This scientific commentary refers to ‘Autonomic dysfunction is a major feature of cerebellar ataxia, neuropathy, vestibular areflexia “CANVAS” syndrome’, by Wu et al. (doi: 10.1093/brain/awu196).

A series of papers published in the 1990s by the Bronstein group triggered—albeit unintentionally—intensified research into a clinical syndrome characterized by a combination of selective bilateral vestibulopathy and cerebellar ataxia (Bronstein et al., 1991; Waterston et al., 1992; Rinne et al., 1995). The term ‘cerebellar ataxia, neuropathy, vestibular areflexia syndrome’ (CANVAS) was subsequently coined in 2011 by Szmulewicz and colleagues, following a retrospective analysis of case records of patients with cerebellar ataxia and bilateral vestibulopathy with an impaired visually enhanced vestibulo-ocular reflex (Szmulewicz et al., 2011). The latter reflects a combined failure of all three compensatory eye movement systems, and can be demonstrated clinically by turning a patient’s head slowly from side to side, with the test considered to be positive if compensatory eye movements are saccadic rather than smooth. Our understanding of CANVAS syndrome has improved over recent years and there have been numerous publications on specific symptoms. The existence of affected sibling pairs suggests that CANVAS is a late-onset recessive disorder, although its genetic basis remains to be elucidated (Szmulewicz et al., 2011). There has also been extensive research into the underlying pathophysiological mechanisms, and it was recently shown that a dorsal root ganglionopathy causes the sensory impairment in CANVAS (Szmulewicz et al., 2014). In this issue of Brain, Wu and colleagues convincingly report that autonomic failure is another integral part of CANVAS syndrome (Wu et al., 2014).

In their study, Wu and colleagues found that among 23 patients with CANVAS syndrome without concomitant diabetes mellitus, all reported at least one autonomic symptom; in fact, 91% had at least two. Cold feet (78%), erectile dysfunction (78% of men), light-headedness (65%), constipation (65%) and dry mouth or eyes (52%) were the most common symptoms reported. Formal autonomic testing revealed evidence of parasympathetic and/or sympathetic involvement in 83% of patients. Seventeen (77%) patients had an abnormal diastolic response to handgrip and seven (30%) patients fulfilled criteria for orthostatic hypotension. An abnormal heart rate response to deep breathing was noted in 11 (52%) patients. Intriguingly, an inadequate heart rate response to standing was detected in 45% of patients. The Valsalva ratio was also found to be abnormal in 10 patients (45%).

These findings have two significant clinical implications: (i) it is important to recognize and appropriately diagnose autonomic symptoms within the CANVAS spectrum because some can be alleviated by treatment, thereby reducing the disease burden; and (ii) based on these findings, CANVAS emerges as an important differential diagnosis in the work-up of adult-onset progressive ataxias with autonomic failure. The most important differential diagnosis in patients with prominent autonomic failure combined with progressive cerebellar ataxia is multiple system atrophy (Klockgether, 2010). However, these two conditions can be separated clinically. Bilateral vestibulopathy is unusual in multiple system atrophy; thus, an impaired visually enhanced vestibulo-ocular reflex is a warning sign suggesting CANVAS. Furthermore, in comparison to CANVAS, multiple system atrophy is associated with a more prominent urogenital involvement with early and frequent urinary incontinence (Wenning et al., 2013). In addition, the lesion site is different in the two conditions. Multiple system atrophy is considered to feature pre-ganglionic autonomic failure, whereas (post-)ganglionic degeneration appears to be present in CANVAS. To this end, a study on the integrity of post-ganglionic cardiac sympathetic fibres using [123I]metaiodobenzylguanidine myocardial scintigraphy is highly warranted, as this may constitute an additional marker for distinguishing the two disorders. Another important differential diagnosis is spinocerebellar ataxia type 3 (Machado-Joseph-Disease), with its triad of reduced visually enhanced vestibulo-ocular reflex gain, sensory peripheral neuropathy and cerebellar ataxia (Szmulewicz et al., 2011). A pattern of autonomic failure similar to that in CANVAS is frequently present in spinocerebellar ataxia type 3, thus these two disorders cannot be differentiated on the basis of autonomic features alone. However, one would expect a mixed motor and sensory neuropathy and a pedigree consistent with dominant inheritance in spinocerebellar ataxia type 3.

Wu et al. hypothesize that autonomic dysfunction in CANVAS is part of a primary ganglionopathy involving the autonomic, vestibular, facial, trigeminal and sensory ganglia (Szmulewicz et al., 2014; Wu et al., 2014), although supportive immunohistochemical analyses are lacking and would be of great interest. We hold the belief that autonomic dysfunction in CANVAS is exclusively mediated by peripheral neuropathy. To this end, testing for denervation hypersensitivity of the pupils and a lack of induction of...
sweating following local pilocarpine application would be important measures to establish a post-ganglionic lesion site.

Another important avenue of research will be the establishment of symptomatic treatment of autonomic changes in CANVAS. There is good cause to believe that symptomatic treatments established in other autonomic neuropathies (e.g. diabetic autonomic neuropathy) will also mitigate autonomic symptoms in CANVAS. However, given the lack of data regarding this approach in CANVAS, treatment decisions will need to be made on an individual basis and extensive monitoring will be required.

In summary, the study by Wu et al. provides evidence that sympathetic and parasympathetic autonomic failure is an integral part of CANVAS. In clinical practice this finding adds to difficulties in the differential diagnosis of adult-onset, progressive ataxias. Additional studies assessing the safety and efficacy of existing drugs for counteracting autonomic symptoms in CANVAS are urgently required. Finally, from a scientific point of view, it will be interesting to establish the site of the lesion in CANVAS-associated autonomic failure, and we are convinced that future clinical and pathological studies in CANVAS will shed light on the pathomechanisms involved.

Florian Krismer and Gregor K. Wenning
Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

Correspondence to: Prof. Gregor K. Wenning, MD, PhD, MSC
E-mail: Gregor.Wenning@i-med.ac.at

doi:10.1093/brain/awu220

Identification of the SCA21 disease gene: remaining challenges and promising opportunities

This scientific commentary refers to ‘TMEM240 mutations cause spinocerebellar ataxia 21 with mental retardation and severe cognitive impairment’, by Delplanque et al. (doi:10.1093/brain/awu202).

For nearly one and a half centuries, physicians have observed that disorders of coordination often run in families, and have documented how variable these disorders can be in terms of their natural history and symptomatology (Friedreich, 1863; Menzel, 1891). Transmission of such afflictions from parent to child led to the realisation that they show an autosomal dominant pattern of inheritance. The disorders were named ataxias, from the Greek ‘taxis’ meaning order, and were associated with dysfunction of the cerebellum and its connections. For a century, they were classified mainly based upon their neuropathology, and were collectively known as olivopontocerebellar atrophies (Konigsmark and Weiner, 1970). Anita Harding refined this classification in the 1980s to account for the mode of inheritance and clinical features, and created a very useful classification scheme consisting of three types of autosomal dominant cerebellar ataxia (ADCA). According to the Harding ADCA classification system, patients with type I ADCA present with ataxia in combination with extracerebellar signs, type II ADCA patients display ataxia, extracerebellar signs, and also retinal degeneration, and type III ADCA patients exhibit a pure cerebellar ataxia without any extracerebellar signs (Harding, 1982). With the advent of molecular genetics, the ADCA were further defined based upon their genetic linkage location and became known as the spinocerebellar ataxias, or ‘SCAs’. Today, there are more than 35 known SCA genetic loci, within which 22 causative genes have been identified (Matilla-Duenas et al., 2012). The SCAs that belong to Harding’s type I ADCA category are a very heterogeneous group of diseases, with highly pleiotropic phenotypes and complex pyramidal and extrapyramidal symptoms, including cognitive decline, motor neuron disease, neuropathy, and depression. In this month’s issue of Brain, Delplanque and colleagues add another piece to the SCA puzzle by refining the clinical description and defining the genetic basis of SCA21 (Delplanque et al., 2014).

References


