Journal of the Neurological Sciences 250 (2006) 110–113

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Cambodian founder effect for spinocerebellar ataxia type 3 (Machado–Joseph disease)

Suman Jayadev [a], Sara Michelson [a,b], Hillary Lipe [a,c], Thomas Bird [a,b,c,*]

[a] *Department of Neurology, University of Washington, USA*
[b] *Department of Medicine, University of Washington, USA*
[c] *Geriatric Research Education and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, USA*

Received 5 July 2006; received in revised form 7 August 2006; accepted 10 August 2006
Available online 5 October 2006

Abstract

Four families from the same region of Cambodia immigrated to the Pacific Northwest of the United States. All four families have been discovered to have spinocerebellar ataxia type 3 (SCA 3; Machado–Joseph disease) with a similar clinical phenotype. CAG repeat expansions in the *ATXN3* gene range from 72 to 77. Mean age of onset has varied from 19 to 44 years and mean age at death of 4 individuals has been 60 years. The prevalence of the various subtypes of SCA varies worldwide from country to country. Neurologists should be alert to the possibility of SCA 3 in Cambodian patients with unexplained cerebellar ataxia.

Keywords: Ataxia; Spinocerebellar ataxia; Machado–Joseph disease; Neurogenetics; Cambodia; Trinucleotide repeats

1. Introduction

The autosomal-dominant inherited spinocerebellar ataxias (SCA) now number 28 at the time of this report [1,2]. The prevalence of each type varies from country to country and even from region to region. For example, SCA 8 is the most common type in Finland [3] whereas SCA 3 (Machado–Joseph disease) is the most common type in the United States [2]. In Japan, SCA 3 is relatively common, but it is uncommon in the region of Nagano [4].

As noted by Zhao [5], relative to the West, there is a paucity of information about SCA in Asian countries. Especially little is known about the prevalence of SCA in Southeast Asia. We report here several families of Cambodian origin with SCA 3 and provide evidence for a founder effect in this ethnic group. We also review the known frequencies of SCA 3 in Asian countries.

* Corresponding author. S-182-GRECC, VA Medical Center, 1660 S Columbian Way, Seattle, WA 98108, USA. Tel.: +1 206 277 4522; fax: +1 206 764 2569.
E-mail address: tomnroz@u.washington.edu (T. Bird).

0022-510X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2006.08.006

2. Families

All four families originated from different villages and towns in the northwest region of Cambodia near the border with Thailand (Fig. 1). The pedigree of Family A is shown in Fig. 2. The clinical and molecular characteristics of the families are summarized in Table 1. The proband (II-4) of Family A developed unsteady gait at age 39 followed by slowly progressive ataxia associated with horizontal jerk nystagmus, paralysis of upgaze, hyperactive tendon-reflexes and decreased vibratory sensation in the feet. He died of pneumonia at age 62. He had 75 CAG repeats in the ataxin-3 gene (*ATXN3*; repeat expansion detected by previously described methods [6]). His two daughters have had earlier onset at ages 19 and 25 years with 77 and 76 CAG repeats, respectively (III-11, 13). Both his sons are affected on examination but have not yet undergone DNA testing. In addition to ataxia, one of his daughters (III-13) has had prominent fasciculations of facial muscles associated with trismus of her jaw treated with Botoxulim toxin injections. The family has had 9 affected individuals over three generations. Only family member II-4 had paralysis of upgaze

Fig. 1. Map of Cambodia. Arrow indicates region of origin of all 4 families with SCA 3 reported here.

and only III-13 had trismus of the jaw. No family member has had cognitive decline.

Family B (Table 1) is an affected pair of sisters with onset at 25 and 39 years of age with ataxia, dysarthria, nystagmus, poor upgaze, hypoactive tendon reflexes and normal sensation.

Family C (Table 1) includes a man with onset at age 38 whose affected mother died in Cambodia. He has ataxia, dysarthria, nystagmus, a right 6th cranial nerve palsy and hyperactive tendon reflexes with Babinski signs.

Family D (Table 1) is represented by a man with onset of ataxia at age 44 whose affected father died in his forties. This man has ataxia, nystagmus, restricted eye movements, hyperactive tendon reflexes, and fasciculations of tongue and eyelids.

CT and MRI imaging early in the disease of persons in these families have either been normal or shown mild cerebellar atrophy.

3. Discussion

The phenotype demonstrated in the families reported here is typical of the wide variety of clinical manifestations seen

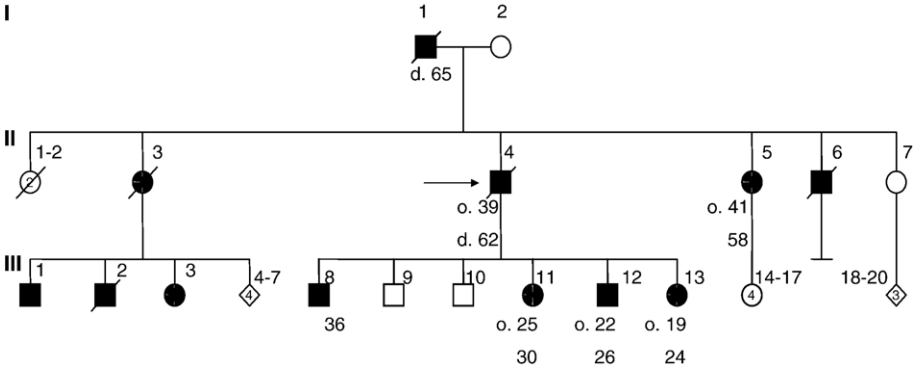

Fig. 2. Pedigree of family A with SCA 3. Circles=females; squares=males; arrow=proband; filled symbols=affected with ataxia; diagonal line=deceased; o=onset age; d=death age; present age under each symbol.