Idiopathic Late Onset Cerebellar Ataxia (ILOCA), and Cerebellar plus Syndrome

98

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Abstract

Spinocerebellar ataxias (SCAs), also called spinocerebellar degenerations, comprise a large group of slowly progressive neurodegenerative diseases characterized by truncal and limb ataxias as the cardinal clinical features. Sporadic degenerative ataxias include idiopathic late-onset cerebellar ataxia (ILOCA), ILOCA with cerebellar-plus syndrome, and multiple system atrophy (MSA). The clinical presentations of ILOCA (CCA) are characterized by late ages at onset with slow progression and pure cerebellar ataxia with markedly ataxic gait with relative preservation of coordination in the upper limbs. ILOCA with cerebellar-plus syndrome is characterized by cerebellar ataxia together with additional neurological features including pyramidal signs, mild dementia, supranuclear ophthalmoplegia, optic atrophy, dysphagia, parkinsonism, sphincter disturbances, hypopallaesthesia, or chorea. MSA is a sporadic neurodegenerative disorder characterized by various combinations of autonomic dysfunction, cerebellar symptoms, parkinsonism, and pyramidal signs. MSA has recently been classified into two subtypes: MSA-C (characterized by cerebellar ataxia) and MSA-P (characterized predominantly by parkinsonism). Among these sporadic neurodegenerative ataxias, ILOCA (CCA) is characterized by slow progression rate, while patients with MSA-c show faster progression compared to other neurodegenerative ataxias. Although there are no curative treatments available to prevent disease progression, continuous physiotherapeutic interventions in ataxia patients are encouraged.

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Introduction

Spinocerebellar ataxias (SCAs), also called spinocerebellar degenerations, comprise a large group of slowly progressive neurodegenerative diseases characterized by truncal and limb ataxias as the cardinal clinical features. The age at onset broadly ranges from childhood to late adulthood. The etiologies of SCAs are diverse, including those of both hereditary and sporadic diseases. Recent advances in the molecular genetics of SCAs have revealed a number of loci and causative genes for hereditary ataxias, of which dominantly inherited SCAs include SCA1 to SCA36, and dentatorubral-pallidoluysian atrophy (DRPLA) (Manto and Marmolino 2009), Schols (2004). Ataxias with autosomal recessive inheritance include Friedreich ataxia, ataxia with isolated vitamin E deficiency (AVED), ataxia, early-onset ataxia with ocular motor apraxia and hypoalbuminemia/A ataxia with oculomotor apraxia type 1 (EAOH/AOA1), ataxia with oculomotor apraxia type 2 (AOA2), ataxia-telangiectasia, ataxia-telangiectasia-like disorder, spinocerebellar ataxia with axonal neuropathy, Charlevoix-Saguenay spastic ataxia, Marinesco-Sjögren syndrome, various forms of congenital ataxias and metabolic ataxias including cerebrotendinous xanthomatosis, aceruloplasminemia, abetalipoproteinemia, and various forms of sphingolipidosis. X-linked form of ataxias includes Fragile-X tremor ataxia syndrome (FXTAS).

In the diagnostic algorithm for degenerative SCAs (Manto and Marmolino 2009), differential diagnosis of sporadic ataxias from hereditary ataxias is first required, which is accomplished mainly based on the family history and the clinical presentations. It should be noted that an isolated case of hereditary ataxia due to mutations with reduced penetrance or de novo mutations is occasionally experienced in the clinical practice. Isolated cases of autosomal recessive ataxia are also infrequently experienced. In these cases, mutational analyses are needed to make a correct diagnosis. Besides hereditary ataxias, diverse sporadic diseases presenting with ataxia, including ataxias associated with structural anomalies, intoxication, paraneoplastic cerebellar degeneration need to be excluded (Darnell and Posner 2003; Furneaux et al. 1990; Sillevis Smitt 2000), as well as presence of antibodies against glutamic acid decarboxylase (Abele et al. 1999; Saiz et al. 1997), gluten-sensitive enteropathy (Hadjivassiliou et al. 1996, 1998), infections/parainfectious diseases, endocrine abnormalities including hypothyroidism (Selim and Drachman 2001), and vitamin E deficiency (Eggermont 2006; Sitrin et al. 1987).

Once hereditary ataxias and those disorders of secondary ataxias are excluded, the category of sporadic degenerative ataxias, including idiopathic late-onset cerebellar ataxia (ILOCA), ILOCA with cerebellar-plus syndrome, and multiple system atrophy, needs to be considered. In this chapter, this category of diseases will be described in detail.

Idiopathic Late-Onset Cerebellar Ataxia (ILOCA)

The eponym of ILOCA was first introduced by Harding (1981). She reviewed the clinical features of 36 patients with late-onset cerebellar ataxia of unknown cause.
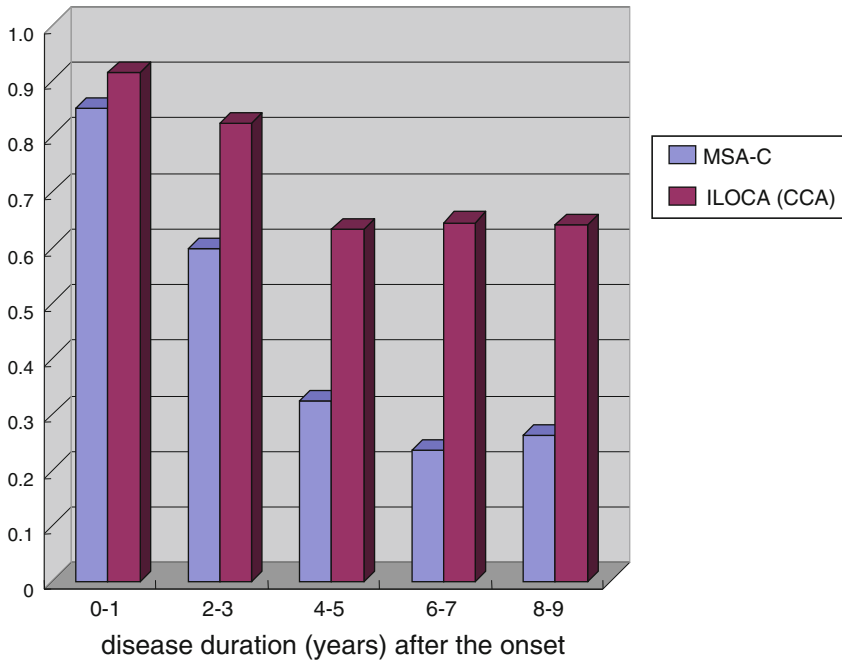
fractions

Fig. 98.1 Natural history of ILOCA (CCA) and MSA-C. Fractions of patients who are able to walk at least with one stick (Tsuji et al. 2008)

She divided the patients into three groups based on the clinical presentations. The first was characterized by pure cerebellar ataxia with the onset being relatively late (mean 54.75 years). She related this group to the Marie-Foix-Alajouanine type of cerebellar degeneration (Marie et al. 1922). The second group contained six patients with prominent tremor in the upper limbs, both resting and during action. The age at onset was 52.83 years. The third group was composed of 18 patients with a cerebellar-plus presentation similar to patients previously reported as sporadic examples of olivopontocerebellar atrophy (OPCA; mean age at onset 45.22 years).

In 1922, Marie, Foix and Alajouanine described four patients with cerebellar ataxia with the age of onset ranging from 40 to 78, presenting with pure cerebellar ataxia (Marie et al. 1922). An autopsy revealed cortical cerebellar ataxia (CCA) consisting of neuronal loss confined to the cerebellum, with extensive Purkinje cell loss in the vermis and flocculonodular lobe (Baloh et al. 1986; Critchley and Greenfield 1948; Fox et al. 2003; Greenfield 1954; Kanazawa et al. 1985; Marie et al. 1922). The clinical presentation of CCA, which corresponds to the first group of ILOCA (Harding), is pure cerebellar ataxia characterized by markedly ataxic gait with relative preservation of coordination in the upper limbs. MRI findings of patients with CCA are characterized by atrophic changes confined to cerebellar vermis and hemisphere.

The mean age at onset in patients with ILOCA (CCA) is 56.1 years of age in the Japanese population. The disease progression of ILOCA (CCA) is slow with more than 60% of the patients being able to stand with at least one stick 5 years after the onset (Fig. 98.1) (Tsuji et al. 2008).

Although there are no curative treatments available to prevent disease progression, an intensive coordinative training has been shown to lead to short-term improvements in motor performance, and furthermore, despite gradual decline of motor performance and gradual increase of ataxia symptoms, long-term improvement by continuous coordinative training has also been shown (Ilg et al. 2009, 2010). Thus, continuous physiotherapeutic interventions in ataxia patients are encouraged.

The etiology of CCA, however, is still poorly understood, and there may be heterogeneities in the etiologies for CCA. It should also be mentioned that patients with various SCAs can present with pure cerebellar syndrome especially at the early stage.

ILCOA with Cerebellar-Plus Syndrome

The clinical presentations of ILOCA with cerebellar-plus syndrome, which corresponds to the third group of ILOCA (Harding) (Harding 1981), are characterized by cerebellar ataxia together with additional neurological features including pyramidal signs, mild dementia, supranuclear ophthalmoplegia, optic atrophy, dysphagia, parkinsonism, sphincter disturbances, hypopallaesthesia, or chorea (Harding 1981; Ormerod et al. 1994; Polo et al. 1991). In the majority of patients in this group, MRI findings are characterized by combined cerebellar and brainstem atrophy. The relationship between ILOCA with cerebellar-plus and multiple system atrophy (MSA) is controversial. According to Gilman et al., only 16 (33%) of 48 cases with cerebellar-plus syndrome fulfill the criteria for multiple system atrophy (MSA-C) (Gilman et al. 1999). In other words, all patients with ILOCA with cerebellar-plus syndrome do not necessarily have MSA. Thus, ILOCA with cerebellar-plus syndrome can be heterogeneous in terms of disease entity with a portion of the patients fulfilling the criteria for MSA-C (Berciano et al. 2006).

Multiple System Atrophy (MSA)

Multiple system atrophy (MSA) is the most common form of sporadic ataxia (Tsuji et al. 2008). OPCA was first described by Déjerine and André-Thomas (1900). They described two clinical cases and one autopsy case. The clinical presentations included gait ataxia, dysarthria, increased tendon reflexes, increased muscle tone, and urinary incontinence. The autopsy finding was neuronal loss in the cerebellum, pons, and inferior olive. Recently, glial cytoplasmic inclusions that contain abnormally phosphorylated α-synuclein have been identified as the pathognomonic neuropathological abnormalities not only in OPCA but also in Shy-Drager syndrome and striatonigral degeneration (SND) (Spillantini et al. 1998; Wakabayashi et al. 1998). These findings established the clinical entity of MSA (Graham and
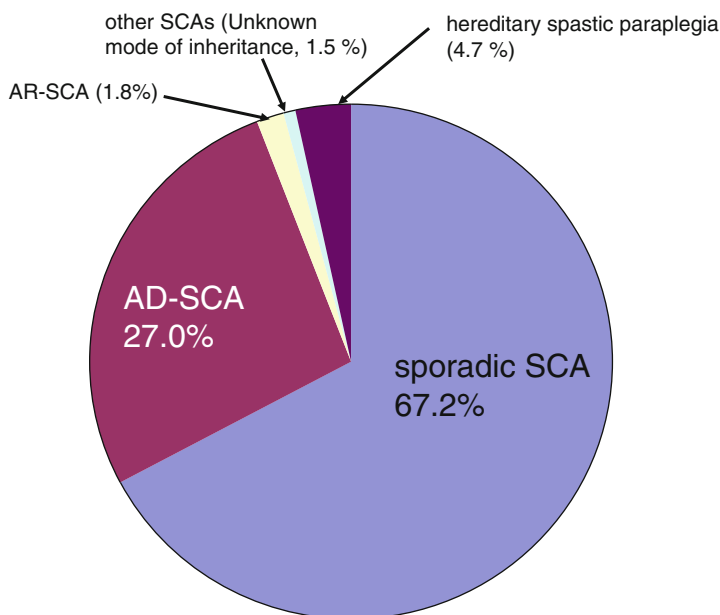
Fig. 98.2 Relative frequencies of SCAs in Japanese population (Tsuji et al. 2008)

Oppenheimer 1969), which includes OPCA, SND (Adams et al. 1964), and Shy-Drager syndrome (SDS) (Shy and Drager 1960). The consensus diagnostic criteria for MSA (Gilman et al. 1999) and the rating scale specifically designed for MSA (the unified multiple system atrophy rating scale (UMSARS)) (Wenning et al. 2004) have been proposed. Very recently, revised diagnostic criteria for MSA have been proposed (Gilman et al. 2008). MRI findings of MSA-C include atrophic changes in cerebellar vermis and hemisphere, middle cerebellar peduncle, and pontine basis. "Hot cross bun" sign of the ventral part of pons, accountable for by demyelination and gliosis of transverse fibers of the pons, is a characteristic MRI finding (Berciano et al. 2006; Massano et al. 2008).
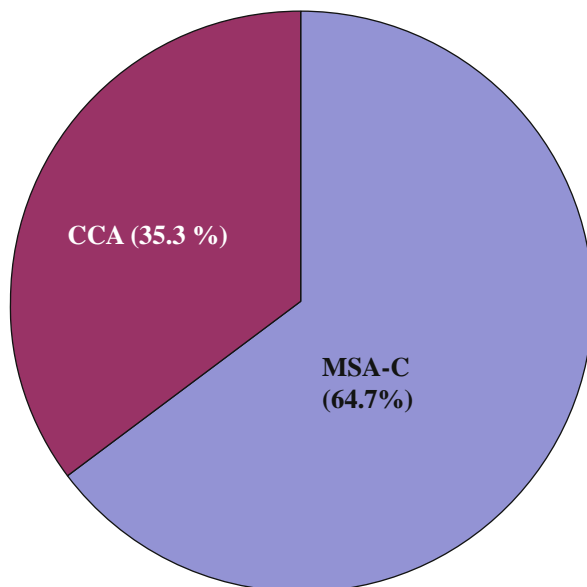
The mean age at onset in patients with MSA-C is 56.3 years of age in the Japanese population. The disease progression of MSA is faster compared to other degenerative ataxias. Only 33% of patients with MSA-C were able to walk at least with one stick 4–5 years after the onset (Fig. 98.1) (Tsuji et al. 2008).

Although there are no curative treatments available to prevent disease progression, continuous physiotherapeutic interventions in ataxia patients are also encouraged (Ilg et al. 2009, 2010).

Epidemiology of SCAs in Japan

A nation-wide epidemiological survey for SCAs in Japan based on the electronic data from the clinical inquiry sheets of 11,691 patients was conducted (Tsuji et al.

2008). The total number of registrations was 23,483, indicating that information on 49.8% of all the registered patients was collected. As shown in Fig. 98.2, sporadic ataxias accounted for 67.2% of SCAs, and hereditary ataxias for 28.8%. Among the hereditary ataxias, autosomal-dominant ataxias by far predominated. Among the sporadic ataxias, OPCA corresponding to MSA-C is the most common form of sporadic ataxia (64.7%) (Fig. 98.3). It should be noted that MSA-P was not included in the survey conducted in this study. The remaining patients were diagnosed as having CCA. The mean ages at onset for MSA-C and CCA are 56.3 and 56.1 years of age, respectively.

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