Spinal and Bulbar Muscular Atrophy - Clinical Features and Pathogenesis

Clinical features

SBMA, or Kennedy's disease, is an inherited lower motor neuron disease characterised by adult-onset muscle atrophy, weakness, contraction, fasciculations, and bulbar involvement[1,2]. The onset of weakness is usually between 30 and 50 years, but often preceded by nonspecific symptoms such as tremor, muscle cramps and fatigue[3,4]. Muscle atrophy and weakness are predominant in the tongue and proximal musculature. Deep tendon reflex is diminished or absent with no pathological reflex. Sensory involvement is largely restricted to vibration sense which is affected distally in the legs[2]. Male patients often demonstrate signs of androgen insensitivity such as gynecomastia, testicular atrophy, impotence and decreased fertility[5,6], some of which are detected before the onset of motor symptoms. Hyperlipidemia, liver dysfunction and glucose intolerance are also seen in some cases[3,7]. SBMA chiefly affects males, whereas females with the mutation are usually asymptomatic even when homozygous[8,9,10]. The prevalence of SBMA has been estimated 1 in 40000 in areas with high ascertainment[11], although a considerable number of patients may have been under diagnosed[12,13].

The disease progresses slowly in general, although repetitive respiratory tract infection often occurs in the advanced stage of the disease, resulting in early death in some patients[4]. No specific treatment for SBMA has been established. Testosterone has been used in some patients, although it has no effects on the progression of SBMA[14,15,16].

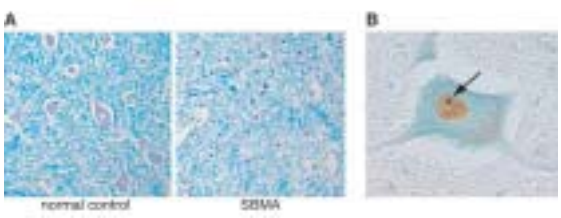
Genetics

The molecular basis of SBMA is the expansion of a trinucleotide CAG repeat, which encodes the polyQ tract, in the first exon of the androgen receptor (AR) gene[17]. The number of CAG repeat within AR is 11 to 35 in normal subjects, but it expands from 40 to 62 in patients[11,17,18]. Expanded polyQ tracts have been found to cause several neurodegenerative diseases including SBMA, Huntington's disease (HD), several forms of spinocerebellar ataxia, and dentatorubral and pallidoluysian atrophy (DRPLA)[19,20,21]. There is an inverse correlation between the CAG repeat size and the age at onset, or the disease severity adjusted for age at examination in SBMA[22,23] as well as other polyQ diseases[19,24]. These observations suggest that common mechanisms underlie the pathogenesis of polyQ diseases, despite the fact that the causative protein for each of the diseases are different except for the existence of polyQ stretch. Although the expansion of polyQ tract in AR disrupts the transcriptional activities of AR[25,26], motor impairment has never been observed in severe testicular feminisation patients lacking AR function[27]. Therefore, as in other polyQ diseases, a toxic gain of mutant AR function has been considered to cause neuromuscular disorder in SBMA.

Pathology

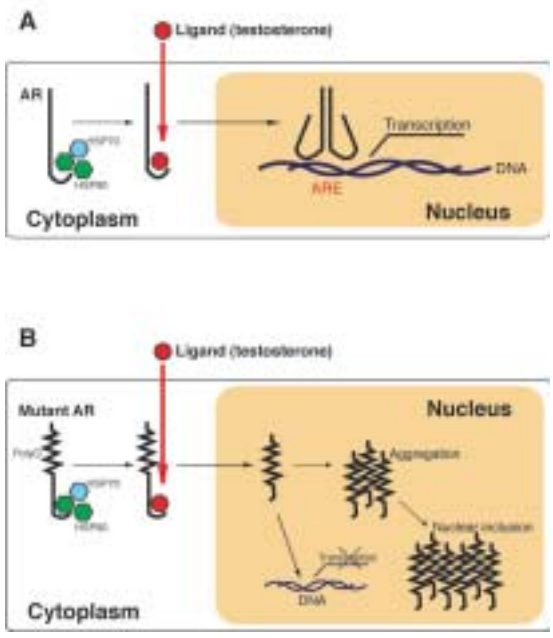
Lower motor neurons are markedly depleted through all spinal segments and in brainstem motor nuclei except for the third, fourth and sixth cranial nerves in autopsy cases of SBMA (Fig. 1A)[2,28]. A striking pathologic hallmark of most polyQ diseases is the presence of nuclear inclusions (NIs), which has been considered relevant to the pathophysiology[19]. In SBMA patients, NIs containing the mutant AR are detected in the residual motor neurons (Fig. 1B)[29] as well as in other visceral organs[30]. Although the exact role of NIs in the pathogenesis is to be elucidated, nuclear accumulation of mutant protein is essential for inducing neuronal cell dysfunction and degeneration in the majority of polyQ diseases[20]. In support of this hypothesis, the dysfunction of nuclear transcriptional regulatory proteins have been considered crucial in polyQ pathogenesis[31,32]. Since ligand facilitates the nuclear translocation of AR, it appears to be logical that SBMA pathogenesis is ligand-dependent (Fig. 2).

Figure 1



Histopathology of SBMA
In Kluver-Barrera's stain of the lumbar anterior horn (A), motor neurons are depleted in SBMA compared with normal control. A residual motor neuron in the lumbar anterior horn shows a nuclear inclusion detected by anti-polyglutamine antibody (B, arrow).

Figure 2



Androgen receptor (AR) dynamics in SBMA
AR is a member of the steroid/thyroid receptor superfamily. In a normal cell (A), AR is confined to a multi-heteromeric inactive complex with heat shock proteins (HSPs) in the cell cytoplasm. Ligand-binding facilitates its dissociation from this complex and translocation into the nucleus. ARs undergo comformational change, form a dimer, bind to androgen response elements (ARE) in the DNA, and function as ligand-dependent transcription factor. In SBMA (B), mutant AR is partially cleaved and translocates into the nucleus in a ligand-dependent manner. In the nucleus, mutant ARs aggregate and form nuclear inclusions as a consequence. This inhibits the function of critical cellular proteins inhibited by soluble and/or aggregated AR, resulting in transcriptional dysregulation. On the other hand, the decreased transactivating function of mutant AR may contribute to the androgen insensitivity and neurodegeneration in SBMA.

Masahisa Katsuno is a Research Fellow in Neurology at Nagoya University Graduate School of Medicine, Nagoya, Japan. He graduated from Nagoya University in 1995. He has worked on molecular mechanism and therapeutic approach of spinal and bulbar muscular atrophy.

Hiroaki Adachi is a Research Fellow in Neurology at Nagoya University Graduate School of Medicine, Nagoya, Japan. He graduated from Nagoya University in 1991. He has worked on molecular mechanism and therapeutic approach of spinal and bulbar muscular atrophy.

Gen Sobue is Professor of Neurology at Nagoya University Graduate School of Medicine, Nagoya, Japan. He graduated from Nagoya University in 1975, and worked at University of Pennsylvania School of Medicine and Aichi Medical University. He has worked on peripheral neuropathy and neurodegenerative diseases.

Ligand-dependent pathogenesis

We generated transgenic mice expressing the full-length human AR containing 97 CAGs under the control of a cytomegalovirus enhancer and a chicken ß-actin promoter[33]. The mice (AR-97Q) showed small body size, short life span, progressive muscle atrophy and weakness as well as reduced cage activity, all of which were markedly pronounced and accelerated in the male AR-97Q mice, but were either not observed or far less severe in the female AR-97Q mice. Western blot analysis and immunostaining showed markedly more abundant nuclear accumulation of mutant AR in male mice than in their female counterparts, in agreement with the symptomatic differences with gender. Gender effect on the phenotypes has also been demonstrated in another transgenic mouse model of SBMA[34].

Castrated male AR-97Q mice showed marked improvement of symptoms, histopathologic findings, and nuclear localisation of the mutant AR compared with the sham-operated male AR-97Q mice. In contrast to castration of the male mice, testosterone caused significant aggravation of symptoms, histopathologic features, and nuclear localisation of the mutant AR in the female AR-97Q mice. Since the nuclear translocation of AR is ligand-dependent, testosterone appears to show toxic effects in the female AR-97Q mice by accelerating nuclear translocation of the mutant AR. By contrast, castration prevented the nuclear localisation of the mutant AR by reducing the testosterone level. In support of this hypothesis, the ligand-dependent neurodegeneration has also been revealed in a Drosophila model of SBMA[35]. Alternatively, castration may enhance the protective effects of heat shock proteins, which exert beneficial effects in cell and mouse models of SBMA[36,37].

Based on successful treatment of AR-97Q mice with castration, we investigated the effects of testosterone blockade therapies, using the LHRH analogue and AR antagonist, in the transgenic mice[38]. Leuprorelin and LHRH analogue reduces testosterone release from the testis and showed marked amelioration of symptoms, histopathologic findings, and nuclear localisation of the transgene protein compared with the vehicle-treated AR-97Q mice. Leuprorelin initially increased the serum testosterone level by agonising the LHRH receptor, but subsequently reduced it to undetectable levels. Leuprorelin-treated AR-97Q mice showed transient deterioration of motor function due to this initial increase in testosterone level. This symptomatic and pathologic aggravation was followed by sustained amelioration along with consequent suppression of testosterone production. Our results indicate that leuprorelin is a promising therapeutic strategy of SBMA, and that polyQ pathogenesis is reversible at least in its dysfunctional stage.

By contrast, flutamide AR antagonist, did not ameliorate symptoms, pathologic features, or nuclear localisation of the mutant AR in the male AR-97Q mice, although there was no significant difference in the androgen blockade effects between flutamide and leuprorelin. Although flutamide suppresses the androgen-dependent transactivation, it does not inhibit, but may even facilitate, the nuclear translocation of AR[39,40]. Flutamide also promotes nuclear translocation of mutant AR containing expanded polyQ in a cell and Drosophila model of SBMA[35,41]. This may be the reason why flutamide demonstrated no therapeutic effect in our transgenic mouse model of SBMA.

Therapeutic perspective

As mentioned above, our recent study indicated that leuprorelin exerts therapeutic effects in the SBMA transgenic mouse model. LHRH analogue can easily be applied to human SBMA therapy, because this drug has extensively been used as medical castration in the therapy of prostate cancer[42]. However, any clinical trial using this approach is difficult as the patient's desire for fertility should be taken into account, and the appropriate clinical dose should be carefully determined.

Acknowledgements

This work was supported by a Center-of-Excellence (COE) grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan, by grants from the Ministry of Health, Labour and Welfare, Japan, by a grant from Naito Foundation, and by a grant from Kanae Foundation.

References

1. Kennedy WR, Alter M, SungJH (1968) *Progressive proximal spinal and bulbar muscular atrophy of late onset: a sex-linked recessive trait.* Neurology 18: 671-680.
2. Sobue G, Hashizume Y, Mukai E, Hirayama M, Mitsuma T, Takahashi A (1989) *X-linked recessive bulbospinal neuronopathy: a clinicopathological study.* Brain 112: 209-232.
3. Sperfeld AD, Karitzky J, Brummer D, Schreiber H, Haussler J, Ludolph AC, Hanemann CO (2002) *X-linked bulbospinal neuropathy: Kennedy disease.* Arch Neurol 59: 1921-1926.
4. Sobue G, Adachi H, Katsuno M (2003) *Spinal and bulbar muscular atrophy (SBMA). In: Dickinson D (ed) Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders.* INS Neuropath Press, Basel, pp275-279.
5. Nagashima T, Seko K, Hirose K, Mannen T, Yoshimura S, Arima R, Nagashima K, Morimatsu Y (1988) *Familial bulbo-spinal muscular atrophy associated with testicular atrophy and sensory neuropathy (Kennedy-Alter-Sung syndrome): autopsy case report of two brothers.* J Neurol Sci 87: 141-152.
6. Dejager S, Bry-Gauillard H, Bruckert E, Eymard B, Salachas F, Leguern E, Tardieu S, Chadarevian R, Giral P, Turpin G (2002) *A comprehensive endocrine description of Kennedy's disease revealing androgen insensitivity linked to CAG repeat length.* J Clin Endocr Metab 87: 3893-3901.
7. Warner CL, Servidei S, Lange DJ, Miller E, Lovelace RE, Rowland LP (1990) *X-linked spinal muscular atrophy (Kennedy's syndrome): a kindred with hypobetalipoproteinemia.* Arch Neurol 47: 1117-1120.
8. Sobue G, Doyu M, Kachi T, Yasuda T, Mukai E, Kumagai T, Mitsuma T (1993) *Subclinical phenotypic expressions in heterozygous females of X-linked recessive bulbospinal neuronopathy.* J Neurol Sci 117: 74-78.
9. 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.
10. 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.
11. Fischbeck KH (1997) *Kennedy disease.* J Inherit Metab Dis 20: 152-158.
12. Parboosingh JS, Figlewicz DA, Krizus A, Meininger V, Azad NA, Newman DS, Rouleau GA (1997) *Spinobulbar muscular atrophy can mimic ALS: the importance of genetic testing in male patients with atypical ALS.* Neurology 49: 568-572.
13. Udd B, Juvonen V, Hakamies L, Nieminen A, Wallgren-Pettersson C, Cederquist K, Savontaus M-L (1998) *High prevalence of Kennedy's disease in western Finland: is the syndrome underdiagnosed?* Acta Neurol Scand 98: 128-133.
14. Danek A, Witt TN, Mann K, Schweikert HU, Romalo G, La Spada AR, Fischbeck KH (1994) *Decrease in androgen binding and effect of androgen treatment in a case of X-linked bulbospinal neuronopathy.* Clin Investig 72: 892-897.
15. Goldenberg JN, Bradley WG (1996) *Testosterone therapy and the pathogenesis of Kennedy's disease (X-linked bulbospinal muscular atrophy).* J Neurol Sci 135: 158-161.

16. Neuschmid-Kaspar F, Gast A, Peterziel H, Schneikert J, Muigg A, Ransmayr G, Klocker H, Bartsch G, Cato AC (1996) *CAG-repeat expansion in androgen receptor in Kennedy's disease is not a loss of function mutation.* Mol Cell Endocrinol 117: 149-156.
17. La Spada AR, Wilson EM, Lubahn DB, Harding AE, FischbeckKH (1991) *Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy.* Nature 352: 77-79.
18. Tanaka F, Doyu M, Ito Y, Matsumoto M, Mitsuma T, Abe K, Aoki M, Itoyama Y, Fischbeck KH, Sobue G (1996) *Founder effect in spinal and bulbar muscular atrophy (SBMA).* Hum Molec Genet 5: 1253-1257.
19. Zoghbi HY, Orr HT (2000) *Glutamine repeats and neurodegeneration.* Annu Rev Neurosci. 23: 217-247.
20. Ross CA (2002) *Polyglutamine pathogenesis: emergence of unifying mechanisms for Huntington's disease and related disorders.* Neuron 35: 819-822.
21. Taylor JP, Hardy J, Fischbeck KH (2000) *Toxic proteins in neurodegenerative disease.* Science 296: 1991-1995.
22. Doyu M, Sobue G, Mukai E, Kachi T, Yasuda T, Mitsuma T, Takahashi A (1992) *Severity of X-linked recessive bulbospinal neuronopathy correlates with size of the tandem CAG repeat in androgen receptor gene.* Ann Neurol 32: 707-710.
23. 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.
24. Margolis RL, Ross CA (2002) *Expansion explosion: new clues to the pathogenesis of repeat expansion neurodegenerative diseases.* Trends Mol Med 7: 479-482.
25. Mhatre AN, Trifiro MA, Kaufman M, Kazemi-Esfarjani P, Figlewicz D, Rouleau G, Pinsky L (1993) *Reduced transcriptional regulatory competence of the androgen receptor in X-linked spinal and bulbar muscular atrophy.* Nat Genet 5: 184-188.
26. Brooks BP, Paulson HL, Merry DE, Salazar-Grueso EF, Brinkmann AO, Wilson EM, Fischbeck KH (1997) *Characterisation of an expanded glutamine repeat androgen receptor in a neuronal cell culture system.* Neurobiol Dis 3: 313-323.
27. Gottlieb B, Pinsky L, Beitel LK, Trifiro M (1999) *Androgen insensitivity.* Am J Med Genet 89: 210-217.
28. Sobue G, Matsuoka Y, Mukai E, Takayanagi T, Sobue I, Hashizume Y (1981) *Spinal and cranial motor nerve roots in amyotrophic lateral sclerosis and X-linked recessive bulbospinal muscular atrophy: morphometric and teased-fiber study.* Acta Neuropath 55: 227-235.
29. Li M, Miwa S, Kobayashi Y, Merry DE, Yamamoto M, Tanaka F, Doyu M, Hashizume Y, Fischbeck KH, Sobue G (1998a) *Nuclear inclusions of the androgen receptor protein in spinal and bulbar muscular atrophy.* Ann Neurol 44: 249-254.
30. Li M, Nakagomi Y, Kobayashi Y, Merry DE, Tanaka F, Doyu M, Mitsuma T, Hashizume Y, Fischbeck KH, Sobue G (1998b) *Nonneural nuclear inclusions of androgen receptor protein in spinal and bulbar muscular atrophy.* Am J Pathol 153: 695-701.
31. Steffan JS, Kazantsev A, Spasic-Boskovic O, Greenwald M, Zhu YZ, Gohler H, Wanker EE, Bates GP, Housman DE, Thompson LM (2000) *The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription.* Proc Natl Acad Sci U S A 97: 6763-6768.
32. Nucifora FC Jr, Sasaki M, Peters MF, Huang H, Cooper JK, Yamada M, Takahashi H, Tsuji S, Troncoso J, Dawson VL, Dawson TM, Ross CA (2001) *Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity.* Science 291: 2423-2428.
33. 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.
34. McManamny P, Chy HS, Finkelstein DI, Craythorn RG, Crack PJ, Kola I, Cheema SS, Horne MK, Wreford NG, O'Bryan MK, De Kretser DM, Morrison JR (2002) *A mouse model of spinal and bulbar muscular atrophy.* Hum Mol Genet 11: 2103-2111.
35. Takeyama K, Ito S, Yamamoto A, Tanimoto H, Furutani T, Kanuka H, Miura M, Tabata T, Kato S (2002) *Androgen-dependent neurodegeneration by polyglutamine-expanded human androgen receptor in Drosophila.* Neuron 35: 855-864.
36. Kobayashi Y, Kume A, Li M, Doyu M, Hata M, Ohtsuka K, Sobue G (2000) *Chaperones Hsp70 and Hsp40 suppress aggregate formation and apoptosis in cultured neuronal cells expressing truncated androgen receptor protein with expanded polyglutamine tract.* J Biol Chem 275: 8772-8778.
37. Adachi H, Katsuno M, Minamiyama M, Sang C, Pagoulatos G, Angelidis C, Kusakabe M, Yoshiki A, Kobayashi Y, Doyu M, Sobue G (2003) *Heat shock protein 70 chaperone overexpression ameliorates phenotypes of the spinal and bulbar muscular atrophy transgenic mouse model by reducing nuclear-localised mutant androgen receptor protein.* J Neurosci 23: 2203-2211.
38. Katsuno M, Adachi H, Doyu M, Minamiyama M, Sang C, Kobayashi Y, Inukai A, Sobue G (2003) *Leuprorelin rescues polyglutamine-dependent phenotypes in a transgenic mouse model of spinal and bulbar muscular atrophy.* Nat Med 9 768-773.
39. Lu S, Simon NG, Wang Y, Hu S (1999) *Neural androgen receptor regulation: effects of androgen and antiandrogen.* J Neurobiol 41: 505-512.
40. Tomura A, Goto K, Morinaga H, Nomura M, Okabe T, Yanase T, Takayanagi R, Nawata H (2001) *The subnuclear three-dimensional image analysis of androgen receptor fused to green fluorescence protein.* J Biol Chem 276: 28395-28401.
41. Walcott JL, Merry DE (2002) *Ligand promotes intranuclear inclusions in a novel cell model of spinal and bulbar muscular atrophy.* J Biol Chem 277: 50855-50859.
42. Huggins C, Hodges CV (1941) *Studies on prostatic cancer. I. The effects of castration, of strogen and of androgen injection on serum phosphates in metastatic carcinoma of the prostate.* Cancer Res. 1: 293-297.

Correspondence address:
Gen Sobue, MD
Department of Neurology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Tel: +81-52-744-2385,
Fax: +81-52-744-2384
E-mail: sobueg@med.nagoya-u.ac.jp