CHAPTER 27

THE SPINOCEREBELLAR ATAXIAS:
Clinical Aspects and Molecular Genetics

Antoni Matilla-Dueñas,*1 Marc Corral-Juan,1 Victor Volpini2 and Ivelisse Sanchez1
1Basic, Translational and Neurogenetics Research Unit, Department of Neurosciences, Health Sciences Research Institute Germans Trias i Pujol (IGTP), Universitat Autònoma de Barcelona, Barcelona, Spain;
2Molecular Diagnosis Center of Inherited Diseases, Institut d’Investigacions Biomèdiques de Bellvitge (IDIBELL), L’Hospitalet de Llobregat, Barcelona, Spain
*Corresponding Author: Antoni Matilla-Dueñas—Email: amatilla@igtp.cat; amatilla@neurodeg.net

Abstract: Spinocerebellar ataxias (SCAs) are a highly heterogeneous group of inherited neurological disorders, based on clinical characterization alone with variable degrees of cerebellar ataxia often accompanied by additional cerebellar and noncerebellar symptoms which in most cases defy differentiation. Molecular causative deficits in at least 31 genes underlie the clinical symptoms in the SCAs by triggering cerebellar and, very frequently, brain stem dysfunction. The identification of the causative molecular deficits enables the molecular diagnosis of the different SCA subtypes and facilitates genetic counselling. Recent scientific advances are shedding light into developing therapeutic strategies. The scope of this chapter is to provide updated details of the spinocerebellar ataxias with particular emphasis on those aspects aimed at facilitating the clinical and genetic diagnoses.

INTRODUCTION

Ataxia is a neurological disorder characterised by loss of control of body movements. Patients suffering from ataxia are clumsy and unable to walk steadily, have slurred speech and eventually lose the ability to swallow and breathe smoothly. Ataxia results from variable degeneration of neurons in the cerebellar cortex, brain stem, spinocerebellar tracts and their afferent/effenter connections. Such neurodegeneration can result from multiple sclerosis, brain tumour, alcoholism, or an inherited genetic defect. There are over 60 different types of inherited ataxias striking during childhood or adulthood.

Neurodegenerative Diseases, edited by Shamim I. Ahmad.
Differential diagnosis of hereditary ataxia includes acquired, nongenetic causes of ataxia, such as alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumours, or paraneoplastic diseases associated with occult carcinoma of the ovary, breast, or lung. The possibility of an acquired cause of ataxia needs to be considered in each individual with ataxia because a specific treatment may be available. The hereditary ataxias have been extensively reviewed, and a comprehensive description can be found online. The hereditary ataxias are usually subdivided by their mode of inheritance (i.e., autosomal dominant, autosomal recessive, X-linked and mitochondrial) and the causative gene or chromosomal locus. The term “spinocerebellar ataxias” is commonly used for those inherited ataxias presenting an autosomal dominant inheritance. Synonyms for spinocerebellar ataxias (SCAs) used prior to the identification of the molecular genetic basis of these disorders are Marie’s ataxia, inherited olivopontocerebellar atrophy, cerebello-olivary atrophy, autosomal dominant cerebellar ataxias (ADCAs) or the more generic term, spinocerebellar degenerations.

In all SCAs, ataxia is the predominant clinical manifestation which patients frequently present with additional non-ataxia symptoms. Several scales have been developed to measure the severity of ataxia. Among them, the Scale for the Assessment and Rating of Ataxia (SARA) has been recently developed and validated and has proven useful to measure ataxia severity by assigning scores ranging from 0 to 40 with 0 indicating absence of ataxia and 40 the most severe degree of ataxia. Non-ataxia symptoms have been conveniently assessed with the Inventory of Non-Ataxia Symptoms (INAS). INAS consists of 30 items, each of which is related to one of the following 16 symptoms or syndromes: areflexia, hyperreflexia, extensor plantar response, spasticity, paresis, amytrophy, fasciculations, myoclonus, rigidity, chorea, dystonia, resting tremor, sensory symptoms, brainstem oculomotor signs (horizontal and vertical ophthalmoparesis, slowing of saccades), urinary dysfunction and cognitive impairment. These recently developed rating scales and SCA functional indexes are proving very valuable to validate neurological assessment methods and therapeutic interventions by measuring the severity of the ataxia and non-ataxia symptoms in ongoing and future clinical trials in SCA patients.

The treatment of hereditary ataxia is currently primarily supportive and is the scope of the following chapter. With very few exceptions (e.g., ataxia associated with vitamin E deficiency), there are no disease-modifying therapies. Despite the lack of disease-modifying treatments, obtaining an accurate diagnosis of the specific hereditary ataxia subtype is of great value. Benefits include determining prognosis, facilitating family counselling, improving research access and providing some psychological benefit in ending the often frustrating search for an accurate aetiology. Spinocerebellar ataxias may have certain clinical features that respond very well to symptomatic medical therapy. Parkinsonism, dystonia, spasticity, urinary urgency, sleep pathology, fatigue and depression are all common in many of the ataxia subtypes and very often respond to pharmacologic intervention as in other diseases. Much of the clinical interaction between the neurologist and ataxia patients should focus on identifying and treating these symptoms. Treatment of the core clinical feature of these diseases—ataxia—is predominantly rehabilitative. The value of good physical therapy far exceeds any potential benefit from medications that a physician might prescribe to improve balance and coordination. Speech and swallowing are often affected. In more severe cases, aspiration risk can be very significant and life-threatening. Routine monitoring of swallowing by speech therapists, often including modified barium swallowing tests, is indicated in most patients. Recently there have been very encouraging advances in clinical ataxia research. Collaborative study groups throughout the world