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 5q13 (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 complications 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). Electrodagnostic (EDX) test demonstrate fascication, fibrillation, sharp waves with high amplitude. Electromyography (EMG) might show neurogenic damage in some patients with SMA (11). Muscle biopsy
shows atrophy. Genetic analyses are necessary to confirm SMA diagnosis (8). In (Table 1) 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

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

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**

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