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# Widening the spectrum of extra-neuromuscular involvement in sbma: is there a role for brain pathology?

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## Editorial

Spinal and Bulbar Muscular Atrophy (SBMA), also known as Kennedy Disease (KD), is an X-linked, adult onset, slowly progressive, lower motor neuron disease characterized by limb and bulbar muscle atrophy and weakness.[1]

The disease is caused by a CAG repeat expansion in the first exon of the androgen receptor gene (AR), with a number of CAG repeats bigger than 38 retained to be pathogenic.[2] It usually affects only adult males and the CAG repeat size correlates inversely with disease onset, but not with disease progression or severity.[3] SBMA belongs to the family of polyglutamine diseases, which also includes Huntington's disease, dentatorubral-pallidoluysian atrophy, and spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, and 17. Within the family of polyglutamine diseases, SBMA is unique in its gender-specificity, with full disease manifestation restricted to males. Since the disease is ligand (androgen)-dependent, SBMA manifests primarily in males, which have high levels of circulating androgens in the serum, while females are usually asymptomatic.[4] Indeed, the polyglutamine-expanded AR is converted to a neurotoxic species upon binding to androgens.[5]

From a clinical point of view, the disease is characterized by slowly progressive lower motor neurons (LMN) degeneration in brainstem and spinal cord, which is associated with multisystem involvement manifesting as androgen insensitivity, heart rhythm abnormalities, metabolic syndrome and sensory neuropathy.[6] The prevalent clinical features of the disease include wasting of proximal limbs muscles with progressive motor impairment,[3] associated with mild bulbar involvement. Respiratory failure is rare, but anyway possible. Death usually occurs after about 20 years disease duration.

In the last years, the extense of non-neural phenotype in SBMA has been extensively explored. Accumulation of pathological AR has been found in several visceral organs including the brain. Recent studies have focused on the morpho-functional consequences of polyQ-AR accumulation on the central nervous system. Neuropsychological involvement has been investigated in some small studies with partially contrasting results. Two single case report[7,8] evidenced the presence of alterations referable to fronto-temporal involvement with impaired visuo-spatial and visuo-constructive abilities, visual short-term memory deficits, and a personality disorder prompting an altered social conduct.

Another more comprehensive study found impairments in attention, executive functions, and verbal memory in four blood-related SBMA patients.[9] The first systematic study in this field, involving 20 SBMA patients,[10] showed a predominantly prefrontal pattern of cognitive dysfunction, in terms of subtle deficits in executive functions and an altered short and long-term memory, justified by the frontal lobe's involvement in organizing and processing memory content. Moreover, from a clinical viewpoint, it is not uncommon for patients with SBMA to present with peculiar psychological characteristics such as diffidence, marked emotional sensitivity and concentration problems.

Magnetic resonance and electrophysiological studies[11] showed subclinical abnormalities in the primary motor cortex and other frontal areas of the brain in SBMA patients. More recently, three magnetic resonance imaging (MRI) studies using voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) reported widespread white matter and subtle gray matter changes in the frontal regions. Kassubek et al.[12] found extensive white matter atrophy in frontal areas and, to a lesser extent, in some subcortical areas, in the cerebellum and in the brainstem. Further research[13] found widespread white matter changes in the corticospinal tract and in the limbic system, while another study[14] described multifocal white matter changes, mainly in the brainstem. A recent positron emission tomography (PET)[11] study also identified hypometabolism in the frontal regions, even without neuron loss, in ten patients with SBMA. Moreover, a recent study from our group,[15] pointed out that SBMA patients present with a normal cognitive profile, but with an abnormal theory of mind (ToM). ToM can be defined as a "social cognitive skill that refers broadly to the capacity to understand others' mental states, and to appreciate that these may differ from our own" and is strongly related to empathy.[16] It can be retained a superior frontal function, with the inferior medial prefrontal cortex, the lateral and orbitomedial prefrontal cortex, and the temporal–parietal junction working as the core neural substrate in ToM operations.[17] From the literature, it seems now quite clear that there is an association between empathy and androgen levels.[18] The gender-related differences may also reflect developmental differences in brain structure and function due to the influence of fetal testosterone, to which the male fetuses are more exposed than the female ones.[19] The SBMA patient's insensitivity to testosterone in all

tissues, including the brain, could therefore work as a protective factor for affective empathy.

Altogether, increasing evidence shows an important multi-system involvement in SBMA. Recently, several studies, described brain involvement with presence of pathologic nuclear inclusions, associated with diffused white matter alterations at MRI studies and neuropsychological impairment involving mainly pre-frontal patterns. Analysis of higher frontal-related functions through ToM tasks confirmed the presence, even if at a subclinical level, of frontal involvement. Interestingly, such abnormalities could be related not only to a diffuse accumulation of the mutated AR, but also with androgen insensitivity influencing empathy and social behavior. Such theory needs to be confirmed through wider studies and will be of extreme importance to define the entity of neuropsychological involvement in SBMA patients and to establish definitely which functions are involved and the entity of such alterations. In the perspective of the every-day clinical practice, such neuropsychological impairment could be related with a reduced quality of life and compliance to follow up and therapies, which could influence clinical outcomes and survival of the patients.

## Disclosure

The authors report no conflict of interest.

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## Conflicts of interst

None.

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