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VALPROIC ACID – A POSSIBLE THERAPEUTIC ALTERNATIVE IN SPINAL MUSCULAR ATROPHY MANAGEMENT

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Abstract. Spinal muscular atrophy (SMA) is an autosomal-recessive disorder caused by homozygous mutations in the survival motor neuron (SMN) gene. This can lead to dysfunction and loss of motor neurons of the anterior horn of the spinal cord and lower brain stem. The molecular pathophysiology of the disease is incompletely understood. Authors have reviewed current concepts on the treatment strategies for patients with spinal muscular atrophy. Valproic acid, known as an anticonvulsant, is a histone deacetylase inhibitor that can increase SMN protein levels in some SMA cells or SMA patients, through activation of SMN2 gene.
Keywords: spinal muscular atrophy, valproic acid, clinical trials

Introduction

The human survival motor neuron (*SMN)* gene is located on chromosome 5q and exists in two copies: *SMN1* and *SMN2*. The genetic cause for SMA is a homozygous deletion/mutation of the SMN1 gene. *SMN1* is the telomeric copy and produces a full-length survival motor neuron (FL-SMN) protein necessary for a normal lower motor neuron function. *SMN2 is t*he centromeric copy which produces a less stable protein. This protein is not sufficient to prevent the progressive degeneration of motor neuron when *SMN1* is absent (figure 1).

Spinal muscular atrophy results from loss of the SMN1gene and malfunction of the remaining SMN-2gene. Perhaps severity of the disease is influenced by the SMN2 copy number, which can be in SMA patients between 1-5 copies. Since an increased number of SMN2 copies strongly correlates with a milder SMA phenotype, activation or stabilization of SMN2 is considered as a therapeutic strategy [1].

In some rare cases patients are asymptomatic despite carrying the same SMN1 mutations. Plastin 3 (PLS3) was recently identified as the first SMA modifying gene that fully protects females from developing SMA [2].

Clinically, the disease gradually affects the limb muscles, respiratory muscles, with no evidence of cerebral affliction or malfunction of the central motor neurons. The patients' IQ levels are normal. The clinical distinction between SMA type I to IV reflects different age of onset, the degree of mobility acquired and the disease severity.

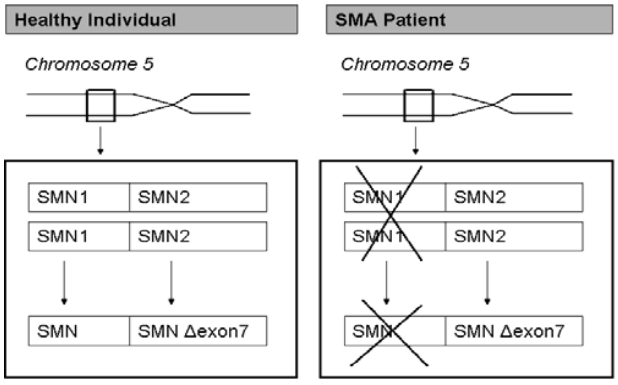

Figure1. Schematic diagram showing the SMN gene locus in healthy individuals and SMA patients. SMN Δexon7 is a truncated and non-functional protein (Natasha G. et al, 2008)

- Type I SMA (Werdnig-Hoffmann disease) is characterized by onset within the first 6 months of age. The children never achieve the ability to sit and death usually occurs by 2 years age.
- Type II SMA is characterized by onset after six months of age with muscle weakness and hypotony. Children are able to sit but unable to walk.
- Type III SMA (Kugelberg-Welander disease) occurs after 18 months of age and the patients achieve the ability to walk.

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- Type IV SMA is a mild form with an adult onset of muscle weakness.

All four types of SMA show a progressive course, which is severe in type I and mild in type III and IV SMA.

Treatment

Treatment of all forms of SMA is symptomatic, supportive and needs a multidisciplinary approach.

Nowadays therapeutic strategies for SMA include: induction of SMN2 gene expression, modulation of splicing of SMN2-derived transcripts, stabilization of SMN protein, neuroprotection of SMN deficit neurons and SMN1 gene replacement.

Current treatment

The International Standard of Care Committee for SMA established in 2006 practice guidelines for the clinical care of SMA patients: Diagnostic/ New Interventions, Pulmonary, Gastrointestinal/ Nutrition, Orthopedics/Rehabilitation, and Palliative Care [3].

Pulmonary care. Pulmonary complications are the main cause of morbidity and mortality in SMA. The main respiratory problems are: impaired cough, hypoventilation during sleep, chest wall and lung underdevelopment, recurrent infections. In time they develop a daytime respiratory failure. Pulmonary management includes: airway clearance, cough assistance (manually or assisted with mechanical insufflation-exsufflation) when cough is inefficient. Nocturnal noninvasive ventilation reduces symptoms of disordered breathing during sleep. Routine immunizations are also recommended.

Gastrointestinal and nutritional care. Gastrointestinal problems such as: feeding and swallowing problems, delayed gastric emptying and gastroesophageal reflux complicated sometimes with aspiration pneumonia, constipation. Medical treatment includes acid neutralizers, inhibitors of acid secretion, promotility agents and probiotics. It is important to maintain an ideal weight. Especially children with SMA type 2 are at risk of overnutrition and their functional status is more affected. These children must have an assessment of nutritional intake made by a dietician.

Rehabilitation and orthopedics care. Weakness and reduced mobility place these children at risk for contractures, scoliosis, reduced independence. With weakness of the paraspinal muscles, scoliosis is slowly progressive in these patients.

Orthopedic management includes: posture management, contracture and pain management, therapy for activities of daily living and assistive equipment, wheelchairs for mobility, limb orthotics. Regular physical and occupational therapy are encouraged: stretching, aquatherapy, nonfatiguing exercise. Spinal orthoses may be used for postural support and in some cases scoliosis surgery should be considered.

Palliative care. A multidisciplinary team approach including appropriate medical, social and psychological support is needed.

Sodium valproate treatment

The existence of the partially functional protein derived from SMN2 gene is a potential target for therapeutic intervention. The modulation of *SMN2* expression is in part controlled by acetylation and deacetylation of histones in the promoter region. The inhibitors of histone deacetylases (HDAC) could promote the acetylation of the DNA increasing the gene expression and the level of full-length SMN protein.

Valproic acid (VPA) is a short-chained fatty acid originally synthesized as an analogue of valeric acid found in Valeriana officinalis. It is an FDA-approved drug which prevents seizures.

Nowadays VPA is an experimental treatment strategy for SMA. Valproic acid acts as histone deacetylase inhibitor (HDAC) and stimulates the SMN2 gene transcription and/or restores the splicing pattern, elevating the levels of FL-SMN2 protein. It has not been clarified what concentration of VPA is required.

Several "in vitro" and "in vivo" studies with valproic acid in cell lines and patients with spinal muscular atrophy (SMA) demonstrate increased expression of SMN, supporting the possibility of therapeutic benefit.

Brichta L. et al [4]. provided the first proof of the "in vivo" activation of a the SMN2 gene by valproic acid. Twenty patients were treated with valproic acid, seven demonstrated elevated levels of SMN2 messenger RNA and unchanged or decreased levels were found in thirteen patients.

In an open label study, Swoboda et al. assessed 42 patients treated with VPA during 12 months and observed a significant improvement almost restricted to children aged less than 5 years [5].

Recently in another study "SMA CARNI-VAL " (2010), Swoboda KJ et al. assessed 61 nonambulatory children with SMA randomized 1:1 to placebo or treatment with VPA (20mg/kg/day) and L-carnitine (50 mg/kg/day) for six months and no benefit was demonstrated [6].

A study on 22 patients with type II and III SMA was ended in May 2011. Children aged between 2 and 18 years, were treated with VPA (20 mg/kg/day) and L-Carnitine (100 mg/kg/day). VPA level range was maintained between 50–100 mg/dL. They were evaluated five times during a one-year period using the Manual Muscle Test (Medical Research Council scale-MRC), the Hammersmith Functional

Motor Scale and the Barthel Index. The group of children with SMA type II presented a significant gain in HFMS scores during the treatment which was not observed in the group of type III patients. Authors noticed also that there was an improvement of the daily activities at the end of the VPA treatment period [7].

There are ongoing studies of VPA in ambulatory SMA type III patients called "VALIANT SMA" to help us further expand our knowledge about possible biologic impact of VPA in subjects with SMA.

At this moment the clinical efficacy of VPA in patients with SMA still remains controversial.

Conclusions

Treatment of SMA children with VPA may be a potential alternative to alleviate the progression of the disease. Pharmacological treatments and supportive therapies are aimed to delay progression of the disease and to improve muscle function offering a better quality of life.

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