J Mol Neurosci (2016) 58:321–329
DOI 10.1007/s12031-015-0663-x

Onset Manifestations of Spinal and Bulbar Muscular Atrophy (Kennedy's Disease)

Josef Finsterer[1] · **Gianni Soraru**[2]

Received: 9 June 2015 / Accepted: 5 October 2015 / Published online: 19 October 2015

Abstract Spinal and bulbar muscular atrophy (SBMA) is regarded as a disorder with adult onset between third and fifth decade of life. However, there is increasing evidence that SBMA may start already before adulthood. The present study investigated the following: (1) Which clinical manifestations have been described so far in the literature as initial manifestations? (2) Which was the age at onset of these manifestations? and (3) Is age at onset dependent on the CAG-repeat length if non-motor manifestations are additionally considered? Data for this review were identified by searches of MEDLINE using appropriate search terms. Onset manifestations in SBMA can be classified as frequent, rare, motor, non-motor, or questionable. Frequent are muscle weakness, cramps, fasciculations/twitching, tremor, dysarthria, dysphagia, or gynecomastia. Rare are myalgia, easy fatigability, exercise intolerance, polyneuropathy, hyper-CKemia, undermasculinized genitalia, scrotal hypospadias, microphallus, laryngospasm, or oligospermia. Questionable manifestations include sensory disturbances, cognitive impairment, increased pituitary volume, diabetes, reduced tongue pressure, elevated creatine-kinase, or low androgens/high estrogens. Age at onset is highly variable ranging from 4–76 years. Non-motor manifestations develop usually before motor manifestations. Age at onset depends on what is considered as an onset manifestation. Considering non-motor onset manifestations, age at onset is independent of the CAG-repeat size. In conclusion, age at onset of SBMA depends on what is regarded as onset manifestation. If non-motor manifestations are additionally considered, age at onset is independent of the CAG-repeat length. Since life expectancy is hardly reduced in SBMA, re-investigation of patients from published studies with regard to their initial disease profiles is recommended.

Keywords Spinal and bulbar muscular atrophy · Early symptoms · Initial manifestations · Kennedy's disease · Bulbar functions · CAG-repeats · Poly-Q · Bulbospinal neuronopathy · Spinobulbar muscular atrophy · Motor neuron disease

Introduction

Spinal and bulbar muscular atrophy (SBMA) is a rare, progressive motor neuron disease (MND) with multisystem involvement manifesting as androgen insensitivity, diabetes, sensory neuropathy, or autonomic nervous system involvement (Kennedy et al. 1968). The dominant phenotypic characteristics of the disease include muscle weakness and wasting of the limb muscles, bulbar muscles and respiratory muscles, muscle cramps, fasciculations, tremor, sensory neuropathy, breast enlargement, and erectile dysfunction (Kennedy et al. 1968; Fratta et al. 2014). The autonomic nervous system may be subclinically involved (Rocchi et al. 2011). SBMA is a microsatellite (trinucleotide) expansion disorder due to an enlargement of a CAG-repeat >38 in exon 1 of the androgen receptor (AR) gene on the long arm of chromosome X (Fratta et al. 2014; La Spada et al. 1991). Rarely, contracted repeats are associated with disease which is not SBMA (Kooy et al. 1999). Mouse models have shown that the CAG-repeat expansion is not sufficient for disease and that the presence of androgen is crucial to initiate disease development (Mariotti et al. 2000; Chevalier-Larsen et al. 2004; Schmidt et al. 2002; Katsuno et al. 2002).

✉ Josef Finsterer
fifigs1@yahoo.de

[1] Krankenanstalt Rudolfstiftung, Postfach 20, 1180 Vienna, Austria

[2] Department of Neurosciences, University of Padova, Padova, Italy

SBMA is usually regarded as a disorder with adult onset (Mariotti et al. 2000) between the third and fifth decade of life (Vandenberghe et al. 2009). However, there is an increasing number of reports showing that in single cases SBMA starts already before adulthood (Sperfeld et al. 2002; Echaniz-Laguna et al. 2005; Ogata et al. 2001). Clinical manifestations (symptoms, signs, instrumental findings) at onset are highly variable between the studies, and it is under debate which of these is the most frequent and if age at onset is truly dependent on the CAG-repeat length if uncommon clinical or subclinical manifestations are included as initial manifestations. Considering classical onset motor manifestations, there is a clear negative relation between age at onset and the CAG-repeat size. The longer the CAG-repeat-expansion, the earlier the onset of SBMA (Fratta et al. 2014; Rhodes et al. 2009; Atsuta et al. 2006; La Spada et al. 1992; Xie et al. 2010) but CAG-repeat length is not associated with disease progression or the severity of the disease (Atsuta et al. 2006; Lu et al. 2009). However, <47 repeats is associated with a sensory dominant phenotype and leg tremor and >46 repeats with a motor-dominant phenotype (Nishiyama et al. 2014).

The present study aimed at answering the following questions: (1) Which clinical manifestations have been described so far in the literature as initial manifestations? (2) Which was the age at onset of these clinical manifestations? and (3) Is age at onset dependent on the CAG-repeat length if non-motor manifestations are additionally considered? Recognising the true onset of SBMA is crucial since potential treatment should start before neuronal degeneration evolves.

Methods

A systematic PubMed literature search was carried out by application of the search terms "bulbospinal muscular atrophy," "spinal and bulbar muscular atrophy," "Kennedy's disease," "motor neuron disease," "weakness," "tremor," "cramps," "fasciculations," "twitches," "breast enlargement," "androgen receptor," "CAG-repeats," "poly-Q," in combination with "human," "onset," "initial presentation," "presenting manifestation," and "symptom." Additionally, references in these articles were searched for further papers suitable to be included in the discussion. Only studies in which the diagnosis was genetically confirmed were included.

Results

Upon application of the applied search terms, 221 hits were achieved (Fig. 1). Among these only 67 articles were assessed as suitable to answer the questions addressed in the introduction (Fig. 1). Twenty-two of the papers were only accessible as an abstract (Vandenberghe et al. 2009) and six were written in

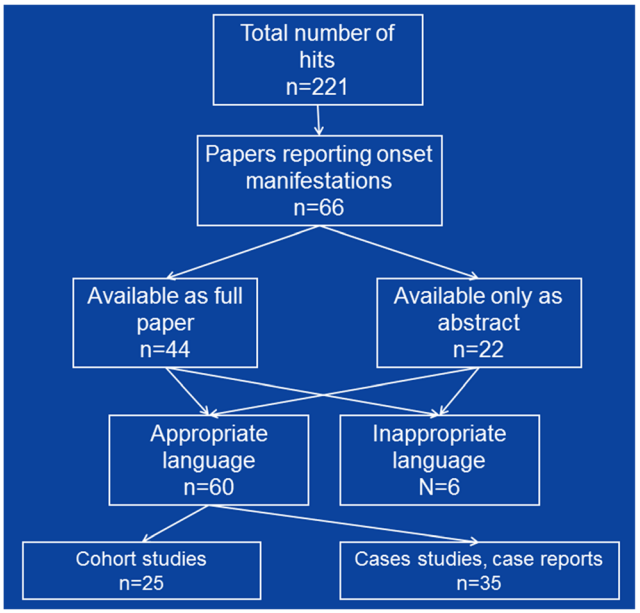

Fig. 1 Selection tree of the included papers

an inappropriate language (Fan et al. 2014; Yang et al. 2010). Sixteen of the included papers were cohort studies, 23 reported case series, and 12 were single case reports. The rest were reviews, editorials, or letters. The publication years ranged from 1968 to 2015.

The five largest clinical trials covering onset manifestations of SBMA are the ones by Atsuta et al. 2006, by Rhodes et al. 2009, by Fratta et al. 2014, by Mariotti et al. 2000, and by Sperfeld et al. 2002 (Fratta et al. 2014; Mariotti et al. 2000; Sperfeld et al. 2002; Rhodes et al. 2009; Atsuta et al. 2006). In the Japanese study of 223 patients, median age at onset of hand tremor (n = 126) was 33 years, of muscle weakness 44 years (n = 217), of dysarthria 50 years (n = 98), and of dysphagia 54 years (n = 79) (Table 1) (Atsuta et al. 2006). Non-motor manifestations were not assessed. Individual values of age at onset were provided only in a figure according to which tremor started between 20 and 52 years of age, weakness between 32 and 58 years, dysarthria between 35 and 64 years, and dysphagia between 36 and 65 years (Atsuta et al. 2006). All initial manifestations showed a wide range of individual onset age variability between 25 and 30 years (Atsuta et al. 2006). The number of CAG-repeats ranged from 40 to 57. Age at onset of evaluated manifestations correlated negatively with the CAG-repeat size (Atsuta et al. 2006).

In a study of 57 American SBMA patients, the most common presenting symptoms were muscle cramps (n = 22 (32 %)), tremor (n = 16 (23 %)), and leg weakness (n = 16 (23 %)) (Rhodes et al. 2009). More rarely, breast enlargement (7 %), upper limb weakness (7 %), and other non-specified manifestations were described (Rhodes et al. 2009). In half of the patients weakness occurred first in the lower limbs followed by bulbar weakness (33 %) (Rhodes et al. 2009). Age at

Table 1 Studies of SBMA patients reporting type or frequency of onset manifestations

Reference	PY	NOP	OM	FOM (%)	AO (year)	NR
(*Atsuta et al.* 2006)	2006	223	Hand tremor	np	33	40–57
			Weakness	np	44	
			Dysarthria	np	50	
			Dysphagia	np	54	
(*Rhodes et al.* 2009)	2009	57	Cramps	32	np	41–53
			Tremor	23	np	
			Leg weakness	23	18–64	
			Breast enlargement	7	np	
			Arm weakness	7	18–64	
(*Fratta et al.* 2014)	2014	46	Leg weakness	39	43	40–53
			Arm weakness	10	43	
			Tremor	6	35 (18–62)	
			Bulbar weakness	3	50, 60	
			Breast enlargement	3	39.1	
			Cramps	3	39.5	
			Muscle twitches	np	41.8	
			Numbness, tingling	np	50	
(*Mariotti et al.* 2000)	2000	36	Lower limb weakness	63	np	39–50
			Cramps	17	np	
			Upper limb weakness	11	np	
			Dysphagia	3	np	
			Tremor	3	np	
(*Sperfeld et al.* 2002)	2002	34	Gynecomastia	52	np	41–52
			Premature exhaustion	28	np	
			Tremor	26	np	
			Cramps	16	np	
			Myalgia	12	np	
			Muscle weakness	4	np	
			Bulbar involvement	4	np	
(*Fu et al.* 2013)	2013	21	Tremor, cramps	np	24 ± 8 (15–36)	42–53
(*Hui et al.* 2004)	2004	18	Fatigability	39	np	43–55
			Tremor	22	np	
			Focal weakness	17	np	
			Cramps	11	np	
			Muscle twitching	11	np	
(Xie et al. 2010)	2010	12	Weakness	np	np	43–57
(Vandenberghe et al. 2009)	2009	11	Myasthenia	na	na	np
			Cramps	na	na	
			Fasciculations	na	na	
			Polyneuropathy	na	na	
			Exercise intolerance	na	na	
(*Dias et al.* 2011)	2011	10	np	np	19–49	41–53
(Gomez-Calero et al. 2013)	2013	5	Tremor and cramps	20	np	43–49
			Weakness and cramps	60	np	
			Weakness	20	np	
(Yang et al. 2010)	2010	3	np	np	39–41	47, 48, 49
(Hemmi et al. 2009)	2009	2	Motor symptoms	np	66, 78	42
(Ogata et al. 2001)	2001	1	Non-masculinized genitalia	np	<11	44
			Microcephaly	np	np	
			Hypospadia	np	np	

Authors in italic indicate that the full article was available

PY publication year, *NOP* number of included patients, *OM* onset manifestation, *FOM* frequency of onset manifestation, *AO* age at onset (mean or range), *NR* number of CAG-repeats (mean or range), *LW* leg weakness, *np* not provided, *na* not available

onset was not provided for any of these manifestations but onset of muscle weakness ranged from 18 to 64 years (Rhodes et al. 2009). The number of CAG-repeats ranged from 41 to 53 (Rhodes et al. 2009).

In a study of 46 SBMA patients from the Great Britain, the most common initial manifestations were lower limb weakness (39 %) followed by upper limb weakness (10 %), tremor (6 %), bulbar weakness (3 %), breast enlargement (3 %), and muscle cramps (3 %) (Fratta et al. 2014). Age at onset of all onset symptoms ranged from 14 to 75 years (mean: 43.4 years) (Fratta et al. 2014). Age at onset of tremor ranged from 18 to 62 years (Fratta et al. 2014). Muscle weakness appeared between age 25 and 61 years. Erectile dysfunction appeared between age 38 and 63 years. Dysarthria started between 40 and 65 years of age (Fratta et al. 2014). Dysphagia had its onset between age 38 and 64 years. Breast enlargement occurred at a mean age of 39.1 years (Fratta et al. 2014). The first deficit noticed by patients in this study was hand tremor at a mean age of 35 years, followed by muscle weakness at a mean age of 43 years, dysarthria, and dysphagia, first recognized between 50 and 60 years of age (Fratta et al. 2014). Muscle cramps were noticed at a mean age of 39.5 years (Fratta et al. 2014). Muscle twitches were first reported at a mean age of 41.8 years (Fratta et al. 2014). Numbness or tingling was first reported at a mean age of 50 years (Fratta et al. 2014). CAG-repeat length ranged from 40 to 53.

In a study of 36 Italian patients, the authors provided individual values for age at onset and CAG-repeat size of all patients. Unfortunately, they did not consider non-motor onset manifestations. The 36 patients belonged to 30 unrelated families (Mariotti et al. 2000). Initial manifestations were lower limb weakness ($n = 23$), cramps ($n = 6$), upper limb weakness ($n = 4$), dysphagia ($n = 1$), and tremor ($n = 1$) (Mariotti et al. 2000). In four patients, the initial manifestations were not reported (Mariotti et al. 2000). Age at onset of these manifestations ranged from 25 to 60 years (Mariotti et al. 2000). Age at onset was not available in four patients. The number of CAG-repeats ranged from 39 to 50 (Mariotti et al. 2000).

In a study of 34 German patients, the initial manifestations were gynecomastia (52 %), premature exhaustion (28 %), tremor (26 %), cramps (16 %), myalgia (12 %), muscle weakness (4 %), or bulbar involvement (4 %) (Sperfeld et al. 2002). Unfortunately, age at onset of these abnormalities was provided only in a figure (Sperfeld et al. 2002). Number of CAG-repeats ranged from 41 to 52 (Sperfeld et al. 2002). The authors concluded that onset of SBMA is already in adolescence, thus earlier than commonly assumed (Sperfeld et al. 2002). In a study of 155 Chinese patients, onset was defined as onset of muscle weakness (Ni et al. 2015). Age at onset of muscle weakness ranged from 24 to 71 years (mean 44.2 ± 10.2 years) (Ni et al. 2015). Type and onset of non-motor manifestations was not provided. The CAG-repeat length ranged from 42 to 61 (Ni et al. 2015). In a study of 133 patients of whom 99 were in the placebo arm of a treatment study and 34 untreated control SBMA patients, age at onset ranged from 23 to 66 years (Hashizume et al. 2012). No further information about onset manifestations or CAG-repeat length was provided. In a study of 47 Japanese patients, examining tongue pressure age at onset ranged from 30 to 59 years (mean 44.4 ± 7.6 years) (Mano et al. 2014). Individual onset manifestations were not mentioned. The number of CAG-repeats ranged from 41 to 57 (mean 48.3 ± 3.3) (Mano et al. 2014). No individual values of these parameters were provided and no correlation between these parameters had been calculated (Mano et al. 2014).

A number of other studies, which included <25 patients or single patients and described onset manifestations, have been published (Table 1). In a study of 21 Taiwanese patients, mean age at onset of muscle weakness was 39 ± 7 years (Fu et al. 2013). Six patients noted hand tremor and two patients muscle cramps prior to onset of muscle weakness (Fu et al. 2013). Tremor and muscle cramps occurred between 15 and 36 years of age (mean 24 ± 8 years) (Fu et al. 2013). All patients developed bulbar manifestations at age 26 to 51 years (mean 39.7 years) (Fu et al. 2013). Among the 20 patients with muscle weakness, weakness began proximally in 70 % (Fu et al. 2013). CAG-repeat length ranged from 42 to 53 (Fu et al. 2013).

In a study of 18 Chinese patients from 16 families, age at onset ranged from 19 to 48 years (mean 31 years) (Hui et al. 2004). Initial manifestations were fatigability (39 %), tremor (22 %), focal weakness (17 %), cramps (11 %), and muscle twitching (11 %) (Hui et al. 2004). Non-motor manifestations were considered. CAG-repeat length ranged from 43 to 55 (Hui et al. 2004). In a study of 12 Chinese patients, limb weakness was the initial manifestation in all patients (Xie et al. 2010). There was no mentioning at which age muscle weakness occurred but mean disease duration at diagnosis was 14, years (Xie et al. 2010). The number of CAG-repeats ranged from 43 to 57 (Xie et al. 2010).

In a study of 11 French SBMA patients, 7 had unusual initial manifestations (Vandenberghe et al. 2009). These included myasthenia, cramps, fasciculation syndrome, polyneuropathy, post-traumatic monomelic neuronopathy, effort-dependent muscle intolerance, and/or muscular dystrophy (Vandenberghe et al. 2009). In a study of 11 Italian patients from the region of Reggio Emilia, mean age at onset was 44.8 ± 10.1 years (Guidetti et al. 2001). In a tremor study of 10 Brazilian SBMA patients from 7 families, age at onset was provided for each of the patients but, unfortunately, onset symptoms were not mentioned (Dias et al. 2011). Age at onset ranged from 19 to 49 years (Dias et al. 2011). The number of CAG-repeats was provided for each patient ranging from 41 to 53 (Dias et al. 2011).

In 10 Taiwanese SBMA patients participating in a FDG-PET study showing hypometabolism of the frontal lobes, age at onset ranged from 14 to 37 years (Lai et al. 2013). Mean age

at onset was 27.3 ± 6.3 years. The number of CAG-repeats in these patients ranged from 46 to 56 (mean 49.9 ± 3.1) (Lai et al. 2013). In a study of 5 Peruvean patients, age at onset ranged from 31 to 63 years (Gomez-Calero et al. 2013). Manifestations at onset in these patients were tremor and cramps (n = 1), weakness and cramps (n = 3), or weakness exclusively (n = 1) (Gomez-Calero et al. 2013). The number of CAG-repeats varied between 43 and 49 (Gomez-Calero et al. 2013). In a study of 5 Italian SBMA patients, age at onset was 50, 43, 45, 36, and 28 years of age, respectively (Rocchi et al. 2011). The number of CAG-repeats was given as 43, 46, 43, 49, and 48, respectively (Rocchi et al. 2011). Unfortunately, the type of onset manifestations was not provided.

In a study of 3 Chinese patients from two families, age at onset of first clinical manifestations was 39, 39, and 41 years, respectively (Yang et al. 2010). The number of CAG-repeats amounted to 49, 48, and 47, respectively (Yang et al. 2010). Manifestations at onset were not provided. In a study of 3 German patients, the initial manifestations were symmetric proximal weakness, starting at age 39 years (patient A); muscle cramps in the lower limbs and symmetric proximal weakness in the upper as well as lower limbs starting at age 32 years (patient B); and symmetric proximal weakness of the upper limbs at age 45 years (patient C) (Kuhlenbäumer et al. 1998). The number of CAG-repeats was 51 in each of the three patients (Kuhlenbämuer et al. 1998). In a study of 2 Japanese brothers with SBMA, age at onset of muscle weakness was 66 and 78 years, respectively (Hemmi et al. 2009). The number of CAG-repeats was 42 in both of them (Hemmi et al. 2009). In the younger brother, gynecomastia appeared already in his 20s. Ostensibly, there was a clear negative correlation between onset and CAG-repeat size but considering gynecomastia as initial symptom, the correlation became non-significant (Hemmi et al. 2009). In an 11-year-old boy with SBMA and a CAG-expansion of 44, the patient presented with undermasculinized genitalia, microphallus, and scrotal hypospadia since age 4 years (Ogata et al. 2001).

Taken together, 16 different clinical manifestations were reported as onset manifestations of SBMA (Table 2). Age at onset of these manifestations ranged from 4 (Ogata et al. 2001) to 78 years (Hemmi et al. 2009). There was no consensus on the clinical presentation of SBMA at onset. Onset manifestations varied according to the definition of onset symptoms. Most studies regarded only motor manifestations as initial manifestation of the disease. Only in a few studies that non-motor manifestations were accepted as onset manifestations (Ogata et al. 2001). When correlating age at onset with CAG-repeat length by including data from studies which provided individual values and also included non-motor onset manifestations (Rocchi et al. 2011; Ogata et al. 2001; Yang et al. 2010; Hui et al. 2004; Lai et al. 2013; Gomez-Calero et al. 2013; Kuhlenbäumer et al. 1998; Hemmi et al. 2009), there was no significant correlation between age at onset and CAG-repeat length (r = 0.56) (Fig. 2). Differential diagnoses which had been considered before diagnosing SBMA included spinal muscular atrophy, amyotrophic lateral sclerosis (ALS), Parkinson's disease, adrenoleucodystrophy, Becker muscular dystrophy, polyneuropathy, limb girdle muscular dystrophy, myasthenia, and hexosaminidase deficiency (Fratta et al. 2014; Vandenberghe et al. 2009; Kuhlenbäumer et al. 1998).

Discussion

This study shows that not only classical or motor manifestations should be considered as initial manifestations in SBMA but also more rare and less well-appreciated phenotypic features, as shown in Table 2. Particularly, subclinical and non-motor manifestations should be added to the list of onset manifestations. Secondly, this study shows that individual age at onset, type of manifestations at onset, and the frequency of onset manifestations are frequently not provided. Only ranges or mean or median values are available. Some studies provided age at onset but did not provide the typical onset manifestations or their frequency and vice versa. The previously propagated notion that age at onset is dependent on the CAG-repeat length has to be revised.

Initial manifestations of SBMA and age at onset may be missed because the history is not taken thoroughly enough, because certain manifestations, particularly rare or subclinical manifestations, are not regarded as onset manifestations of the disease, or because only motor symptoms are considered as onset manifestations of the disease (Mariotti et al. 2000; Tanaka et al. 2014). A further reason why onset of the disease may be missed could be a patient's poor awareness of certain symptoms, such as tremor or easy fatigability, about which only unreliable information is provided. Exclusion of subclinical or non-motor manifestations is misleading, may delay diagnosis and symptomatic treatment, and may prevent early genetic counseling. There is currently no study available which assesses if creatine-kinase is elevated long before any motor manifestations develop or if androgen levels are decreased and estrogen levels increased long before any clinical endocrine manifestations occur. Subclinical parameters which could be assessed before appropriate clinical manifestations develop include tongue pressure, which has been shown to reflect swallowing function in patients with SBMA and appears to decrease before awareness of subjective dysphagia (Mano et al. 2014). Tongue pressure measurement could become a novel biomarker of SBMA, which is applicable for early-stage detection of the disease (Mano et al. 2014). Whether the increased size of the pituitary gland should be regarded as subclinical initial manifestation remains speculative (Pieper et al. 2013). Though 10 % of SBMA patients

Table 2 Initial manifestations in SBMA reported in the literature

Initial manifestation	Reference
Frequent	
Proximal weakness	(Echaniz-Laguna et al. 2005; Yang et al. 2010; Fu et al. 2013; Gomez-Calero et al. 2013)
Proximal wasting	(Echaniz-Laguna et al. 2005; Yang et al. 2010; Fu et al. 2013)
Muscle cramps	(Vandenberghe et al. 2009; Fu et al. 2013; Lai et al. 2013; Gomez-Calero et al. 2013)
Fasciculations, twitching (perioral, tongue)	(Fratta et al. 2014; Rhodes et al. 2009)
Action tremor	(Fu et al. 2013; Dias et al. 2011; Lai et al. 2013; Gomez-Calero et al. 2013)
Dysarthria	(Fratta et al. 2014)
Dysphagia	(Fratta et al. 2014)
Gynecomastia (breast enlargement)	(Fratta et al. 2014; Rhodes et al. 2009; Fu et al. 2013; Dias et al. 2011; Lai et al. 2013; Kuhlenbäumer et al. 1998)
Rare	
Myalgia	(Sperfeld et al. 2002)
Myasthenia	(Vandenberghe et al. 2009)
Fasciculation syndrome	(Vandenberghe et al. 2009)
Polyneuropathy	(Vandenberghe et al. 2009)
Post-traumatic monomelic neuronopathy	(Vandenberghe et al. 2009)
Effort-dependent muscle intolerance	(Vandenberghe et al. 2009)
Muscular dystrophy	(Vandenberghe et al. 2009)
Isolated hyper-CKemia	(Echaniz-Laguna et al. 2005)
Under-masculinized genitalia	(Ogata et al. 2001)
Scrotal hypospadia	(Ogata et al. 2001)
Microphallus	(Ogata et al. 2001)
Decreased libido, impotence	(Fu et al. 2013)
Oligospermia	(Ou-Yang et al. 2011)
Laryngospasm	(Sperfeld et al. 2005)
Questionable	
Sensory disturbances	(Rocchi et al. 2011; Serratrice et al. 1988)
Impaired cognitive functions	(Soukup et al. 2009)
Increased pituitary volume	(Pieper et al. 2013)
Diabetes	(Kuhlenbäumer et al. 1998)
Tongue pressure	(Mano et al. 2014)
Creatine-kinase	(Grunseich et al. 2014)
Low androgens, high estrogens	(Finsterer 2010)

develop diabetes during the disease course (Kuhlenbäumer et al. 1998), it is unclear if diabetes can be an initial manifestation of the disease. Sensory symptoms because of polyneuropathy have been only rarely assigned as onset manifestations (Vandenberghe et al. 2009). Concerning the frequency of onset manifestations, there is a wide range of variability. Depending on which manifestations are regarded as onset manifestations, and if only motor manifestations or also non-motor manifestations are considered, the most frequent onset manifestations include weakness, cramps, tremor, gynecomastia, and fatigability (Table 1) (Fratta et al. 2014; Mariotti et al. 2000; Sperfeld et al. 2002; Rhodes et al. 2009; Hui et al. 2004).

The issue of the relation between the number of CAG-repeats and age at onset of clinical manifestations is still unsolved (Hemmi et al. 2009). This is due to inconsistency concerning the definition of what should or should not be considered as an onset manifestation. Most studies define onset of SBMA as muscle weakness first recognized by the patient (Mariotti et al. 2000; Tanaka et al. 2014). However, motor functions are frequently not the initial clinical manifestation why the correlation between age at onset and CAG-repeat length needs to be newly assessed by including more rare manifestations as has been tried in this study (Fig. 2). With regard to the correlation between motor functions and

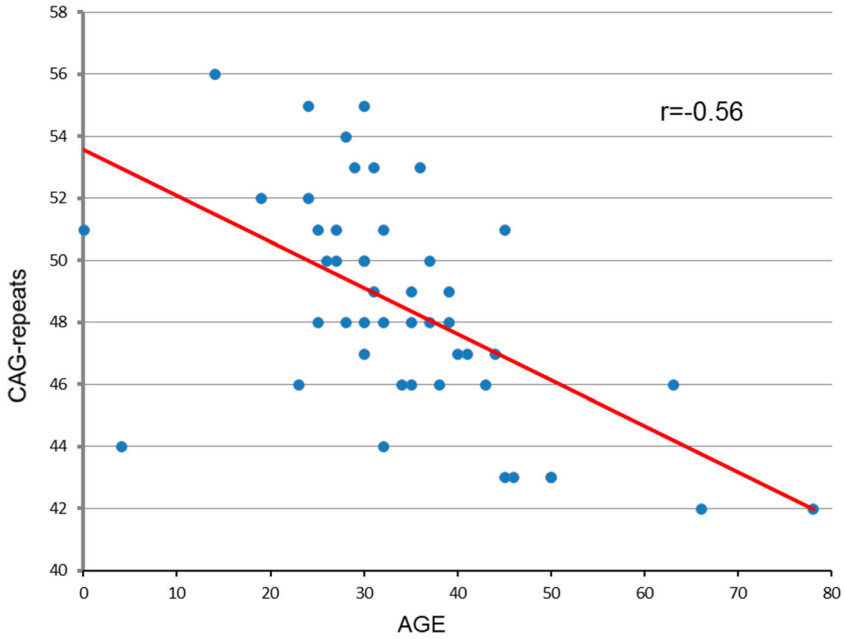

Fig. 2 Correlation (Pearson correlation coefficient) between age at onset and CAG-repeat length calculated from data taken from eight different studies, which provided individual figures and of which some also considered non-motor initial manifestations (Rocchi et al. 2011; Ogata et al. 2001; Yang et al. 2010; Fu et al. 2013; Dias et al. 2011; Lai et al. 2013; Gomez-Calero et al. 2013; Kuhlenbäumer et al. 1998)

CAG-repeat length, there is no consensus in the literature. Various authors found a significant negative correlation between initial motor manifestations and CAG-repeat length (Mariotti et al. 2000; Atsuta et al. 2006; Igarashi et al. 1992; Shimada et al. 1995), whereas others did not (Mano et al. 2014; Guidetti et al. 1996; Amato et al. 1993; Biancalana et al. 1992; MacLean et al. 1995; Morrison et al. 1998). The significant negative correlation in some studies suggests that the pace of initial cellular events leading to motor neuron damage may be timed by the size of the genetic expansion in a CAG-repeat length-dependent manner, whereas the CAG-repeat length has only a limited predictive value for the severity of clinical impairment (Mariotti et al. 2000). Particularly, when all different types of onset manifestations were considered, the correlation between age at onset and CAG-repeat length became weak and non-significant (Fu et al. 2013). Hemmi et al. found that CAG-repeat expansions were not related to age at onset of androgen insensitivity but only to age at onset of motor functions (Hemmi et al. 2009). Unfortunately, there is no large study available, which includes and evaluates all different onset manifestations given in Table 2, including non-motor manifestations. The lack of a large study of this kind is responsible for the uncertainty about the correlation between CAG-repeat length and age at onset. However, calculating the correlation between age at onset and CAG-repeat expansion upon integration of all data available from studies providing individual data of any possible onset manifestation, it was not significant in the present study.

In conclusion, this study shows that age at onset depends on the definition of what shall be regarded as an onset manifestation. Non-motor and subclinical manifestations need to be recognized as onset manifestations as well. If unusual, non-motor manifestations or subclinical manifestations are additionally considered, age at onset is independent of the CAG-repeat length. SBMA patients need to be thoroughly investigated for their onset manifestations to treat these patients as early as possible in case effective measures become available in the future. Since life expectancy is hardly reduced in SBMA, it could be helpful to reinvestigate patients from previous studies with regard to their initial disease profiles.

References

Amato AA, Prior TW, Barohn RJ, Snyder P, Papp A, Mendell JR (1993) Kennedy's disease: a clinicopathologic correlation with mutations in the androgen receptor gene. Neurology 43:791–794

Atsuta N, Watanabe H, Ito M, Banno H, Suzuki K, Katsuno M, Tanaka F, Tamakoshi A, Sobue G (2006) Natural history of spinal and bulbar muscular atrophy (BSMA): a study of 223 Japanese patients. Brain 129:1446–1455

Biancalana V, Serville F, Pommier J, Julien J, Hanauer A, Mandel JL (1992) Moderate instability of the trinucleotide repeat in spino bulbar muscular atrophy. Hum Mol Genet 1:255–258

Chevalier-Larsen ES, O'Brien CJ, Wang H, Jenkins SC, Holder L, Lieberman AP, Merry DE (2004) Castration restores function and neurofilament alterations of aged symptomatic males in a transgenic mouse model of spinal and bulbar muscular atrophy. J Neurosci 24: 4778–4786

Dias FA, Munhoz RP, Raskin S, Werneck LC, Teive HA (2011) Tremor in X-linked recessive spinal and bulbar muscular atrophy (Kennedy's disease). Clinics (Sao Paulo) 66:955–957

Echaniz-Laguna A, Rousso E, Anheim M, Fleury M, Cossée M, Tranchant C (2005) A clinical, neurophysiological and molecular study of 12 patients from 4 families with spinal and bulbar muscular atrophy. Rev Neurol (Paris) 161:437–444

Fan R, Zhang L, Zhang J, Shao B, Pan D, Lyu J (2014) Investigation of a family with Kennedy disease by genetic analysis. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 31:750–753

Finsterer J (2010) Perspectives of Kennedy's disease. J Neurol Sci 298:1–10

Fratta P, Nirmalananthan N, Masset L, Skorupinska I, Collins T, Cortese A, Pemble S, Malaspina A, Fisher EM, Greensmith L, Hanna MG (2014) Correlation of clinical and molecular features in spinal bulbar muscular atrophy. Neurology 82:2077–2084

Fu SC, Kuo HC, Chu CC, Wu YR, Ro LS, Liu CS, Huang CC (2013) Long-term follow-up of spinal and bulbar muscular atrophy in Taiwan. J Formos Med Assoc 112:326–331

Gómez-Calero V, Cornejo-Olivas M, Ortega O, Marca V, Lindo-Samanamud S, Flores M, Torres-Ramírez L, Mazzetti P (2013) Kennedy disease in Peru: first cases with molecular diagnosis. Rev Peru Med Exp Salud Publica 30:331–335

Grunseich C, Rinaldi C, Fischbeck KH (2014) Spinal and bulbar muscular atrophy: pathogenesis and clinical management. Oral Dis 20:6–9

Guidetti D, Sabadini R, Ferlini A, Torrente I (2001) Epidemiological survey of X-linked bulbar and spinal muscular atrophy, or Kennedy disease, in the province of Reggio Emilia, Italy. Eur J Epidemiol 17:587–591

Guidetti D, Vescovini E, Motti L, Ghidoni E, Gemignani F, Marbini A, Patrosso MC, Ferlini A, Solime F (1996) X-linked bulbar and spinal muscular atrophy, or Kennedy disease: clinical, neurophysiological, neuropathological, neuropsychological and molecular study of a large family. J Neurol Sci 135:140–148

Hashizume A, Katsuno M, Banno H, Suzuki K, Suga N, Tanaka F, Sobue G (2012) Difference in chronological changes of outcome measures between untreated and placebo-treated patients of spinal and bulbar muscular atrophy. J Neurol 259:712–719

Hemmi S, Inoue K, Kutoku Y, Rikimaru M, Murakami T, Sunada Y (2009) Two brothers with very late onset of muscle weakness in X-linked recessive spinal and bulbar muscular atrophy. Rinsho Shinkeigaku 49:22–26

Hui AC, Cheung PT, Tang AS, Fu M, Wong L, Kay R, Hong Kong Neuromuscular Disease Study Group (2004) Clinical and electrophysiological features in Chinese patients with Kennedy's disease. Clin Neurol Neurosurg 106:309–312

Igarashi S, Tanno Y, Onodera O, Yamazaki M, Sato S, Ishikawa A, Miyatani N, Nagashima M, Ishikawa Y, Sahashi K, et al. (1992) Strong correlation between the number of CAG repeats in androgen receptor genes and the clinical onset of features of spinal and bulbar muscular atrophy. Neurology 42:2300–2302

Katsuno M, Adachi H, Kume A, Li M, Nakagomi Y, Niwa H, Sang C, Kobayashi Y, Doyu M, Sobue G (2002) Testosterone reduction prevents phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. Neuron 35:843–854

Kennedy WR, Alter M, Sung JH (1968) Progressive proximal spinal and bulbar muscular atrophy of late onset. A sex-linked recessive trait. Neurology 18:671–680

Kooy RF, Reyniers E, Storm K, Vits L, van Velzen D, de Ruiter PE, Brinkmann AO, de Paepe A, Willems PJ (1999) CAG repeat contraction in the androgen receptor gene in three brothers with mental retardation. Am J Med Genet 85:209–213

Kuhlenbäumer G, Bocchicchio M, Kress W, Young P, Oberwittler C, Stögbauer F (1998) X-chromosomal recessive spinobulbar muscular atrophy (Kennedy type). Description of a family, clinical aspects, molecular genetics, differential diagnosis and therapy. Nervenarzt 69:660–665

La Spada AR, Roling DB, Harding AE, Warner CL, Spiegel R, Hausmanowa-Petrusewicz I, Yee WC, Fischbeck KH (1992) Meiotic stability and genotype-phenotype correlation of the trinucleotide repeat in X-linked spinal and bulbar muscular atrophy. Nat Genet 2:301–304

La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH (1991) Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 352:77–79

Lai TH, Liu RS, Yang BH, Wang PS, Lin KP, Lee YC, Soong BW (2013) Cerebral involvement in spinal and bulbar muscular atrophy (Kennedy's disease): a pilot study of PET. J Neurol Sci 335:139–144

Lu M, Wang XZ, Zhang J, Zhao HY, Sun AP, Song LG, Fan DS (2009) The correlation of CAGs repeat size with age of onset in patients with Kennedy's disease. Zhonghua Nei Ke Za Zhi 48:284–286

MacLean HE, Choi WT, Rekaris G, Warne GL, Zajac JD (1995) Abnormal androgen receptor binding affinity in subjects with Kennedy's disease (spinal and bulbar muscular atrophy). J Clin Endocrinol Metab 80:508–516

Mano T, Katsuno M, Banno H, Suzuki K, Suga N, Hashizume A, Araki A, Watanabe H, Tanaka S, Yamamoto M, Sobue G (2014) Tongue pressure as a novel biomarker of spinal and bulbar muscular atrophy. Neurology 82:255–262

Mariotti C, Castellotti B, Pareyson D, Testa D, Eoli M, Antozzi C, Silani V, Marconi R, Tezzon F, Siciliano G, Marchini C, Gellera C, Donato SD (2000) Phenotypic manifestations associated with CAG-repeat expansion in the androgen receptor gene in male patients and heterozygous females: a clinical and molecular study of 30 families. Neuromuscul Disord 10:391–397

Morrison PJ, Mirakhur M, Patterson VH (1998) Discordant repeat size and phenotype in Kennedy syndrome. Clin Genet 53:276–277

Ni W, Chen S, Qiao K, Wang N, Wu ZY (2015) Genotype-phenotype correlation in Chinese patients with spinal and bulbar muscular atrophy. PLoS One 10(3):e0122279. doi:10.1371/journal.pone.0122279.eCollection2015

Nishiyama A, Sugeno N, Tateyama M, Nishiyama S, Kato M, Aoki M (2014) Postural leg tremor in X-linked spinal and bulbar muscular atrophy. J Clin Neurosci 21:799–802

Ogata T, Muroya K, Ishii T, Suzuki Y, Nakada T, Sasagawa I (2001) Undermasculinized genitalia in a boy with an abnormally expanded CAG repeat length in the androgen receptor gene. Clin Endocrinol 54:835–838

Ou-Yang ZY, Song SJ, Liu JR, Zhang BR, Wu DW (2011) Clinical and genetic analysis of a pedigree of Kennedy disease. Zhejiang Da Xue Xue Bao Yi Xue Ban 40:555–558

Pieper CC, Teismann IK, Konrad C, Heindel WL, Schiffbauer H (2013) Changes of pituitary gland volume in Kennedy disease. AJNR Am J Neuroradiol 34:2294–2297

Rhodes LE, Freeman BK, Auh S, Kokkinis AD, La Pean A, Chen C, Lehky TJ, Shrader JA, Levy EW, Harris-Love M, Di Prospero NA, Fischbeck KH (2009) Clinical features of spinal and bulbar muscular atrophy. Brain 132:3242–3251

Rocchi C, Greco V, Urbani A, Di Giorgio A, Priori M, Massa R, Bernardi G, Marfia GA (2011) Subclinical autonomic dysfunction in spinobulbar muscular atrophy (Kennedy disease). Muscle Nerve 44:737–740

Schmidt BJ, Greenberg CR, Allingham-Hawkins DJ, Spriggs EL (2002) Expression of X-linked bulbospinal muscular atrophy (Kennedy disease) in two homozygous women. Neurology 59:770–772

Serratrice G, Pellissier JF, Pouget J (1988) X-linked bulbo-spinal neuronopathy. Kennedy's syndrome. Rev Neurol (Paris) 144:756–758

Shimada N, Sobue G, Doyu M, Yamamoto K, Yasuda T, Mukai E, Kachi T, Mitsuma T (1995) X-linked recessive bulbospinal neuronopathy: clinical phenotypes and CAG repeat size in androgen receptor gene. Muscle Nerve 18:1378–1384

Soukup GR, Sperfeld AD, Uttner I, Karitzky J, Ludolph AC, Kassubek J, Schreiber H (2009) Frontotemporal cognitive function in X-linked spinal and bulbar muscular atrophy (BSMA): a controlled neuropsychological study of 20 patients. J Neurol 256:1869–1875

Sperfeld AD, Hanemann CO, Ludolph AC, Kassubek J (2005) Laryngospasm: an underdiagnosed symptom of X-linked spinobulbar muscular atrophy. Neurology 64:753–754

Sperfeld AD, Karitzky J, Brummer D, Schreiber H, Häussler J, Ludolph AC, Hanemann CO (2002) X-linked bulbospinal neuronopathy: Kennedy disease. Arch Neurol 59:1921–1926

Tanaka S, Banno H, Katsuno M, Suzuki K, Suga N, Hashizume A, Mano T, Araki A, Watanabe H, Adachi H, Tatsumi H, Yamamoto M, Sobue G (2014) Distinct acoustic features in spinal and bulbar muscular atrophy patients with laryngospasm. J Neurol Sci 337:193–200

Vandenberghe N, Bouhour F, Petiot P, Gonnaud PM, Latour P, Broussolle E, Vial C (2009) Multiple phenotypic manifestations of X-linked spinobulbar muscular atrophy. Rev Neurol (Paris) 165:31–37

Xie MQ, Li XG, Cui LY, Liu MS, Li BH, Zhao YH (2010) Clinical features and genetic diagnosis of Kennedy disease. Zhonghua Yi Xue Za Zhi 90:2498–2500

Yang J, Zhang C, Hu ZH, Zhan YX, Cao JQ, Ren H (2010) Study on clinical manifestation, genotype and genetic characteristics of two Kennedy disease pedigrees. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 27:125–131