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Review Article

Spinal Muscular Atrophy: A Short Review

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Abstract

Spinal muscular atrophy (SMA) is a genetic disorder which affect nervous system and is characterized with progressive distal motor neuron weakness. The Survival motor neuron (SMN) protein level reduces in patients with SMA. Two different genes code survival motor neuron protein in human genome. Skeletal and intercostal muscles denervation lead to weakness, hypotony, hyporeflexia, respiratory failure, symmetric muscle atrophy and paralysis in patients with SMA. Manifestations are prominent in proximal muscle of lower extremities. There is no curative treatment for spinal muscular atrophy, and supportive treatment should be considered to improve patients' quality of life and independency. New treatment strategies focus on gene therapy or invent method to increase survival motor neuron protein level. The aim of this study is to review spinal muscular atrophy clinical and molecular manifestations.

Key words: Molecular analysis, Spinal muscular atrophy, Survival motor neuron protein.

Introduction

Spinal muscular atrophy (SMA) is a genetic disorder which affect nervous system and is characterized with progressive distal motor neuron weakness. SMA is a hereditary (autosomal recessive) neuromuscular disease which leads to paralysis and death in childhood (1). Four form of SMA were identified; type zero is the fetus form of disease which causes death in early infancy.

1)Type I: Infantile (Werdnig-Hoffmann disease).
2)Type II: Intermediate (Dubowitz disease).
3)Type III: Juvenile (Kugelberg–Welander disease).
4)Type IV: adult onset (2).

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Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a type of distal spinal muscular atrophy with diaphragm involvement; its clinical manifestation varies in different patients.

Infants had severe symptoms from birth with frog like position or bell shaped deformity in chest. Foot deformities and contractures are common in SMARD1 patients (3). Disease pathology base is anterior horn motor neuron degeneration like SMA, and it is also an autosomal recessive disorder. SMARD1 is a rare condition and there are about 100 case report of this condition from all around the world (4).

The survival motor neuron (SMN) protein level reduces in patients with SMA. Two different genes code survival motor neuron protein in human genome. In SMA patients have homozygous changes of SMN1 with at least unique copy of SMN2. Genetic changes in chromosome 5 q 13 (mutation, deletion, or rearrangement) are responsible for SMA (5-7). More than (95%) of children with SMA have homozygous deletion of SMN I gene axons 7 and 8. Other patients might have changes in SMN II gene (5). Spinal muscular atrophy is the second common neuromuscular disease after Duchenne muscular dystrophy(DMD) and its incidence is one in every 10000-25000 birth. SMA mortality and morbidity depends on the age at disease onset. Early onset form of SMA such as type zero and I are mortal in (95%) of cases (6). Pulmonary compli-cations like respiratory failure and infections are the most common cause of death (5). Males were affected in type I and II in comparison with females individuals (7). Consanguineous marriages are frequent in Iranian population, so it is estimated that SMA prevalence might be higher in our country (8).

Skeletal and intercostal muscles denervation lead to weakness, hypotony, hyporeflexia, respiratory failure, symmetric muscle atrophy and paralysis in patients with SMA. Manifestations are prominent in proximal muscle of lower extremities (9).

Children who suffer from spinal muscular atrophy show no sign of central nervous system involvement; loss of muscle tone (hypotony) poor sucking reflex, and floppy baby are the most common presentation in acute infantile form of SMA. Mean survival life is estimated about 6 months in this children and death happens due to Respiratory failure (10). Chronic infantile form manifestations are developmental motor lag, difficulties in standing or walking. Patients might survive for 30 years (2). Respiratory infections cause death in this type of SMA. Chronic juvenile type (Kugelberg–Welander disease) occurs after 18 months old and most of them have normal life span. Motor skills might disrupt in some cases. Type IV is similar to type III, and disease is benign (1). The aim of this study is to review SMA clinical and molecular manifestations.

Materials and Methods

For reviewing SMA, we searched Pubmed. Our key word was spinal muscle atrophy in children. We filtered our results to abstract available, english articles in the past 5 years. We found 262 articles. Finally 8 articles we selected for review. Almost all articles were case reports or case series.

Results

The Creatine kinase (CK) serum is in normal range in patients with SMA type I, CK level is slightly raised in other type of SMA (1). It was confirmed that CK level is normal in young patients and rises in older ones (11). Cerebrospinal fluid (CSF) indexes are normal in all patients (7). Electrodiagnostic (EDX) test demonstrate fasciculation, fibrillation, sharp waves with high amplitude. Electromyography (EMG) might show neroguenic damage in some patients with SMA (11). Muscle biopsy

shows atrophy. Genetic analyses are necessary to confirm SMA diagnosis (8). In (Table1) result of molecular analysis in SMA patients showed. It seems that deletion in SMN gene is responsible for SMA pathology and other deletion associate with severe presentation of SMA. SMN2 copy number is related to spinal muscular atrophy.

Prenatal diagnosis can be confirmed by placental biopsy at 10 weeks of gestation.

Some studies suggested that ELIZA could detect small changes in SMN protein concentration and might be useful in SMA diagnosis (12).

Table1: Result of genetic assessment in SMA

Author	Publication year	Patients No	Homozygous-deletion frequency of *SMN* exons 7 and 8	Other deletion	Conclusion
Nguyen (10)	2003	-	41-50%	-	-
Harada (12)	2002	27	95%	-	SMN2 copy number is related with disease severity.
Derakhshandeh-Peykar (9)	2007	75	97%	deleted NAIP exons 5 and 6: 83%	Molecular gene analysis is useful for SMA diagnosis.
Watihayati (13)	2009	42	95%	deleted NAIP: 21.4%	SMN2 copy number is related with disease severity.
Omrani (8)	2009	75	90%	deleted NAIP: 57.3%	The incidence of NAIP deletion is higher in more severe SMA.
Miskovic (14)	2011	89	94.4%	deleted NAIP: 20.2%	Screening is important in families with SMA history.
Liu (15)	2013	113	91.2%	Mutation in SMN exon 5 in two patients	Some patients had SMN1-unrelated SMA.
He (16)	2013	157	94.4%		inverse correlations between SMN2, the NAIP copy number, and the clinical severity of the disease

Discussion

Children who suffer from spinal muscular atrophy show no sign of central nervous system involvement; loss of muscle tone (hypotony) poor sucking reflex, and floppy baby are the most common presentation in acute infantile form of SMA.

Mean survival life is estimated about 6 months in this children and death happens due to Respiratory failure (10). Chronic infantile form manifestations are developmental motor lag, difficulties in standing or walking. Patients might survive for 30 years (2). Respiratory infections cause death in this type of SMA. Chronic juvenile type (Kugelberg–Welander disease) occurs after 18 months old and most of them have normal life span. Motor skills might disrupt in some cases. Type IV is similar to type III, and disease is benign (1).There is no curative treatment for spinal muscular atrophy, and supportive treatment should be considered to improve patients' quality of life and independency. Splint, braces and orthoses could be used if needed (9).

Chest physiotherapy, oxygen and antibiotics could be customized to each case (10). Fibroblast culture confirmed Hydroxyurea (HU) might promote SMN mRNA production and increases SMN2 gene expression (13). Sodium valproate could improve muscle function in SMA type III and IV, valproate probable mechanism is promoting SMN2 gene transcription (14).

New treatment strategies focus on gene therapy or invent method to increase survival motor neuron protein level. In one study it was shown that salbutamol could be used in spinal muscular atrophy as a therapeutic option, but response to treat depends on SMN2 copy numbers (15-18).

Conclusion

Spinal muscle atrophy is a relatively common neuromuscular disease, and genetic findings are important for its diagnosis and predict patients prognosis.

References

1.Fraidakis MJ, Drunat S, Maisonobe T, Gerard B, Pradat PF, Meininger V, et al. Genotype-phenotype relationship in 2 SMA III patients with novel mutations in the Tudor domain. Neurology 2012 Feb 21;78(8):551-6.

2.He J, Zhang QJ, Lin QF, Chen YF, Lin XZ, Lin MT, et al. Molecular analysis of SMN1, SMN2, NAIP, GTF2H2, and H4F5 genes in 157 Chinese patients with spinal muscular atrophy. Gene 2013 Apr 15;518(2):325-9.

3. Wong VC, Chung BH, Li S, Goh W, Lee SL. Mutation of gene in spinal muscular atrophy respiratory distress type 1. Pediatr Neurol 2006;34(6):474–7.

4. AlSaman A, Tomoum H. Infantile spinal muscular atrophy with 214espiratory distress type 1: a case report. J Child Neurol 2010;25(6):764–9.

5. Kuźma-Kozakiewicz M, Jędrzejowska M, Kaźmierczak B. SMN1 gene duplications are more frequent in patients with progressive muscular atrophy. Amyotroph Lateral Scler Frontotemporal Degener 2013 Sep; 14 (5-6): 457-62.

higher SMN2 gene expression after 4 phenylbutyrate (PBA) treatment in SMA type I, II, III (11).

6. Majid A, Talat K, Colin L, Caroline R, Helen K, Christian de G. Heterogeneity in spinal muscular atrophy with respiratory distress type 1. J Pediatr Neurosci 2012 Sep;7(3):197-9.

7. Martinez TL, Kong L, Wang X, Osborne MA, Crowder ME, Van Meerbeke JP, et al. Survival motor neuron protein in motor neurons determines synaptic integrity in spinal muscular atrophy. J Neurosci 2012 Jun 20;32(25):8703-15.

8. Omrani O, Bonyadi M, Barzgar M. Molecular analysis of the SMN and NAIP genes in Iranian spinal muscular atrophy patients. Pediatr Int 2009 Apr;51(2):193-6.

9. Derakhshandeh-Peykar P, Esmaili M, Ousati-Ashtiani Z, Rahmani M, Babrzadeh F, Farshidi S, et al. Molecular analysis of the SMN1 and NAIP genes in Iranian patients with spinal muscular atrophy. Ann Acad Med Singapore 2007 Nov;36(11):937-41.

10. Nguyen DB, Sadewa AH, Takeshima Y, Sutomo R, Tran VK, Nguyen TN, et al. Deletion of the SMN1 and NAIP genes in Vietnamese patients with spinal muscular atrophy. Kobe J Med Sci 2003;49(3-4):55-8.

11. Wang YY, Feng SW, Cao JQ, Yang J, Li YQ, Li J, et al. [Genotypic and clinical features of spinal muscular atrophy type 3]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2012 Apr;29(2):218-21.

12. Piepers s, Cobben J, Sodaar P, Jansen M, Wadman R, Meester-Delver A. Quantification of SMN protein in leucocytes from spinal muscular atrophy patients: effects of treatment with valproic acid. J Neurol Neurosurg Psychiatry 2011;82(8):850e852.

13. Harada Y, Sutomo R, Sadewa AH, Akutsu T, Takeshima Y, Wada H, et al. Correlation between SMN2 copy number and clinical phenotype of spinal muscular atrophy: three SMN2 copies fail to rescue some patients from the disease severity. J Neurol 2002 Sep;249(9):1211-9.

14. Watihayati MS, Fatemeh H, Marini M, Atif AB, Zahiruddin WM, Sasongko TH, et al. Combination of SMN2 copy number and NAIP deletion predicts disease severity in

spinal muscular atrophy. Brain Dev 2009 Jan;31(1):42-5.
15. Miskovic M, Lalic T, Radivojevic D, Cirkovic S, Vlahovic G, Zamurovic D, et al. Lower incidence of deletions in the survival of motor neuron gene and the neuronal apoptosis inhibitory protein gene in children with spinal muscular atrophy from Serbia. Tohoku J Exp Med 2011;225 (3):153-9.
16. Liu WL, Li F, He ZX, Ai R, Ma HW. Molecular analysis of the SMN gene mutations in spinal muscular atrophy patients in China. Genet Mol Res 2013 Sep 13;12(3):3598-604.
17. He J, Zhang QJ, Lin QF, Chen YF, Lin XZ, Lin MT, et al. Molecular analysis of SMN1, SMN2, NAIP, GTF2H2, and H4F5 genes in 157 Chinese patients with spinal muscular atrophy. Gene 2013 Apr 15; 518 (2):325-9.
18. Tiziano FD, Lomastro R, Di Pietro L, Barbara Pasanisi M, Fiori S, Angelozzi C, et al. Clinical and molecular cross-sectional study of a cohort of adult type III spinal muscular atrophy patients: clues from a biomarker study. Eur J Hum Genet 2013; 21(6):630-6.