alterations in the sensorimotor cortices and the basal ganglia, structural abnormalities in the cerebellum or cerebellar projections have been found in several types of dystonia. Diffusion tensor imaging was used to assess microstructural white matter integrity in different non-hereditary isolated dystonias and demonstrated alterations varying from the white matter tracts underlying several cortical areas (Delmaire et al., 2009; Fabbrini et al., 2008) to connections to the cerebellar lobules and peduncles (Niethammer et al., 2011; Prell et al., 2013; Ramdhani et al., 2014; Sako et al., 2015; Simonyan et al., 2008; Yang et al., 2014). See reviews by Neychev et al. (2011) and Zoons et al. (2011) for a complete overview of the evidence for the role of the cerebellum based on imaging studies. More recent findings come from studies of several groups of hereditary dystonia. In DYT1, DYT6 and DYT11 patients, microstructural abnormalities were found close to the superior cerebellar peduncle (Carbon et al., 2008, 2004; van der Meer et al., 2012). A reduction in structural connectivity of the cerebellothalamic pathway in DYT1 and DYT6 patients was also seen by tractography (Argyelan et al., 2009).

Metabolic imaging using [18F]-fluorodeoxyglucose-PET also shows involvement of the cerebellum in dystonia. The most reported pattern of altered metabolic activity involves the basal