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REVIEW ARTICLE

Causes and symptoms of spinal muscular atrophy

Causas y síntomas de la atrofia muscular espinal

Causas e sintomas da atrofia muscular espinhal

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Abstract

This study aimed to identify and highlight the main causes and symptoms of spinal muscular atrophy (SMA). This is an integrative literature review. The following databases were used as sources for the search: Scientific Electronic Library Online, Google Scholar, Ministry of Health, PubMed, and the Brazilian Journal of Health. Fifty-three articles were found. After applying the inclusion and exclusion criteria, and reading and analyzing the studies, the number of articles selected for this review was 10. The studies showed that SMA results in progressive symmetrical muscle weakness, and atrophy of the proximal voluntary muscles of the legs, arms and occasionally trunk muscles during the progression of the disease. It can be classified into four subtypes, ranging from type 0 (before birth) to type 4 (second or third decade of life), with a correlation between the degree of muscle involvement and the age at which the first symptoms appear. It is concluded that in addition to the serious muscular impairment that can be diagnosed in utero by genetic tests, the progressive and serious loss affects development and makes the vast majority of children dependent on pulmonary ventilation and physiotherapy, and the existing pharmacological and physiotherapeutic treatments are not capable of recovering the muscle cells that have already been lost, they only slow the progression of the disease and offer quality and life expectancy.

Descriptors: Spinal Muscular Atrophy; Causality; Signs and Symptoms; Neuromuscular Diseases; Pathophysiology.

Resumén

El objetivo fue resaltar e identificar las principales causas y síntomas de la atrofia muscular espinal (AME). Esta es una revisión integradora de la literatura. Se utilizaron como fuente de búsqueda las siguientes bases de datos: Scientific Electronic Library Online, Google Scholar, Ministerio de Salud, PubMed y Revista Brasileira da Saúde. Se encontraron 53 artículos, después de aplicar los criterios de inclusión y exclusión, leer y analizar los estudios. una serie de 10 artículos para la construcción de esta revisión. Los estudios han demostrado que la AME produce debilidad muscular simétrica progresiva, atrofia de los músculos voluntarios proximales de las piernas, brazos y, finalmente, de los músculos del tronco durante la progresión de la enfermedad. Se puede clasificar en 4 subtipos, que van desde el tipo 0 (antes del nacimiento) hasta el 4 (segunda o tercera década de la vida), existiendo una correlación entre el grado de deterioro muscular y la edad en la que aparecen los primeros síntomas. Se concluye que además del deterioro muscular severo que puede diagnosticarse in útero mediante pruebas genéticas, la pérdida progresiva y severa afecta el desarrollo y hace que la gran mayoría de los niños dependan de la ventilación pulmonar y la fisioterapia, y los tratamientos farmacológicos y de fisioterapia existentes no lo hacen. son capaces de recuperar células musculares que ya se han perdido, sólo frenando el avance de la enfermedad y ofreciendo calidad y esperanza de vida.

Descriptores: Atrofia Muscular Espinal; Causalidad; Signos y síntomas; Enfermedades Neuromusculares; Fisiopatología.

Resumo

Objetivou-se evidenciar e identificar as principais causas e sintomas da atrofia muscular espinhal (AME). Trata-se de uma revisão Integrativa da literatura. Utilizou-se como fonte de busca as bases de dados: *Scientific Electronic Library Online*, *Google Scholar*, Ministério da Saúde, PubMed e da Revista Brasileira da Saúde. Foram encontrados 53 artigos, após aplicação dos critérios de inclusão e exclusão, leitura e análise dos estudos, chegou-se ao número de 10 artigos para a construção da presente revisão. Os estudos evidenciaram que AME resulta em fraqueza muscular progressiva simétrica, atrofia dos músculos voluntários proximais de pernas, braços e eventualmente de músculos do tronco durante a progressão da doença. Pode ser classificada em 4 subtipos, variando entre o tipo 0 (antes do nascimento) ao 4 (segunda ou terceira década de vida) havendo correlação entre o grau de comprometimento muscular e a idade que surgirem os primeiros sintomas. Conclui-se que além do grave comprometimento muscular que pode ser diagnosticado ainda intraútero por testes génicos, a perda progressiva e grave afeta o desenvolvimento e torna a grande maioria das crianças dependentes de ventilação pulmonar e fisioterapia, e os tratamentos existentes, farmacológicos e fisioterápicos não são capazes de recuperar as células musculares que já foram perdidas, apenas retardam o progresso da doença e oferecer qualidade e expectativa de vida.

Descritores: Atrofia Muscular Espinal; Causalidade; Sinais e Sintomas; Doenças Neuromusculares; Fisiopatologia.

Introduction

Spinal muscular atrophy (SMA) is a rare neurodegenerative disease of genetic origin and autosomal recessive inheritance, characterized by the progressive loss of upper and lower motor neurons and can be classified into four subtypes. Other authors classify SMA into only three categories: mild, intermediate, and severe[1].

SMA occurs from the homozygous deletion of the survival motor neuron 1 gene (SMN1) located in the telomeric region of chromosome 5q13 and the number of copies of a similar gene (SMN2) located in the centromeric region and is the main measure of severity of the disease. This genetic alteration (SMN1) decreases the survival of motor neuron proteins (SMN)[2].

This genetic alteration in the gene (SMN1) is responsible for reducing the levels of the motor neuron survival protein (SMN). The gene (SMN2) does not fully compensate for the lack of expression of (SMN1) because it produces only 25% of the protein (SMN4). The absence of the protein (SMN) results in the degeneration of the alpha α motor neurons located in the anterior horn of the spinal cord, resulting in progressive and symmetrical proximal muscle weakness and paralysis[2].

Since there is only progressive loss of α motor neurons, only motor function is impaired, with sensory neurons preserved. This loss of motor neuron function leads to progressive symmetrical weakness and atrophy of the voluntary muscles of the arms, legs, and eventually trunk muscles throughout the disease. The clinical progression of SMA for individuals who survive beyond childhood shows that loss of muscle strength is usually most noticeable early in the disease. Then residual muscle strength may stabilize over months to years[2].

This study aims to answer the guiding question: "What are the main causes and symptoms of spinal muscular atrophy?" Considering the growing accumulation of information about individuals affected by this condition, the impactful effects and serious consequences it has on health become evident. It is intended that the combination of this knowledge can contribute to guiding guidelines and the development of new research.

Methodology

This study is an integrative literature review. To carry out this type of methodology, the following process is followed, starting with: (1) delimitation of the theme and construction of the guiding research question; (2) survey of publications in the selected databases; (3) classification and analysis of the information found in each manuscript; (4) analysis of the chosen studies; (5) presentation of the results found and (6) critical analysis of the findings and synthesis of the literature review[3].

To develop the guiding question of this study, the PICo strategy (P–Population, I-Intervention, Co–Context) was used. In this sense, the PICo strategy was designed as follows: P – General population, I - Complications, Co – Identify the main complications. It is important to note that the strategy ensures a rigorous search for scientific evidence related to the PICo object, as it establishes a direction[4].

Sendo assim, a questão norteadora desta revisão integrativa de literatura é: "Quais são as principais causas e sintomas da atrofia muscular espinhal?".

The search and selection of studies were carried out from May to July 2022. The following databases were used to search for articles: Scientific Electronic Library Online, Google Scholar, Ministry of Health, Pubmed, and the Brazilian Journal of Health. The following Medical Subject Headings (MeSH) were used: "Spinal Muscular Atrophy" AND "Causality" AND "Signs and Symptoms" AND "Neuromuscular Diseases" AND "Pathophysiology".

Inclusion criteria for publications: studies that addressed the topic and answered the research question; scientific articles available in full; published in Portuguese, English, and Spanish, from 2017 to 2022. Exclusion criteria for publications: letters; reviews; editorials; book publications; book chapters; government documents; newsletters; studies not available online; duplicate studies; studies not related to the topic, being out of context.

Initially, the studies were analyzed by title and abstract to confirm the presence of the inclusion criteria, as well as exclusion criteria. The next step was the complete reading of the research articles. From the search strategy, 53 articles were found. Of these, 10 articles were selected for the construction of this review.

Results and Discussion

According to the latest information released by the Ministry of Health[5], spinal muscular atrophy (SMA) is considered a rare, degenerative, and genetic disease, that is, it is passed from parents to children and ends up interfering with the body's ability to produce a protein essential to the survival of motor neurons, which are responsible for the body's simple vital voluntary gestures, such as breathing, swallowing and moving.

However, it has some variations, which it can range from type 0 (before birth) to 4 (second or third decade of life), and there is a correlation between the degree of muscle involvement and the age at which the first symptoms appear[6].

According to the Brazilian Society of Medical Genetics and Genomics and the Brazilian Academy of Neurology, SMA is the second most common autosomal recessive disorder after cystic fibrosis, with an incidence of approximately 1 in 10,000. Carrier rates are approximately 1 in 50 individuals. Mortality and morbidity are directly related to age of onset. The highest frequency of deaths occurred in recent cases. Among children with type I, the median survival rate is 7 months, and mortality is 95% by 18 months of age. The leading cause of death was respiratory infection. In type II, death is usually caused by respiratory complications in adolescence or young adulthood[6,7].

As the disease develops gradually, establishing an accurate diagnosis is essential. Children with hypotonia present clinical symptoms such as weakness, lack of deep tendon reflexes, and occasional fasciculations, as well as in the tongue, which should be considered when SMA is suspected[6].

Although this manifestation may be present in other neuromuscular diseases, patients with SMA mainly present muscle atrophy and weakness in the lower limbs, respiratory muscles, and bulbar muscles - proximal muscles. The extremities are affected, preferentially, and deep tendon reflexes are affected. Other characteristic signs are fasciculations and mild tremors. There is no evidence of brain damage, generally normal or above-average intelligence level, according to 2021 data collected by the Brazilian Society of Medical Genetics and Genomics and the Brazilian Academy of Neurology[6].

Type I SMA is characterized by symptoms before 6 months of age. Severe movement disorders (hypotonia and muscle weakness) and breathing disorders are experienced. In these cases, there is significant bulbar involvement with dysphagia, weakness in sucking, and dyspnea. The eye muscles are not affected externally, the child is alert, and there is minimal or no facial damage. Tongue spasms may be observed, and children will not be able to sit without support. More than 90% of cases before two years of age evolve into death[8].

SMA type II has milder symptoms, presenting before 18 months of age, with more severe bradykinesia, especially sitting and standing; children can sit without support but are unable to walk; the child has normal facial expressions, but the extremities are severely affected and are more easily observed. Proximal muscles, especially those of the lower extremities, often with skeletal deformities such as muscle retraction and scoliosis, mild tremor, finger posturing, as well as tongue fasciculations, and deep tendon reflexes have disappeared. Survival is variable; death is due to respiratory complications[8].

SMA type III has a milder clinical presentation, with onset after 18 months, and is clinically characterized by weakness and atrophy. Proximal muscles of the extremities, hypotonia, and deep tendon reflexes were absent. Patients may walk at some point in their lives. Regular gait caused by proximal weakness of the lower extremity; Gowers sign is often observed[8].

Spinal cord dysfunction is minimal and occurs late in the disease, although type III disease has a more benign course, with slowly progressive deterioration of motor status observed; loss of the ability to walk may occur during the disease, although survival is close to normal. In type IV SMA, symptoms usually appear after age 20, clinical manifestations are like those of type III, and in general, the course of the disease is slow and progressive, but with normal survival[8].

Chart 1. Summary of general characteristics of SMA subtypes. Matipó, MG, Brazil, 2023

Subtypes of SMA	Proportion	SMN2 copy number	Age of onset of symptoms	Life expectancy (median survival)	Highest motor milestone achieved
SMA type 1	60%	2 – 3 copies	0 - 6 months	< 2 years	Sits with support
SMA type 2	27%	3 copies	7 - 18 months	> 2 years to 35 years	Sits independently
SMA type 3	13%	3 – 4 copies	> 18 months	Normal	Stands and walks without support
SMA type 4	-	4 or more copies	Adults	Normal	Walks during adulthood

Source: Adapted from Ministry of Health[5].

According to the clinical protocols and therapeutic guidelines of SMA, in suspected symptomatic cases, the suspicion includes children up to 6 months of age who present hypotonia or muscle weakness. This weakness is progressive, symmetrical, and affects the proximal muscles more than the distal ones, with greater predominance in the lower limbs, diminished tendon reflexes, with fasciculations present, that is, preserved facial mimicry. It is common to note, clinically, a bell-shaped chest with changes in the respiratory pattern, this being a paradoxical pattern and weakness in the intercostal muscles[9].

In pre-symptomatic patients, clinical suspicion is generated based on family history, and these parents have already had a child diagnosed with SMA and should perform genetic testing on their second child after birth to confirm the diagnosis[9].

As it is a genetic disease, SMA is diagnosed through molecular genetic tests capable of detecting the deletion of exon 7 of the SMN1 gene. In the absence of a mutation in the SMN1 gene, the diagnosis can be made through other complementary tests, such as electroneuromyography, biopsy, and CPK enzyme dosage; although they are not specific, they can be useful in assisting in the diagnosis of SMA[10].

Electroneuromyography is a diagnostic method capable of differentiating whether the motor neuron, peripheral nerve or root involvement, myoneural junction or muscle fiber involvement is involved. In SMA, electroneurography shows denervation and changes in the action potential, with an increase in amplitude and duration, thus indicating chronicity. Other findings also include a reduced interference pattern with neurogenic recruitment to voluntary activity and polyphasic potentials. Spontaneous motor activity is common in SMA type I and occasionally found in type II[11].

Through biopsies of individuals with neurogenic alterations and a probable diagnosis of SMA, it is possible to identify structural alterations in the muscle fiber, such as atrophied muscle fibers with an angled appearance, and a grouping of atrophied fibers. In type I SMA, it is possible to find hypertrophied fibers distributed throughout the muscle fascicles. Neurogenic alterations are nonspecific, as they may be present in other pathologies. However, this type of

examination cannot confirm the diagnosis of SMA but rather be considered a useful tool to aid in the diagnosis[11].

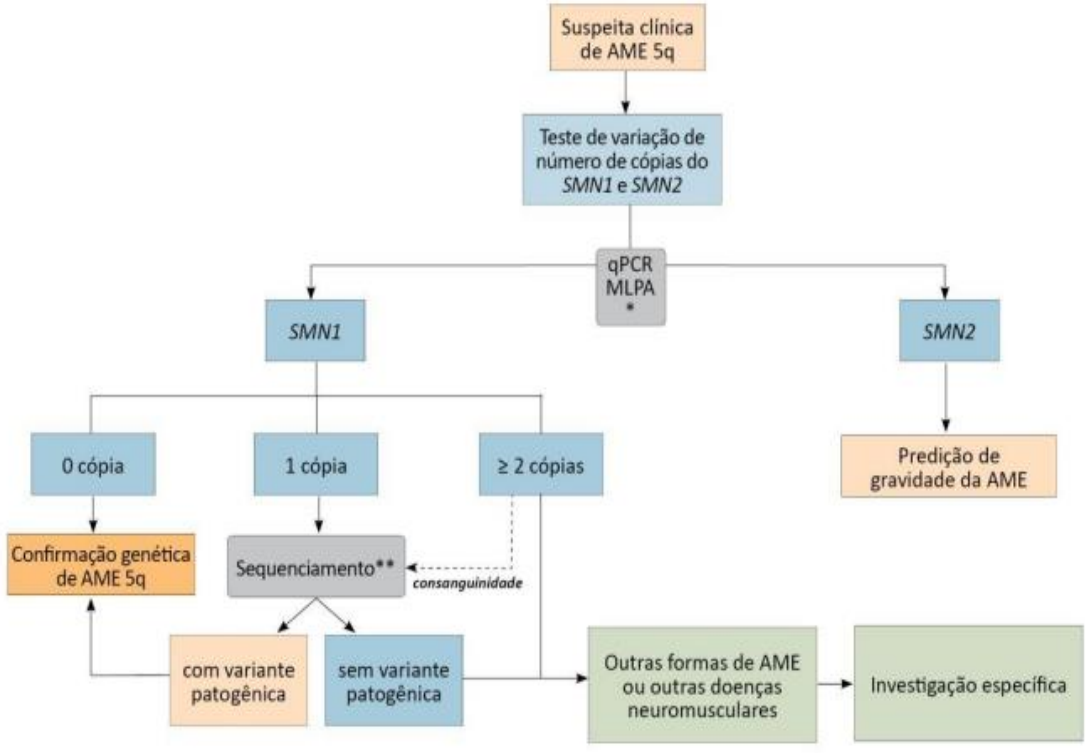
Serum creatine phosphokinase (CK) levels, which is an enzyme that acts on muscle tissue, the brain, and the heart, may be altered, indicating possible damage to these tissues. In some cases of SMA, this change may be 3 to 5 times higher than the reference value, which may cause diagnostic confusion concerning other clinical conditions that affect muscle fibers[11].

In December 2016, the Food and Drug Administration (FDA) approved the first drug, Nusinersen (Spinraza®), for patients with SMA. Until then, treatment had focused solely on supportive measures, as alternatives to improve muscle strength that could alter the natural course of the disease were not yet available. Among the measures, cardiopulmonary monitoring and pulmonary ventilation assistance, when necessary, are among the main measures, in addition to preventing infections, monitoring by a physiotherapist, a high-protein diet, and psychological support, including family support[8].

Another aspect to be considered, according to the Clinical Protocol and Therapeutic Guidelines for Spinal Muscular Atrophy 5q types 1 and 2, established in 2022 by the Ministry of Health, nutritional support is necessary, as children with SMA will lose or will not develop the ability to be fed orally. They can also develop several gastrointestinal problems, including reflux, and reflux is directly related to the morbidity and mortality of these patients, due to the association with silent bronchoaspiration, which leads, in many cases, to pneumonia. Likewise, due to low gastrointestinal motility, they may have severe constipation[8,12].

Patients with SMA type 1 may have weakness of the masticatory muscles, difficulty opening the mouth and moving the head, difficulty swallowing, and respiratory problems, leading to reduced caloric intake and food cravings. Nutritional control and digestive control are the pillars of avoiding problems associated with swallowing, gastrointestinal dysfunction, dietary supplementation, and weight control[8].

Figure 1. Diagnostic flowchart of SMA 5q. Matipó, MG, Brazil, 2023



*MLPA, multiplex ligation-dependent probe amplification; qPCR, PCR quantitativo; **Identificação de mutação por sequenciamento por amplicon.

Source: Mercuri et al[9:103].

Therefore, as seen, SMA can cause several limitations that can prevent these individuals from connecting with society. Thus, to alleviate this situation and this impairment, assistive technologies have promoted the social inclusion of people with disabilities, especially about movement and autonomy, and should be understood to expand the functional ability of the disabled person, provide quality of life, in addition to facilitating the learning of new skills, given this life condition[13].

Conclusion

Spinal muscular atrophy type I is the most severe form of the disease, with symptoms appearing around six months. The main features are changes in the child's motor development stage, in addition to severe respiratory impairment, which makes them dependent on mechanical ventilation in most cases. The natural history of the disease is death due to respiratory failure around three years of age. It is emphasized that similar features are present in most

cases and develop in a severe form, but urgent and intensive treatment by a multidisciplinary team can redefine and prolong the survival of these patients. In December 2016, with the FDA approval of the first specific drug to treat SMA, children with Werdnig Hoffmann disease can have significant improvements in motor function that have a major impact on their survival.

There are cases in which children survive beyond the life expectancy of patients with this syndrome. However, if there is no preventive treatment for the progression of muscle weakness and atrophy, these children will survive only with mechanical ventilators, requiring intensive care, or an appropriate home care program, and remaining under continuous cardiorespiratory monitoring. Specific treatments, in addition to increasing survival expectancy, can only be evaluated after the results of ongoing clinical studies with the potential survival of patients with SMA. We know that treatment that avoids or reduces the need for mechanical ventilation, even if motor impairment still occurs, will greatly improve the quality of life of patients.

Early diagnosis can be made and is essential during the prenatal or neonatal period, since treatment before the onset of symptoms is “effective”, which can change the natural course of the disease. For those who already suffer from the symptoms of SMA, especially movement disorders, treatment and monitoring by a multidisciplinary team, including exercises and respiratory physiotherapy, are of fundamental importance.

Children in-home care also need this support, encouraging their interaction with the environment, which can be done with an eye movement detector combined with communication software. In this way, children with SMA type I are encouraged to learn and communicate, which can prevent cognitive delays resulting from lack of stimulation, which also helps improve the quality of life for patients and their families.

References

1. Marqui ABT, Silva M, Tanaka SCSV, Weffort VRS. Assistência multiprofissional em paciente com Atrofia Muscular Espinhal: relato de caso. Rev Neurocienc. 2021;29:1-12. https://doi.org/10.34024/rnc.2021.v29.12658
2. Baioni MTC, Ambiel CR. Atrofia muscular espinhal: diagnóstico, tratamento e perspectivas futuras. J. Pediatr. 2010;86(4). https://doi.org/10.1590/S0021-75572010000400004
3. Souza MT, Silva MD, Carvalho R. Integrative Review: Whatis It? How To Do It? Einstein (São Paulo). 2010;8(1):102–106. https://doi.org/10.1590/S1679-45082010RW11348.
4. Santos CMDC, Pimenta CADM, Nobre MRC. A Estratégia PICO para a Construção da Pergunta de Pesquisa e Busca de Evidências. Rev. Latino-Am. Enfermagem. 2007.;15(3) https://doi.org/10.1590/S0104-11692007000300023
5. Ministério da Saúde (BR). AME [Internet]. 2022 [acesso em 06 jul 2022] Disponível em: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/a/ame
6. Zanoteli E, Perez ABA, Marrone CD. Atrofia Muscular Espinhal (AME) – Diagnóstico e Aconselhamento Genético [Internet]. AMB; 2021 [acesso em 19 jul 2022]. Disponível em: https://amb.org.br/wp-content/uploads/2021/08/ATROFIA-MUSCULAR-ESPINHAL-FINAL-01.02.2021.pdf
7. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, Swoboda KJ, Reyna SP, Sakonju A, Darras BT, Shell R, Kuntz N, Castro D, Parsons J, Connolly AM, Chiriboga CA, McDonald C, Burnette WB, Werner K, Thangarajh M, Shieh PB, Finanger E, Cudkowicz ME, McGovern MM, McNeil DE, Finkel R, Iannaccone ST, Kaye E, Kingsley A, Renusch SR, McGovern VL, Wang X, Zaworski PG, Prior TW, Burghes AHM, Bartlett A, Kissel JT; NeuroNEXT Clinical Trial Network on behalf of the NN101 SMA Biomarker Investigators. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol. 2017 Dec;82(6):883-891. doi: 10.1002/ana.25101
8. Chrun LR, Costa LRC, Miranda GS, Almeida FM. Atrofia muscular espinhal tipo I: aspectos clínicos e fisiopatológicos /Spinal muscular atrophy type I: clinical and pathophysiological aspects. Rev Med (São Paulo) [Internet]. 2017 [acesso em 07 jul 2022];96(4):281-6. Disponível em: https://www.revistas.usp.br/revistadc/article/view/116499
9. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Qian Y, Sejersen T; SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi: 10.1016/j.nmd.2017.11.005
10. Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, Benichou B, Cruaud C, Millasseau P, Zeviani M, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995 Jan 13;80(1):155-65. doi: 10.1016/0092-8674(95)90460-3
11. Buchthal F, Olsen PZ. Electromyography and muscle biopsy in infantile spinal muscular atrophy. Brain. 1970;93(1):15-30. doi: 10.1093/brain/93.1.15
12. Ministério da Saúde (BR). Secretaria de Atenção Especializada à Saúde. Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde. Portaria Conjunta n.º 03, de 18 de janeiro de 2022. Protocolo Clínico e Diretrizes Terapêuticas Atrofia Muscular Espinhal 5q Tipos 1 e 2 [Internet]. Brasília (DF): Ministério da Saúde, Secretaria de Atenção Especializada à Saúde, Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde; 2022 [acesso em 07 jul 2022]. Disponível em: https://www.gov.br/saude/pt-br/assuntos/protocolos-clinicos-e-diretrizes-terapeuticas-pcdt/arquivos/2022/portal_portaria-conjunta-no-3_pcdt-ame-5q-tipos-i-e-ii.pdf
13. Alcântra JG, Japiassu RB, Rached CDA. Mobilidade de pessoas com deficiência física no Brasil. Glob Acad Nurs. 2021;2(Sup.2):e176. https://dx.doi.org/10.5935/2675-5602.20200176