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Central nervous system abnormalities in spinal and bulbar muscular atrophy (Kennedy's disease)

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ABSTRACT

Spinal and bulbar (bulbospinal) muscular atrophy (BSMA, SBMA, Kennedy's disease) is a progressive motor neuron disease with rare involvement of structures other than the lower motor neuron, such as the endocrine system and the central nervous system (CNS). Aim of the review was to study type and frequency of clinical, imaging, and functional (CNS) abnormalities in SBMA patients. The most frequent clinical CNS manifestations in SBMA are postural or kinetic tremor predominantly of the hands and mild cognitive impairment. The most frequent instrumental CNS abnormality in SBMA patients are white matter lesions, visible on voxel-based morphometry, magnetic resonance spectroscopy, or diffusion tensor imaging. Single patients with enlarged pituitary volume, or diminished somato-sensory representation in the cortex have been also reported. Seizures, epilepsy, ataxia, spasticity, dystonia, or migraine have not been found in SBMA patients. Only supportive treatment is available for CNS manifestations in SBMA. It is concluded that the most frequent CNS abnormalities in SBMA are tremor, cognitive impairment, and white matter lesions on new imaging modalities. CNS involvement in SBMA should not be neglected as a phenotypic manifestation of SBMA and, apart from cognitive involvement, may help to differentiate clinically SBMA from other types of motor neuron disease.

1. Introduction

Spinal and bulbar (bulbopsinal) muscular atrophy (SBMA, SBMA, Kennedy's disease) is a rare, progressive motor neuron disease (MND) with predominant affection of the lower motor neuron [1]. However, it is increasingly recognized that tissues / systems other than the peripheral nerves are affected in SBMA, which include the muscle, endocrine system, manifesting as androgen insensitivity, diabetes, breast enlargement, non-masculinised genitalia, or erectile dysfunction [2,3], and the brain, manifesting as tremor [4], white matter lesions (WMLs) [5], enlarged pituitary volume [6], or reduced somatosensory finger representation [7]. SBMA is a micro-satellite, trinucleotide expansion disorder due to an expansion of a CAG repeat > 38 in exon 1 of the androgen receptor (AR) gene on the long arm of chromosome X [3]. Mutations in this gene are also associated with androgen insensitivity or prostate cancer [8]. Since the expanded CAG repeat is translated into a poly-glutamine stretch, disorders due to CAG repeat expansion are also named as poly-glutamine (poly-Q) disorders [9,10]. CAG repeat expansion is associated with secondary mtDNA depletion in leukocytes [11]. The present review aimed at detecting which cerebral manifestations of SBMA occur, how they can be detected, and if there is a treatment specifically for cerebral involvement in SBMA.

2. Methods

Data for this review were identified by searches of MEDLINE for references of relevant articles published until February 2019. Search terms used for this database were "bulbospinal", "spinal and bulbar", "muscular atrophy", "SBMA", "Kennedy disease", "Kennedy' syndrome", "androgen receptor", "trinucleotide expansion", in combination with "cerebral", "brain", "encephalopathy", "epilepsy", and "cognitive impairment". Results of the search were screened for potentially relevant studies by application of inclusion and exclusion criteria for the full texts of the relevant studies. Included were observational studies with controls, case series, and case reports. Only original articles about humans, and published between 1966 and 2019 were included. Reviews, editorials, and letters were not included. Reference lists of retrieved studies were checked for reports of additional studies.

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Table 1
CNS manifestations of SBMA.

CNS Feature	Characteristics	Reference
Tremor	Postural and kinetic	[4,12,13,14,15,16,17,18,19,20]
NPL deficits	Verbal, non-verbal fluency↓ Concept formation ↓, memory ↓ Learning ↓, naming ↓, dementia, deficits in mentalising	[22,23,24,25,34]
NPL improvements	Improved performance on prose memory test	[35]
WMLs	Corticospinal tract, precentral gyrus, external pallidum, limbic system centrum semiovale	[27]
H-MRS	NAA/creatine ratio ↓, NAA/cholin ratio ↓, myo-inositol ↑	[20,28,29]
Affection of SSS	Invovlement of somato-sensory system	[7]
Enlarged pituitary gland	Normal brain volume	[6]
Poor sleep quality	Due to periodic limb movements	[30]
Frontal deficits	Glucose hypometabolism of frontal lobe	[36]
Tractography	Absence of WMLs	[37,38]

NPL: Neuropsychological deficits, WMLs: white matter lesions, H-MRS: MR-sepctrosocpy, SSS: somato-sensory system.

3. Results

3.1. Clinical CNS abnormalities

3.1.1. Tremor

Though regarded as a rare phenotypic feature of SBMA [4], tremor has been repeatedly reported in SBMA patients (Table 1). In a 58yo male carrying a CAG expansion of 42 repeats in the AR gene, postural and kinetic tremor of the jaw and the hands was found on clinical neurologic exam in addition to typical other stigmata of the disease [4]. Two brothers of the patient and one daughter of the patient also presented with tremor, suggesting that other family members were also affected and that the female was a manifesting carrier [4]. However, since females usually do not manifest clinically [12–14] or only mildly [15,16], it is also conceivable that tremor was non-related to the AR gene mutation. The past medical history of the index case was also positive for arterial hypertension, diabetes, systemic lupus erythematosus, and cutaneous porphyria, conditions which may not explain the occurrence of the tremor [4].

An argument in favour of tremor as a phenotypic feature of SBMA, however, is a report of 12 SBMA males from Japan of whom 3 had postural tremor of the lower legs [17]. Interestingly, all 3 patients had a repeat length of < 47 why the authors concluded that tremor is particularly associated with short CAG repeat sizes [17]. In a study of 12 SBMA patients and female carriers of the disease from France, none of the patients but two of the female carriers presented with kinetic tremor of the hands [15]. Further arguments for tremor representing a feature of SBMA comes from a large Japanese study of 223 patients of whom 126 presented with postural or kinetic hand tremor [18]. Mean age at onset of the tremor was 33y in this cohort [18]. Hand tremor was the most frequent manifestation at onset of the disease [18]. Hand tremor was also reported in a study of 11 Polish patients with SBMA but no correlation with the size of the CAG repeat expansion could be established [19]. In a study of 10 patients by means of cerebral MR spectroscopy, all 10 patients presented with tremor [20]. Unfortunately, type and frequency of tremor were not specified [20]. Since SBMA patients manifest frequently in the liver [21], tremor associated with hepatic disease (flapping tremor) has to be excluded before attributing tremor to primary CNS involvement in SBMA. Flapping tremor is characterised by a brief lapse in tonic innervation which appears as an involuntary jerk superimposed on a postural or intentional movement. These features are not found in tremor of SBMA patients. Arguments for a central origin of the tremor are that it is present before muscle weakness becomes apparent [18] and since it does not resolve upon increasing of a limbs weight.

3.1.2. Neuropsychological deficits

In a recent cross-sectional study of cognitive functions and performance in 20 SBMA patients, neuropsychological assessment of executive functioning, memory, and attentional control, revealed deficits in verbal and non-verbal fluency as well as concept formation [22]. Additionally, these patients showed significant memory deficits in every investigated domain of working memory, and short-term and long-term memory [22]. Concerning attentional control, SBMA patients underperformed in relevant subtests, without reaching statistical significance [22]. The authors concluded that fronto-temporal cognitive functions are subclinically impaired in SBMA and that deficits in SBMA patients are not confined to motor neurons but also affect extramotor networks [22]. In a study of 28 members of an Italian SBMA family, six males were clinically affected [23]. Four of the six patients had abnormal results on neuropsychological testing, which included a battery of eight tests for orientation, attention, logical functions and abstract thinking, verbal fluency, visual-constructive functions, visual-spatial functions, short-term memory, and long-term memory [23]. Interestingly, also three of eight tested female carriers showed abnormal test results for long-term memory tasks (prose memory, paired associate learning, supraspan spatial learning) and for shifting from reading to colour naming in a conflictual situation (Stroop test) [23]. In a single patient with SBMA, fronto-temporal dementia has been described [24]. Presenile dementia as the dominant feature was reported in another SBMA patient in whom autopsy studies showed neuronal depletion and gliosis in the hippocampus and subcortical gliosis in the pre-frontal region [25]. Immunostaining for macrophage markers showed evidence for subtle corticospinal tract pathology [25].

3.2. CNS abnormalities on imaging

Since imaging studies of patients with SBMA are rare, only few reliable data about the type and frequency of CNS abnormalities on imaging are available.

3.2.1. Focal or diffuse atrophy

In a study of 6 Italian SBMA patients, three had diffuse atrophy on cerebral CT scans [23]. Frontal atrophy was also reported in a single SBMA patient with fronto-temporal dementia [24]. On the contrary, cerebral and spinal cord MRIs from two other patients in a study of 7 French patients were normal [15]. A study of 18 SBMA patients by voxel-based morphometry (VBM) brought evidence for extensive white matter atrophy particularly in frontal lobe areas as well as in the brainstem and the cerebellum [5]. The study also found subtle atrophy of the cortical grey matter of the frontal lobe [5]. Grey matter atrophy was interpreted as probably secondary to fibre tract alterations [5].

When studying 19 SBMA patients by means of standard MRI, significant upper spinal cord atrophy at the cervical and thoracic levels were found [26]. Spinal cord atrophy correlated with lower motor neuron axonopathy [26].

3.2.2. White matter lesions

In a recent study of 20 SBMA patients with diffusion tensor imaging (DTI), whole-brain-based DTI analysis revealed widespread white matter impairment within the motor system with predominant affection of the corticospinal tract [27]. A diffuse pattern of WMLs was observed [27]. The relationship between motor and non-motor areas showed only a 1.7-fold higher voxel-count, but two large and nearly symmetrically located clusters were detected along the corticospinal tract of both hemispheres, involving 4574 voxels on the right and 3551 voxels on the left side [27]. Two additional clusters were located adjacent to the left-sided precentral gyrus and in the projection to the external pallidum, suggesting subclinical involvement of the CNS [27]. Other WMLs were located within the limbic system or its projections to the precuneus, the temporal lobe, the inferior frontal lobe of the left hemisphere, and the area adjacent to the posterior cingulum [27]. An additional area of significant reduction of fractional anisotropy was found within the centrum semiovale of the left hemisphere [27]. WMLs particularly in frontal lobe areas as well as in the brainstem and the cerebellum were also found by voxel-based morphometry (VBM) in a study of 18 patients from Germany [5].

In a study of 9 SBMA patients by H-MR spectroscopy (H-MRS) a reduction of the N-acetyl-aspartate (NAA)/choline ratio was found in the brainstem of these patients [28]. In the motor regions a significant reduction of the NAA/choline ratio and of the NAA/creatine ratio were detected [28]. These abnormalities were not related with the size of the CAG expansion [28]. The reduced NAA/choline and NAA/creatine ratios were interpreted to result from neuronal loss and gliosis in supra- and infra-tentorial motor regions [28]. In a study of ten patients the concentration of myo-inositol and macromolecules was slightly increased within the motor cortex [20]. Additionally, the NAA/ creatine (Cr) ratio was negatively correlated with the CAG repeat expansion of the motor cortex area in this study [20]. In a combined MR-spectroscopy/tractography (DTI) study of 18 patients with unknown motor neuron disease, the NAA/choline ratio was significantly reduced but the DTI study was normal in a single, retrospectively diagnosed SBMA patient [29].

3.3. Others

In a study of 7 patients by means of magnetencephalography and somato-sensory evoked potentials, reduced somatosensory finger representation was found [7]. The authors concluded that subclinical sensory neuropathy in SBMA may lead to functional reorganisation of the sensorimotor cortex, reinforcing the notion that the somatosensory system is extensively involved in SBMA [7]. In a study of 8 patients, the volume of the pituitary gland was significantly larger compared to controls whereas the total brain volume was normal (Fig. 1) [6]. Gland volume correlated with the CAG repeat size [6]. Enlargement of the pituitary gland was explained as a compensatory mechanism of the multiple endocrine abnormalities in SBMA patients [6]. Poor sleep quality and periodic limb movements in sleep have also been reported in SBMA patients [30]. Recent pathohistological findings showed extensive diffuse nuclear accumulation of mutant AR in brainstem motor nuclei and spinal motor neurons, in addition to the well known neuronal loss in the spinal cord and brainstem [31]. The observation of diffuse nuclear mutant AR accumulation is closely linked to neuronal dysfunction and the phenotype [31]. Seizures or epilepsy, migraine, ataxia, dystonia, or spasticity have not been reported in SBMA patients so far.

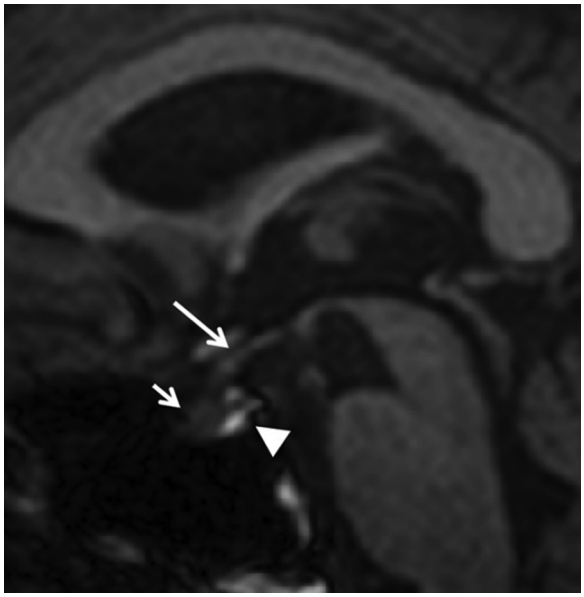

Fig. 1. T1-weighted MRI of the pituitary gland showing enlarged infundibulum (long arrow), anterior lobe (short arrow), and posterior lobe from a 57yo patient with SBMA [reproduced ftom Pieper et al. Am *J* Neuroradiol 2013, permission received].

4. Discussion and conclusions

The review shows that SBMA is a disease not only of the lower motor neuron but also affects the supra-tentorial and infra-tentorial CNS, either clinically or subclinically. Organs other than the CNS may be also affected [32]. The most prevalent clinical CNS manifestations of SBMA are postural and kinetic tremor, fronto-temporal neuropsychological deficits, and behavioural abnormalities. Tremor is regarded to have a cerebral origin since it is one of the earliest manifestations and presents before muscle weakness becomes evident [18]. Subclinical CNS alterations are found on imaging and functional studies of the brain. CT or MRI scans may show diffuse or focal atrophy of the frontal lobe, the brainstem, and the upper spinal cord. Generally, conventional MRI investigations provide little support for documenting CNS involvement. However, advanced MRI methods, such as H-MRS, optimised VBM, and DTI have brought evidence for widespread white matter deterioration in SBMA patients. DTI studies provided evidence that also the limbic white matter structures can be affected. These studies also showed reduced fractional anisotropy in projections to the corticospinal tract of both hemispheres, probably reflecting the anatomical expression of axonal degeneration of the upper motor neuron. The pathogenesis of tremor in SBMA is unknown but it has been proposed that reflex mechanisms or mechanical oscillations are involved in the generation of this tremor [33]. Mechanical oscillations can be explained by reduction of motor units, abnormal feedback from muscle spindles, and thus synchronous firing of motor units [33]. An argument for reflex mechanisms is that tremor in SBMA is affected by postural changes and weight loading, suggesting that it is mediated through reflex loops between peripheral nerves and the CNS, similar to the stretch reflex [33].

The findings discussed above widen the view of the SBMA phenotype since they indicate that extra-motor areas of the CNS are also involved. Investigations not only of individual patients but at the group level were necessary to demonstrate the frequently subtle extra-motor abnormalities of the CNS. These new insights add substantially to our understanding of the underlying pathomorphological processes in SBMA. The widespread subcortical involvement in SBMA is in agreement with CNS abnormalities such as cognitive deficits and behavioural abnormalities. This is why all SBMA patients should be referred for

detailed neuropsychological testing. Although the genotype-phenotype correlation is poor, new imaging techniques (DTI, VBM, H-MRS) are promising for future investigations.

The present review confirmed that SBMA cannot be considered a pure motor neuron disorder but is a multisystem disorder affecting peripheral nerves, the CNS, muscle, and the endocrine system. Though currently there is no specific treatment for cerebral involvement in SBMA and only supportive measures can be offered to these patients, a number of basic studies are under way giving hope that more effective therapy will be available in the future.

Declaration of Competing Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript

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