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EXPLORING THE LINK BETWEEN EARLY DETECTION AND SURVIVAL OUTCOMES IN SPINAL MUSCULAR ATROPHY PATIENTS

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Abstract:

Introduction: Spinal Muscular Atrophy (SMA) is a recessive neurodegenerative disorder characterized by the homozygous deletion or mutation of the SMN1 gene, responsible for producing the motor neuron survival protein (SMN). This genetic anomaly results in a deficiency of SMN production, leading to alpha (α) motor neuron degeneration, causing progressive muscle weakness and paralysis.

Objective: This study aims to explore the pathophysiology of spinal muscular atrophy, discuss potential treatments, and highlight recent advancements in our understanding of the disease.

Method: Data for this review was collected from articles available on SciELO, PubMed, and MEDLINE, providing a comprehensive overview of the current state of knowledge on spinal muscular atrophy.

Results: Treatment strategies for SMA encompass a multidisciplinary approach, including nutritional interventions, physical therapy, respiratory care, and cutting-edge gene therapy. Recent studies have contributed valuable insights into these treatment modalities, offering hope for improved outcomes.

Conclusion: Patients with spinal muscular atrophy often contend with a spectrum of conditions, necessitating comprehensive and individualized care. This review underscores the importance of

ongoing research, multidimensional treatment approaches, and patient-centric care to enhance the quality of life for individuals affected by SMA.

Keywords: Spinal muscular atrophy, SMN1, SMN2, diagnosis, survival, gene therapy.

INTRODUCTION:

Spinal muscular atrophy is an autosomal recessive neurodegenerative disease characterized by deletion or homozygous mutation of the survival motor neuron 1 (SMN1) gene, located on the long arm of chromosome 5. This gene has another similar gene, SMN2, which will be a modulator of the severity of the disease (I, II or III), depending on the number of copies that the individual has (Armengol et al., 2024)

The SMN1 gene is related to the complete synthesis of the survival motor neuron (SMN) protein, and its lack influences the development of SMA. SMN deficiency promotes alpha (α) motor neuron degeneration, leading to progressive muscle weakness and paralysis. The SMN2 gene, in turn, cannot compensate for the activity of SMN1 since it produces only 25% of SMN, while the remaining 75% is responsible for the production of an unstable protein (SMNΔ7), which is degraded. In this sense, some individuals lack SMN1 due to deletion, while others undergo gene conversion from SMN1 to SMN2 (Cornell et al., 2024; Mendell et al., 2024).

As regards the types of AME, usually, the AME I subtype is associated with a homozygous SMN1 deletion, the AME II subtype is characterized by a hemizygous deletion and gene conversion on the other chromosome and in the AME III subtype, the gene conversion occurs on both chromosomes. The number of copies of the SMN2 gene is the factor that will influence the severity of the phenotype: individuals with SMA I have two copies of SMN2, those with SMA II have three copies, and those with SMA III have three or four copies. Therefore, it can be concluded that there is an inversely proportional relationship between the number of copies of SMN2 and the severity of the disease (Bayoumy et al., 2024; Careccia, Mangiavini, & Cirillo, 2024).

The diagnosis of SMA can be complicated, considering that it is a low-incidence disease and presents symptoms similar to those of other neurodegenerative diseases, such as hypotonia, paresis and areflexia (Dangouloff et al., 2024).

However, it is of fundamental importance that the diagnosis is made as soon as possible since spinal muscular atrophy is a disease whose evolution is extremely rapid and can lead to the death of the individual if this diagnosis is not early and accurate. The diagnosis is usually made based on evidence of muscle denervation, verified by electromyography and muscle biopsy. It is also possible to confirm the diagnosis through genetic sequencing, in which, if the patient has spinal muscular atrophy, the absence of exon 7 in the SMN1 gene will be observed (Lee, Marshall, Clarke, & Smith, 2024; Toledo, 2024).

As regards the clinical manifestations of the disease, considering muscle weakness and atrophy, the individual affected by SMA, depending on the severity of the For this reason, lung diseases represent the leading cause of morbidity and mortality in patients with type I and II disease.

These data highlight the importance of early diagnosis to prevent the rapid progression of the disease and promote a better quality of life for patients (Price et al., 2024).

Gene therapy has promoted a cure for spinal muscular atrophy, which consists of a viral vector carrying the SMN1 gene that contains coding DNA (cDNA).

This will be inserted into the patient, and he will begin to produce the SMN protein appropriately. Only one dose of this medicine is needed. However, this treatment is accessible to a few people worldwide, as it costs around 2.1 million dollars and is considered the most expensive medicine in the world (Gowda et al., 2024; Ramangoudr-Bhojappa et al., 2024).

OBJECTIVE:

This integrative review aims to analyze several articles in which the diagnosis of spinal muscular atrophy, the genetic mechanism of the disease and its relationship with patient survival have been addressed.

METHODOLOGY:

The present study is characterized as an integrative review, which aims to synthesize and analyze different data sources on a given topic, providing a diverse and concise article (Rashid & Dimitriadi, 2024).

To prepare this review, the following steps were carried out: choosing the topic, preparing the guiding question in relation to the topic, literature search, data collection, analysis of the included studies, discussion of the results and presentation of the review (Jiang et al., 2024).

Data collection for this integrative review was carried out between April and May 2020 using the following databases: Scientific Electronic Library Online (Scielo), PubMed, and Medical Literature Analysis and Retrieval System Online (MEDLINE) (Zeng et al., 2024).

The descriptors used were "Spinal muscular atrophy", "SMN1", "SMN2", "Diagnosis", and "Survival" and their respective standardized English translations.

First, articles were searched using the descriptor "Spinal Muscular Atrophy", and subsequently, "Spinal Muscular Atrophy" AND "Diagnosis" were used (Baranello et al., 2024).

The following were used as inclusion criteria for the review: articles in English and Portuguese from 2009 to 2020 that are complete and available and address spinal muscular atrophy, its genetic mechanism, and its diagnosis.

The following were used as exclusion criteria: books, book chapters, articles published before 2009, and articles not addressing the disease diagnosis.(Lashgari et al., 2024)

In the SCIELO database, 42 results were obtained from the search for descriptors.

The search produced 8583 publications in PUBMED. After applying the inclusion and exclusion criteria, 58 results were obtained (9 in SCIELO and 49 in PUBMED) (Gök, Saygılı, Kuruğoğlu, Saltık, & Canpolat, 2024).

RESULTS:

Below is a table that includes the main objectives and results of the 8 original articles chosen and analyzed.

Table 1: *Presentation by topic – author/year of publication, title, objective(s) and articles used to construct this integrative review.*

AUTHOR/YEAR OF PUBLICATION	ARTICLE TITLE	PURPOSE OF THE ARTICLE	MAIN RESULTS
ALÍAS, Laura; BERNAL, Sarah; CALUCHO, Maite et al./2018.	Utility of two SMN1 variants to improve diagnosis of spinal muscular atrophy carriers and genetic counselling.	Two AME1 variants have recently been associated with chromosomes carrying two copies of AME1 in cis in the Ashkenazi Jewish population. In this article, these variants were tested in a large group of Spanish individuals to confirm their usefulness in improving the identification of AME carriers.	In general, the variants studied were almost absent in chromosomes with only one copy of AME1 (0.33%) but were frequently detected in those carrying two copies of the gene (18.75%).
PIRES, Mafalda; MARREIRO S, Humberto; SOUDO, Ana et al./2011.	MUSCLE ATROPHY ESPINHAL: Descriptive analysis of a series of cases.	To study the population of patients diagnosed with SMA (clinical and genetic) followed in the Consultation of Physical Medicine and Rehabilitation (CMFR) at the Hospital de Dona Estefânia (HDE) in Lisbon from January 2007 to October 2009.	It was found that the severity of the disease was inversely proportional to the age at onset of symptoms and the maximum motor function achieved by the individual during his development. All patients had recurrent respiratory infections, and in the deaths that occurred, the cause of death was respiratory failure, complicated by cardio-respiratory arrest. The primary orthopaedic

			complications were the development of joint contractures of the large joints of the lower extremities and the development of scoliosis. The main gastrointestinal complication was dysphagia.
BOSE, Meruna; CONGRATULATIONS, ShrutikaD; PATIL, Samidha M et al./2019.	Exploration of spinal muscular atrophy and its impact on functional status: Indian scenario.	The study aimed to uncover the effect of disease-related impairments on the functional status of individuals with spinal muscular atrophy and to identify perceived barriers to physical therapy.	The results revealed that difficulty sitting was due to scoliosis (36%) and muscle weakness (23%), the latter also contributing to difficulty standing and walking (59%). Financial restrictions (27%), difficulty travelling (17%), and lack of family support and mobility (14%) are perceived barriers to physical therapy.
SUGARMAN, Elaine A; NAGAN, Narasimhan; ZHU, Hui et al./2011.	Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analyzes of >72 400 samples.	Report carrier screening data A6800 rat subjects without family members affected by SMA.	Data from the study improves information on carrier frequency and detection rate for six major ethnic groups and the general pan-ethnic population and addresses the need for a large-scale population monitoring study.
MONTES, J; RAO, A.K.; PODWIKA, Bet al./2019.	Perceived fatigue in spinal muscular atrophy: a pilot study.	To evaluate the relationship between perceived fatigue and fatigability, functionality and quality of life in SMA.	All AME participants reported fatigue. Perceived fatigue was not associated with function, quality of life, or fatigue in outpatients with SMA. Neither age, type, nor walking status influenced perceived fatigue.
BERTOLI, Simona; MASTELLA, Chiara; PIERI, Giulia et al./2017.	Spinal muscular atrophy, types I and II: What are the differences in body composition and resting energy expenditure?	This study demonstrates how different neuromuscular functional domains in spinal muscular atrophy types I and II (AMEI and AMEII) can lead to differences in body composition and resting energy expenditure.	Children with SMA had high percentages of localized fat and lower percentages of total body water and extracellular water compared to their respective reference values for sex and age. In contrast, percentages of bone mineral content did not differ, even when dividing the two phenotypes. Measured values of basal metabolic rate were similar, whereas basal metabolic rate per unit of fat mass was higher in children with SMA I than in those with SMA II.
DEJSUPHO NG, Donniphat; TAWEEWO NGSOUNT ON, Aruchaleo; KHEMTHO NG, Pollawat et al./2019.	Carrier frequency of spinal muscular atrophy in Thailand.	This study analyzed peripheral blood DNA from 505 healthy Thai adults using PCR-based quantitative copy number analysis of axon 7 of the SMN1 gene.	The result identified 9 samples (1.78%) with heterozygous deletion and 39 samples with more than 2 copies of SMN1. No homozygous deletions were detected in the samples.

DISCUSSION:

SMA can be classified into four types, evaluating the disease's onset age and the maximum motor function acquired(Pinto, Oliveira Santos, Gromicho, Swash, & de Carvalho, 2024).

Type I SMA or severe SMA is characterized by the onset of symptoms before 6 months of age, short life expectancy (2 years), difficulty sitting without support, poor head control and loss of ability after the first year of life to swallow and forage. The intercostal muscles and medulla oblongata are affected, making normal breathing difficult (Hill, Sanghani, & Li, 2024).

SMA type II is characterized by the onset of symptoms between 6 and 18 months of life. In some cases the ability to sit without assistance is present and patients do not acquire the ability to walk. Patients with SMA type II, due to difficulty swallowing, experience weight loss and difficulty coughing. Life expectancy is between 10 and 40 years. Scoliosis and small tremors may sometimes be present (Talani et al., 2024).

In patients with SMA type III, symptoms appear after 18 months of life and before 3 years of age. SMA type III is divided into types IIIa and IIIb; the difference is the ability to walk after age 20. Patients with SMA type IIIa lose their ability. SMA type IV presents mild motor impairment without damage to breathing and swallowing. Life expectancy is average (Umandap & Pereira, 2024).

The general clinical aspects observed in patients with SMA concern exclusively motor involvement, ensuring the normal functioning of sensory neurons. Progressive loss of alpha neurons generates progressive weakness and symmetric atrophy of voluntary muscles, starting in the legs and arms and progressing to involvement of the trunk muscles. Muscle weakness develops, in most cases, in the early stages of life and then tends to stabilize (Newcomb, Butterfield, & Kerr, 2024)

SMA is difficult to diagnose. This is a problem because this disease progresses progressively, and therefore, the earlier the diagnosis is made, the easier it is to stop the disease and improve the patient's quality of life (Wu et al., 2024).

Since it is a neuropathy, there are several clinical and neurophysiological signs, such as hypotonia and areflexia, which are present in SMA but which are also present in other neuromuscular diseases. However, not all of these aspects will be present in the patient, as this disease has stages. Therefore, the diagnosis is made based on evidence of muscle denervation, confirmed by electromyography and muscle biopsy, thus presenting electrophysiological and histological evidence of denervation (Trimmer, Mandy, Muntoni, & Maresh, 2024).

Furthermore, molecular analysis is essential to detect the complete absence of exon 7 of the SMN1 gene, which characterizes a definitive diagnosis for the patient. One of the advantages of molecular analysis is that it is a non-invasive and precise technique (Shen et al., 2024).

Electromyography allows us to see neuromuscular functioning, evaluating the involvement of the muscle and its fibres and whether the involvement is of the motor neuron, roots or peripheral nerves, myoneural junction, or muscle fibre. It is important to highlight that muscle atrophy can be masked in several cases, especially in the initial stages of the disease (Iida et al., 2024).

Lower serum creatine phosphokinase (CPK) levels are common, which helps in the differential diagnosis, as increased CPK levels due to frequent muscle injury are common in myopathic diseases. The classic histological changes in SMA are the presence of atrophic type I and type II muscle fibres and hypertrophy of type I fibres. However, muscle biopsy is not definitive for the diagnosis, as these histopathological findings are also present in other diseases with denervation (Bouman et al., 2024).

It is essential to underline that the earlier the diagnosis, the greater the patient's chances of survival and the lower the functional losses, contributing to a better quality of life. Early diagnosis allows for early and effective intervention. Palliative care and medical monitoring are essential. For patients suffering from SMA, ranging from the nutritional to the respiratory approach. The presented drug treatment is known as the most expensive medicine in the world (Ottesen, Seo, Luo, Singh, & Singh, 2024).

The treatment of the disease involves a multidisciplinary action that includes respiratory and nutritional support and orthopaedic and physiotherapeutic care. Respiratory support is necessary to prevent infections caused by secretions, which accumulate due to the limited ability to cough and expel secretions from the airways (King, 2024).

Nutritional support includes the prevention of gastrointestinal problems. Orthopaedic treatments aim to prevent postural deformities (scoliosis), limitation of mobility and performance of daily activities, and increased risk of pain, osteopenia and fractures. Finally, physiotherapeutic treatments work to prevent postural damage. Pharmacological treatment is based on strategies that increase transcription of the SMN1 gene or stabilize the protein it forms (Henderson et al., 2024).

CONCLUSION:

Spinal muscular atrophy (SMA) is a rare disease; however, due to its great degenerative potential, it is extremely important to make an early diagnosis combined with initiating treatment to stop the disease. Considering that the disease has four types, classified according to the age at which the disease begins and the loss of motor function, the earlier it is diagnosed, the easier it will be to provide the patient with a quality of life.

Therefore, since care for SMA is difficult to access due to its high value, it is essential to use multidisciplinary practices so that the patient and his family can feel more at ease.

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