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Short communication

Pattern of disease progression in atypical form of pantothenate-kinase-associated neurodegeneration (PKAN) – Prospective study

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ABSTRACT

Introduction: Classic form of pantothenate-kinase-associated neurodegeneration (PKAN), caused by mutation in PANK2 gene, is characterized by early onset, severe neurological impairment and rapid disease progression. In less precisely described form of atypical PKAN, clinical course is associated with late onset, less severe motor impairment and slower disease evolution. The aim of this study was to assess a pattern of disease progression in atypical PKAN, by following development of specific milestones.

Methods: The clinical characteristics and the disease course of 9 genetically confirmed patients with atypical form of PKAN were evaluated. Time latencies from the disease onset to the appearance of specific clinical milestones were estimated in order to assess the disease progression.

Results: Most frequent disease presentation in our patients was characterized with early and prominent oromandibular dystonia (OMD), followed by severe generalized dystonia and early loss of mobility within the first five years of prolonged disease duration (18.7 ± 10.0 years). Eight out of 9 patients reached 7 significant clinical milestones (OMD, generalized dystonia, dysarthria, dysphagia, postural instability, gait difficulties, ADL dependency) in the first 4.6 years of disease course. Afterwards, a long-lasting, relatively stable period of slower progression was complicated predominantly with skeletal deformities (developed after 7.0 ± 2.8 years).

Conclusions: Majority of milestones which might significantly influence functional abilities and quality of life in patients with atypical form of PKAN developed in the course of the first five years of the disease, followed by a long-lasting, relatively stable period of slower progression.

1. Introduction

Pantothenate-kinase-associated neurodegeneration (PKAN), caused by mutation in PANK2 gene, is a progressive and incurable extrapyramidal disorder associated with iron deposition in the brain [1,2]. Classic form of PKAN is characterized by the disease onset before age of 6, often presented with gait disorder and oromandibular dystonia (OMD), with rapid disease progression to severe, generalized dystonia, anarthria, and prominent pyramidal features. Early loss of independent ambulation with consecutive contractures and death due to secondary complications occurs 10–15 years after the disease onset [2,3]. Atypical form of PKAN presents in the second or third decade with prominent speech disorders, isolated dystonic hand tremor, and psychiatric disturbances. Motor involvement, particularly dystonia, is less severe, and seems to have slower rate of progression with a loss of ability for ambulation occurring within 15–40 years from the onset [2–4]. However, particular pattern of disease progression has not been specifically investigated in atypical cases [2–4]. So far, only few studies have dealt with specific milestones in the progression of PKAN [5,6].

Recently, promising therapeutic strategies have been suggested, such as the deep brain stimulation of globus pallidus – internal segment (DBS GPi) [7]. In addition, chelation therapy with significant iron reduction in GP and possible clinical stabilization has gained attention, although a clear clinical benefit is still under

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consideration [8]. Nevertheless, knowledge of the specific pattern of clinical progression, together with a time-frame for the development of milestones of disease severity, would help clinicians not only to anticipate palliative management of PKAN patients, but also to develop a treatment plan.

Therefore, in this study we analyzed phenotypic variations, specific milestones and disease course in patients with atypical PKAN in order to define a specific pattern of disease progression in greater detail.

2. Patients and methods

The study comprised nine patients who were genetically diagnosed as an atypical form of PKAN according to criteria of Hayflick et al. [3], at the Institute of Neurology CCS, School of Medicine University of Belgrade between January 2006 and December 2013. They also underwent MRI brain scans and all had the "eye-of-the-tiger" sign [3]. The study was approved by the local ethical committee.

After signing the informed consent, all patients were clinically examined by three movement disorders specialists (VSK, MS, IP). After initial examination they were afterwards regularly and prospectively followed-up in 4–6 month intervals. However, for the period preceding genetic verification clinical data were retrospectively obtained (detailed analysis of existing medical records, as well as interview with caregivers and relatives, mostly parents).

The age at onset was established according to medical history. In order to evaluate disease progression we estimated time latency from the disease onset to the appearance of 11 clinical milestones which may have particularly significant influence on patients' functional abilities and quality of life: 1) oromandibular dystonia; 2) generalized dystonia; 3) dystonic opistotonus (defined as extensor truncal dystonia with backward arching during standing or lying down) [9]; 4) severe dysphagia (defined as requiring soft food or nasogastric tube); 5) severe dysarthria (marked impairment of speech, difficult to understand or unintelligible most of the time); 6) postural instability (defined as an absence of postural response on pull test or spontaneous loss of balance); 7) loss of independent ambulation (defined as requiring assistive devices or another person's assistance for safe walk); 8) frequent falls (defined as falls occurring more than twice per month); 9) bedridden state; 10) fixed contractures (defined as fixed position with muscle fibrosis due to prolonged dystonia); and 11) dependency in activities of daily living (ADL) (defined as requiring another person's help for most of the ADLs).

3. Results

The study comprised nine patients (5 females and 4 males) with atypical form of PKAN according to the criteria of Hayflick et al. [3] (aged 34.6 ± 12.5 years; range: 19–58 years), with the mean age at onset of 16.2 ± 5.5 years (range: 7–25 years) (Table 1). Duration of the disease was 18.7 ± 10.0 years (range: 9–40 years; Patient 9 was lost to follow-up after 15 years). Period of retrospective follow-up ranged from 0.5 to 13 years (3.2 ± 4.3 years), not including a patient with dystonic tremor that lasted for 33 years prior to diagnosis. Prospective follow-up ranged from 3 to 23 years (11.9 ± 6.4 years). None of the patients died during follow-up period. All of them were treated with conventional pharmacological therapy including baclofen, benzodiazepines, anticholinergic drugs and botulinum toxin injections that ensured only transient symptomatic relief.

The dominant initial presentation was cranial affection in different forms (6 out of 9 patients). Three patients had speech problems in the form of dysarthria, palilalia and lingual dystonia as the first symptoms, while oromandibular dystonia (OMD), alone or associated with upper limb dystonia was present in other three patients. Other initial presentations included isolated upper or lower limb dystonia (two patients), and one patient had dystonic right hand tremor. During disease progression all patient developed severe OMD, whereas generalized dystonia of different severity affected 8 out of 9 patients and further progressed to dystonic opistotonus in 7 patients. Three patients had episodes of dystonic storms (DS), precipitated by abrupt withdrawal of anticholinergic treatment in Patient 6, and by severe respiratory infections in Patients 2 and 4. Patients with DS, treated in Intensive Care Unit with continuous intravenous sedation, ventilation support and botulinum toxin injections, recovered to their baseline conditions within three months. Only one patient (Patient 8) had different disease course with only mild OMD and left hand rest tremor that worsened during walk, in addition to isolated right hand postural dystonic tremor that lasted for 20 years (Video 1).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016.j.qdypi.2009.12.006.

All nine patients harbored two mutations in the *PANK2* gene (Table 1). In total, only two different mutations were identified: one frameshift mutation (c.1418_1424del; p.N474X) in exon 5 and one missense mutation (c.1583C > T; p.T 528M) in exon 6. Four patients from four non-consanguineous families were homozygotes for the missense mutation, while five patients were compound heterozygotes for these two mutations. Five of these patients were already published [10].

Table 1
Demographic and clinical characteristics of PKAN patients.

Pt.	Sex	Age (yrs)	Age at onset (years)	Disease duration (years)	Initial symptoms	Last neurological examination	Mutation	Psychiatric features
1	F	40	25	15	Dysarthria, palilalia	OMD, anarthria, moderate dystonic opistotonus, prominent LL dystonia, postural instability, nonambulatory, fixed contractures	c.1583C > T, p.T 528M, homozygous	No
2	M	32	18	14	Dysarthria, lingual dystonia	OMD, severe dystonic opistotonus, anarthria, nonambulatory, fixed contractures	c.1583C > T, p.T 528M homozygous	Psychotic episode
3	F	41	20	21	LL dystonia	Severe dystonic opistotonus, anarthria, postural instability, nonambulatory, fixed contractures	c.1583C > T, p.T 528M homozygous	No
4	M	19	10	9	OMD	Severe dystonic opistotonus, severe dysphagia, anarthria, nonambulatory, fixed contractures	c.1583C > T, p.T 528M/c.1418_1424del, p.N474X	Anxious-depressive disorder
5	F	38	13	25	UL and OMD	Severe dystonic opistonus, anarthria, severe dysphagia, nonambulatory, fixed contractures	c.1583C > T, p.T 528M/c.1418_1424del, p.N474X	Anxiety disorder
6	F	23	7	16	UL dystonia	Generalized dystonia, moderate dystonic opistotonus, OMD, prominent LL dystonia, postural instability, fixed contractures	c.1583C > T, p.T 528M/c.1418_1424del, p.N474X	Anxious-depressive disorder
7	M	26	16	10	UL dystonia and OMD	OMD, generalized dystonia, prominent UL dystonia, fixed contractures	c.1583C > T, p.T 528M/c.1418_1424del, p.N474X	No
8	M	58	18	40	Dystonic tremor of RUE	Dystonic tremor of RUE, OMD, severe dysarthria, postural instability	c.1583C > T, p.T 528M homozygous	No
9	F	NA	19	NA	Dysarthria, dysphagia, UL dystonia	Severe dystonic opistotonus, anarthria, dysphagia, lingual dystonia, falls, nonambulatory, fixed contractures	c.1583C > T, p.T 528M/c.1418_1424del p.N474X	No

OMD: oromandibular dystonia; UL: upper limb; LL: lower limb; R: right; NA: non-applicable due to lost to follow-up.