Journal of the Neurological Sciences 384 (2018) 30–35

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Idiopathic cerebellar ataxia (IDCA): Diagnostic criteria and clinical analyses of 63 Japanese patients

Kunihiro Yoshida[a,*], Satoshi Kuwabara[b], Katsuya Nakamura[c], Ryuta Abe[c], Akira Matsushima[c], Minako Beppu[b], Yoshitaka Yamanaka[b], Yuji Takahashi[d], Hidenao Sasaki[e], Hidehiro Mizusawa[d], on behalf of The Research Group on Ataxic Disorders

[a] Department of Brain Disease Research, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan
[b] Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan
[c] Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan
[d] Department of Neurology, The National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8551, Japan
[e] Department of Neurology, Hokkaido University Graduate School of Medicine, N15 W7 Kita-ku, Sapporo 060-8638, Japan

ARTICLE INFO

Keywords:
Sporadic ataxia
Cortical cerebellar atrophy (CCA)
Idiopathic cerebellar ataxia (IDCA)
Multiple system atrophy (MSA)
Diagnostic criteria

ABSTRACT

Cortical cerebellar atrophy (CCA) and multiple system atrophy with predominant cerebellar ataxia (MSA-C) are the two major forms of adult-onset sporadic ataxia. Contrary to MSA-C, there are neither diagnostic criteria nor neuroimaging features pathognomonic for CCA. Therefore, it is assumed that the category of CCA in the Japanese national registry include heterogeneous cerebellar ataxic disorders. To refine this category in more detail, we here used a clinical-based term, "idiopathic cerebellar ataxia (IDCA)", and proposed its diagnostic criteria. We collected 346 consecutive patients with the core features of the criteria (sporadic, insidious-onset and slowly progressive cerebellar ataxia in adults, and cerebellar atrophy on brain imaging). Of these, 212 (61.3%) were diagnosed with probable or possible MSA, and 30, who did not meet the diagnostic criteria for MSA at examination, were also excluded because of MRI findings suggestive of MSA. Twenty two were proven to have hereditary spinocerebellar ataxias by genetic testing, and 19 had secondary ataxias. Finally, the remaining 63 (18.2%) were diagnosed with IDCA. The mean (standard deviation) age at onset was 57.2 (10.8) years. Of these, 25 (39.7%) showed pure cerebellar ataxia, and the remaining 38 (60.3%) had some of extracerebellar features including abnormal tendon reflexes (46.0%), positive Babinski sign (9.5%), sensory disturbance (12.7%), cognitive impairment (9.5%), and involuntary movements (7.9%). Our results show that IDCA refined by the diagnostic criteria still includes clinically and genetically heterogeneous ataxic disorders. More extensive genetic analyses will be of significance for further clarification of this group.

1. Introduction

At present, sporadic degenerative ataxia mainly consists of cortical cerebellar atrophy (CCA) and olivopontocerebellar atrophy (OPCA) (or multiple system atrophy with predominant cerebellar ataxia [MSA-C]). Both disease entities are originally based on neuropathological findings [1]. MSA-C is an established entity that can be diagnosed by the consensus diagnostic criteria [2] and has characteristic neuroimaging hallmarks, such as hot cross bun sign and hyperintensities in the middle cerebellar peduncles on T2-weighted magnetic resonance imaging (MRI). Furthermore, the key molecule tightly involved in the pathogenesis, α-synuclein, has been identified and utilized as an imaging biomarker of MSA [3].

On the other hand, the diagnosis of CCA largely depends on exclusion of other causes of cerebellar ataxia. The main reason for this is that there is no biomarker specific for restricted cerebellar or cerebello-olivary degeneration, which is a neuropathological hallmark of CCA. Therefore, ataxic patients are easily classified into CCA when their family history is not suggestive of hereditary ataxia or is not informative, and they are unlikely to be MSA-C at examination. As a result, the present category of CCA in the Japanese national registry of intractable diseases is considered to consist of cases with heterogeneous ataxic syndromes. It probably includes not only early stage MSA-C but also undefined hereditary ataxias, acquired ataxias (immune-mediated, alcoholic, drug-induced, metabolic, etc.), or non-spinocerebellar degeneration (non-SCD) with predominant cerebellar ataxia (progressive supranuclear palsy with predominant cerebellar ataxia [PSP-C], etc.).

To refine the category of CCA in Japan in more detail, we used a

* Corresponding author at: Department of Brain Disease Research, Shinshu University School of Medicine, Japan.
E-mail address: kyoshida@shinshu-u.ac.jp (K. Yoshida).

https://doi.org/10.1016/j.jns.2017.11.008
Received 21 June 2017; Received in revised form 18 October 2017; Accepted 6 November 2017
Available online 07 November 2017

Table 1
Diagnostic criteria for idiopathic cerebellar ataxia (IDCA).

1. Core features

1) Sporadic (negative family history)[a]
2) Cerebellar ataxia with insidious onset in adults (> 30 years old) and a slowly progressive course
3) Cerebellar atrophy (bilateral) on brain CT/MRI

2. Exclusion criteria

1) Multiple system atrophy (probable or possible MSA)[b]
Patients with MRI findings suggestive of MSA[c] are excluded, even if they don't meet the criteria for possible MSA.

2) Hereditary ataxias
Negative for SCA1, 2, MJD/SCA3, 6, 8, 17, 31, or DRPLA by genetic testing[d]
3) Other diseases (no evidence of established or symptomatic causes):
- Neoplastic (tumor)
- Cerebrovascular
- Infectious (Epstein-Barr virus, varicella-zoster virus, etc.)
- Immune-mediated (Hashimoto encephalopathy, paraneoplastic cerebellar degeneration, gluten ataxia, anti-GAD antibody-positive ataxia, parainfectious, etc.)
- Non-specific inflammation (sarcoidosis, Behçet's disease, etc.)
- Demyelinating (multiple sclerosis, etc.)
- Mitochondrial
- Toxic (alcoholic, drugs, etc.)
- Metabolic (vitamin B1, B12, or E deficiency, hypothyroidism, etc.)
- Others (progressive supranuclear palsy with predominant cerebellar ataxia (PSP-C), Creutzfeldt-Jakob disease, superficial siderosis, etc.)

< Probable IDCA > fulfill core features 1–3 and exclusionary diseases 1–3.
< Possible IDCA > fulfill core features 1–3 and exclusionary diseases 1 and 3, but genetic tests have not been performed yet.
In any case, a patient with a disease duration < 5 years is included into < possible > .

[a] Fulfill the following: i) no similar diseases in first- and second-degree relatives; ii) no consanguinity of parents, iii) parents older than 60 years, or if not alive, age at death of > 60 years (Abele et al. [6], with a slight modification).

[b] Fulfill the second consensus criteria for MSA (Gilman, et al. [2]).

[c] Atrophy of putamen, middle cerebellar peduncle (MCP) or pons, or T2-signal changes in the basal ganglia and brainstem, including posterior putaminal hypointensity, hyperintense lateral putaminal rim, hot cross bun sign, and MCP hyperintensities (Gilman, et al. [2]).

[d] Exclusion of these subtypes, which account for approximately 80% of ADCA families in Japan, is a minimal requirement. Exome sequencing is recommended for the exclusion of rare subtypes of ADCA or ARCA, if possible.

clinical-based, but not neuropathological-based, term, idiopathic cerebellar ataxia (IDCA) [4,5], in this study and proposed the diagnostic criteria for IDCA for the Japanese patients. According to these criteria, we screened sporadic ataxia patients retrospectively, extracted IDCA patients, and clarified the clinical characteristics of IDCA. This validation process suggested that the concept of IDCA and its diagnostic criteria would be very useful in clinical practice.

2. Methods

2.1. Diagnostic criteria for IDCA

We tentatively established the diagnostic criteria (Table 1) based on those for sporadic adult-onset ataxia of unknown etiology (SAOA) [6,7], with slight modifications for the Japanese. The core features were: 1) sporadic; 2) cerebellar ataxia with insidious onset in adults (> 30 years old) and a slowly progressive course; and 3) cerebellar atrophy (bilateral) on computed tomography (CT)/MRI. The definition of "sporadic" fulfilled the following items: i) no similar disorders in first- and second degree relatives; ii) no consanguinity of parents; and iii) the parents older than 60 years, or if not alive, age at death of > 60 years. Items i) and ii), but not item iii), were indispensable for the judgement of "sporadic". When item iii) was not fulfilled, the age at and cause of death were specified for the deceased parent(s).

In addition, the diseases to be excluded (Exclusionary diseases) were MSA, hereditary ataxias, and others. The diagnosis of MSA (probable or possible MSA) followed the second consensus statement [2]. We also excluded patients with MRI findings suggestive of MSA [2], even if they did not meet the criteria for possible MSA. The exclusion of hereditary ataxias required negative results for SCA1, 2, 3 (Machado-Joseph disease, MJD), 6, 8, 17, 31, and DRPLA by genetic testing. These hereditary ataxias account for approximately 80% of autosomal dominant cerebellar ataxia (ADCA) in Japan.

In comparison with the inclusion criteria for SAOA by Abele et al. [6,7], our criteria missed genetic testing for Friedreich's ataxia (FRDA) and fragile X tremor ataxia syndrome (FXTAS), instead of adding SCA31. This was simply because of the consideration on the disease frequency in the Japanese population and accessibility of the testing.

We defined probable and possible IDCA depending on the availability of genetic testing (Table 1). To exclude MSA patients from probable IDCA category to the utmost, we considered patients with a disease duration from onset of < 5 years as possible IDCA, even if they were proven not to have any major subtypes of ADCA by genetic testing. This was based on the fact that the time from onset to diagnosis of MSA was 3.3 ± 2.0 years in Japanese MSA patients [8].

2.2. Patients

We searched the medical records retrospectively at the university hospitals of Shinshu University and Chiba University and collected 346 consecutive patients who fulfilled the core features. Patients with insufficient clinical and neuroradiological information or with poor description of differential diagnosis were excluded. The process by which we extracted probable or possible IDCA patients is shown in Fig. 1. We excluded 212 probable or possible MSA patients (61.3%, MSA-C and MSA-P with apparent cerebellar ataxia). Thirty patients were excluded because of MRI findings suggestive of MSA [2]. They did not meet the criteria for probable or possible MSA at examination, but might be MSA in the early stage, a milder variant of MSA [6] or basal ganglia disorders like PSP-C (Supplementary Fig. 1). Of the 346 patients, genetic testing for ADCA was conducted in 82 (23.7%), of which 21 (25.6%) were proven to have ADCA (SCA31: 10; SCA6: 8; MJD/SCA3: 3). Furthermore, 19 patients were excluded because they were diagnosed as having one of the exclusionary diseases listed in Table 1 (Hashimoto encephalopathy: 4; paraneoplastic cerebellar degeneration: 1; chronic intake of phenytoin: 3; alcoholic: 6; others: 5). Others included hepatic encephalopathy, Niemann-Pick type C, myoclonus epilepsy, etc.

3. Results

Of the 346 patients who fulfilled the core features of the diagnostic criteria for IDCA, 64 patients (29 men/35 women) were extracted as IDCA in our cohort. Of these 64 patients, 27 were negative for SCA1, 2, MJD/SCA3, 6, 7, 8, 17, 31, and DRPLA, but 11 of them were classified as "possible" IDCA because disease duration from onset was < 5 years at evaluation (Table 1). After the extraction of 64 patients, we conducted whole exome sequencing or panel-based targeted resequencing in 12 patients. One patient was demonstrated to carry a homozygous frame-shift mutation in *ANO10*, and diagnosed as SCAR10 [9]. Excluding this patient from the probable IDCA group, a total of 63 IDCA patients (15 probable; 48 possible) were identified.

The average age at onset was 57.2 ± 10.8 years (mean ± standard deviation [SD], range: 30-77 years), and the average age at examination (or diagnosis) was 64.2 ± 11.2 years (range: 36–82 years). The clinical characteristics of the IDCA patients are shown in Table 2. Of the 63 probable or possible IDCA patients, 25 (39.7%, probable: 6; possible: 19 patients) were considered as pure cerebellar ataxia, while the remaining 38 had some of extracerebellar features. The age at onset was not significantly different between patients with pure cerebellar ataxia and those with extracerebellar features. The most frequent extracerebellar signs were abnormalities of