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Spinal Muscular Atrophy

Developed by Johanie Victoria Piché and Dr. Maryam Oskoui for PedsCases.com.
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Introduction

Hello everyone! My name is Johanie Victoria Piché, and I am a fourth-year medical student at McGill University. In today's episode of PedsCases, we are going to discuss spinal muscular atrophy or SMA. This episode was created in collaboration with Dr. Maryam Oskoui, pediatric neurologist at the Montreal Children's Hospital.

Clinical Case

Let's start off with a clinical case.

Leo is a 6-month-old boy, born at term without any perinatal adversity, who presents to your office because of delayed motor milestones. His parents mention that he is not able to hold his head up when prone, that he cannot roll from side to side and that he cannot sit in a tripod position. On further history, the parents mention that he tends to cough with feeds. The parents deny any regression in his motor milestones. With regards to his language, his social abilities, his cognition and his fine motor movements, there is no evidence of delay.

On examination, you observe an alert, non-dysmorphic infant with a weak cry, tongue fasciculations, who adopts a frog-like position when supine and who "slips through" the examiner's hands on vertical suspension. He shows very little spontaneous movements of his lower limbs, no antigravity movements in his upper limbs and is areflexic throughout.

During this podcast, we will revisit and highlight the key findings of this case.

Objectives

After listening to this podcast, the learner will be able to:

1. Define and understand the pathophysiology of SMA
2. Identify the clinical presentations of the different subtypes of SMA
3. Describe the differential diagnosis of SMA
4. Describe the screening guidelines and diagnostic evaluations of SMA
5. Describe the management of SMA

Part 1 - Definition and Pathophysiology

Spinal muscular atrophies encompass a group of inherited disorders causing degeneration of the anterior horn cells of the spinal cord during fetal development and the postnatal period. They are characterized by progressive muscle weakness and muscle atrophy.[1] This episode will focus specifically on 5q SMA, the most common of these disorders.

About 95% of cases of 5q SMA are due to homozygous deletions of exon 7, exon 8 or both, in the *survival motor neuron 1* gene (*SMN1)* gene, leading to loss of function of the SMN protein.[1] 5q SMA is most frequently inherited in an autosomal recessive manner, but also occurs *de novo* in about 2% of cases.[2] Carrier frequency is observed across all ancestries, however it is most common in people with European and Asian descent, with approximately 1 in 50 being carriers. In people with African ancestry the frequency is lower at 1 in 100 and in people with Hispanic ethnicity the frequency is 1 in 76[3].

There are two forms of the *SMN* gene, which are located on chromosome 5q. First, there is the *SMN1* gene which is located on the telomeres of the chromosome, and which produces full-length functional SMN proteins. Second, there is the *SMN2* gene which is located on the centromere of the chromosome, and which can produce both functional and non-functional SMN proteins.[1]

The two genes are almost identical, but a critical difference lies in a cytosine to tyrosine substitution in the *SMN2* gene. This base substitution is significant as it creates an exonic splicing suppressor in exon 7. This leads to the exclusion of exon 7 during splicing of the pre-mRNA in most of the SMN2 transcripts. Therefore, the *SMN2* gene produces mostly nonfunctional, truncated SMN proteins that are quickly degraded.[1] However, it is important to note that the *SMN2* gene also produces a reduced amount (about 10%) of functional SMN protein in which the exon 7 has not been spliced out. [4] This will later be relevant when we discuss further the disease severity of the different SMA subtypes.

You may be asking yourself, “What are the functions of the SMN protein and what is its role in the pathophysiology of SMA?” The answers to these questions remain to be fully understood. On a molecular level, it is known that SMN proteins are expressed both in the cytoplasm and in the nucleus of cells. SMN is also expressed in motor neuron axons. Some of the known functions of the SMN protein include facilitating the assembly of spliceosome complexes, which are critical for pre-mRNA splicing, and transporting axonal mRNAs in motor neurons. It is therefore hypothesized that spinal motor neurons, which are known to have long axons and which are most likely very dependent on axonal mRNA transport, may be especially vulnerable to decreased SMN protein expression [5]. Moreover, the SMN protein is known to be critical in the embryological development of the anterior horn cells of the spinal cord. Indeed, when its function is altered, it can result in continued apoptosis of the anterior horn cells [6]. In short, more research is needed to

determine whether a splicing defect due to SMN protein deficiency, a disruption of the embryological development of the anterior horn cells, an unknown function of the SMN protein or a combination of all is responsible for the pathogenesis of SMA.

Part 2 - Clinical Presentations and Classification of SMA

There is a wide spectrum of severity in patients with SMA, as the more severe subtypes have their onset *in utero* and the less severe phenotypes may present only in adulthood[1].

When evaluating a child in whom we suspect SMA, red flags on history and on physical examination should raise our clinical suspicion for SMA. First, delayed motor milestones can be reported by the parents. Let's recall Leo from our introductory case presentation. His parents reported that he has poor head control when prone, that he cannot sit in the tripod position and that he is unable to roll over. All of these motor milestones are typically attained by his age. Second, appendicular hypotonia, meaning hypotonia in the limbs, may be observed on examination. In our case, Leo was adopting a "frog-like" posture when lying, which is suggestive of appendicular hypotonia. Third, Leo was also "slipping through" on vertical suspension, which is characteristic of axial hypotonia. Fourth, the finding of fasciculations of Leo's tongue is a sign of denervation, which is typical of motor neuron disorders. Finally, Leo was found to be areflexic on examination, which is also characteristic of a disorder of the peripheral nervous system. In short, an important learning point is that the combination of gross motor delay, axial and appendicular hypotonia, proximal weakness, tongue fasciculation and areflexia should all raise our suspicion for SMA.

The clinical classification of SMA ranges from type 0, the most severe form of disease, to type 4, the least severe form of disease. One of the factors influencing the severity of the phenotypes is the number of copies of the *SMN2* gene. Indeed, the *SMN2* gene can produce a small amount of functional SMN protein. Therefore, a lower copy number of *SMN2* gene is associated with a lower amount of functional SMN protein and therefore with more severe phenotypes and earlier presentation of the disease. Studies have shown that patients with SMA type 1, one of the most severe forms of SMA, have the lowest copy number of the SMN2 gene. Absent SMN protein level is incompatible with life and embryonically lethal [1].

I will now go over each type of SMA. This classification is based on the anticipated progression of motor development in the natural history of the disease, as understood prior to the availability of newer disease-modifying therapies. It helps determine the expected motor developmental regression and life expectancy without supportive care[1] Therefore, as you listen to this section, please keep in mind that outcomes for patients receiving these treatments may differ from the descriptions I am about to provide. We will discuss the newly observed phenotypes following the administration of disease-modifying therapies in the management section of this podcast.

SMA Type 0

SMA type 0 represents the most severe form of the disease, as the onset of muscle weakness begins in utero. Infants are symptomatic at birth. They present with hypotonia, areflexia, contractures from limited mobility in utero and respiratory failure. In terms of developmental milestones without disease modifying therapies, they don't acquire the ability to roll nor sit. In these infants, respiratory failure is inevitable without supportive care [1].

SMA Type 1

Infants with SMA type 1 present before 6 months of age with axial hypotonia and proximal weakness. Without disease modifying therapies, these infants don't achieve the ability to stay seated without support, but some may learn to roll over. They develop respiratory failure at a median of 1 year of age [1]. In addition, upon examination, the examiner may note tongue fasciculations, a weak cry and areflexia. On history, feeding difficulties may be reported by the parents.

SMA Type 2

Children with SMA type 2 are able to sit independently, though some may lose this ability over time. Some children with SMA type 2 may also be able to stand with or without support and crawl, although they do not achieve the ability to walk independently without disease modifying therapies. The onset of SMA type 2 usually starts between the ages of 6 and 18 months, and parents describe concerns about their inability to bear weight on their legs. On examination, fine tremor of the fingers, hyporeflexia or areflexia, proximal weakness, and a nasal voice may be noted. After two years of age, risks of aspiration and the need for ventilatory support become greater [1].

SMA Type 3

Whereas children with SMA type 2 could not walk independently, children with SMA type 3 can achieve the ability to walk independently without support. However, they may lose this ability over time without disease modifying therapy. These children usually present by 3 years of age as parents are concerned for lower limb weakness. On examination, some children may have preserved deep tendon reflexes, but they may lose them over time[1]. They may also display a positive Gower sign. Remember, a positive Gower sign, indicating proximal leg weakness, means that when the patient rises from a sitting position on the floor, the patient presses their hands along their thighs for support.

SMA Type 4

Finally, SMA type 4 refers to individuals in whom symptom onset begins only after the age of 21 years with slowly progressive proximal limb weakness [1].

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I know that this is a lot of information to digest, but let's summarize the most important points to remember. The SMA types range from the most severe form, SMA type 0, to the milder phenotype, SMA type 4. An important factor influencing disease severity is the number of copies of the *SMN2* gene, as the amount of SMN protein is inversely correlated to disease severity.

Part 3 – An Approach to the Differential Diagnosis of SMA

As the differential diagnosis of pediatric neuromuscular disorder is quite wide, it is important to use a systematic approach. You can listen to the PedsCases podcast on Neonatal Hypotonia for more details to this approach in infants.

Let's recall the four components of the motor unit [7]:

1. The motor neuron within the anterior horn of the spinal cord
2. The peripheral nerve
3. The neuromuscular junction
4. The muscle

The most important goal of the detailed history and physical examination is to localize the primary site of dysfunction within the motor unit, thereby narrowing the differential diagnosis. I now will describe some key findings, which can orient us in the process of localization of the lesion within the motor unit.

First, the findings of proximal weakness, areflexia, muscle atrophy, fasciculations without sensory deficits make an anterior horn cell disorder more likely. Other than SMA, diseases affecting the anterior horn cells include SMARD1 (or spinal muscular atrophy with respiratory distress type 1) or Hiramaya disease.

Second, the combination of distal weakness, hyporeflexia or areflexia with sensory deficits makes a disorder of peripheral nerves more likely. For instance, Charcot Marie Tooth disease is a peripheral nerve disorder where different gene variants cause impaired growth or function of the axons or the Schwann cells.

Third, fatiguability and fluctuating weakness without sensory deficits, without muscle atrophy and with preserved deep tendon reflexes are more suggestive of a neuromuscular junction disorder. Examples of neuromuscular junction disorders include botulism and Lambert-Eaton myasthenic syndrome.

Finally, proximal weakness accompanied by muscle atrophy without fasciculations, without sensory involvement and with preserved or reduced deep tendon reflexes is more suggestive of a muscle disorder. Examples of congenital myopathies include X-linked myotubular myopathy or Nemaline myopathies.

Part 4 – Screening Guidelines and Diagnostic Evaluations

Screening Guidelines

Affected babies with SMA are diagnosed through two different clinical pathways: first, as part of routine newborn screening programs and second, after a symptomatic presentation.

Newborn screening programs in Canada play a significant role in the early diagnosis of SMA and help identify presymptomatic newborns. In the recent years, almost all Canadian provinces and territories have added SMA to their newborn screening program [8]. Indeed, knowing that disease-modifying therapies are available and most effective if initiated before significant loss of motor neurons occurs, early diagnosis allows for earlier access to treatment and a better overall prognosis.

Newborn screening programs use single gene testing as a screening method. In 95% of cases, we will find a homozygous deletion of the *SMN1* gene, which is essentially 100% specific for the diagnosis of SMA [9].

Diagnostic Evaluations

When a child presents with signs of peripheral hypotonia and weakness and when SMA is suspected clinically, the first line of investigations is targeted genetic testing looking for *SMN1* deletion. The absence of the two *SMN1* copies confirms the diagnosis of 5q SMA. If one full copy of *SMN1* is detected and the clinical presentation is suggestive of 5q SMA, this remaining *SMN1* copy should be sequenced to evaluate for point mutations. If two full copies of *SMN1* are detected, a diagnosis of 5q SMA is unlikely and other motor neuron disorders should be considered. Therefore, neuromuscular gene panels should be sent, and, depending on the clinical picture, electromyography (EMG) and nerve conduction studies could be considered. Although the number of *SMN2* copies may not be essential to reach a diagnosis of SMA, it should be routinely assessed as it is an important prognostic factor in terms of severity of the SMA phenotype [10].

Part 5 – Management

Disease-Modifying Treatments

Disease-modifying therapies have revolutionized the management of SMA. These treatments target the underlying cause of SMA, aiming to improve motor function, in some cases maintain acquired abilities and, in other cases, to extend survival. In this section, we'll discuss the most prominent therapies, their mechanisms and their impact on the natural history of disease.

Understanding the pathophysiology of SMA is central to understand the principles behind the available disease-modifying treatments. Indeed, these medications aim to increase SMN protein production in one of two ways: either by acting as a splicing modifier in the *SMN2* gene to promote inclusion of exon 7 or either by introducing functional copies of the *SMN1* gene that will get translated into full-length SMN proteins.

Let's go over 3 disease-modifying treatments currently available in Canada, which are Onasemnogene abeparvovec, Risdiplam and Nusinersen.

Onasemnogene abeparvovec, or OA, is a form of gene replacement therapy that introduces a functional copy of the *SMN1* gene. It is administered as a one-time intravenous injection, leading to the expression of the SMN protein. Its efficacy was studied in two important phase 3 trials: the *SPR1NT* and *STR1VE* studies. The *SPR1NT* study, which evaluated the efficacy of OA in presymptomatic children with biallelic *SMN1* mutations, showed significant improvements in motor function, with all participants able to stand independently prior to 14 months of age and most able to walk independently. It also demonstrated survival benefits without the need for ventilatory or feeding support.[11] In the *STR1VE* study, OA was shown to be effective in symptomatic patients with SMA type 1, as most patients achieved the ability to sit independently at 18 months of age and survived without requiring permanent ventilation.[12]

Risdiplam is a molecule that modifies the splicing of SMN2 pre-mRNA. It is administered orally as a liquid solution on a daily basis. Three pivotal studies have assessed the efficacy of Risdiplam in different stages of the disease. First, the ongoing *RAINBOWFISH* study demonstrated Risdiplam's efficacy in presymptomatic children, with results showing that the infants were alive without permanent ventilation and maintained their swallowing and feeding abilities.[13] Second, the *FIREFISH* study evaluated symptomatic infants with SMA type 1 and found that Risdiplam improved developmental motor milestone achievement, with many infants able to sit without support.[14] Finally, the *SUNFISH* study demonstrated that Risdiplam improved motor function in patients aged 2 to 25 years with type 2 or non-ambulant type 3 SMA[15].

Finally, Nusinersen, which is administered by intrathecal injections, is a molecule that modifies the splicing of SMN2 pre-mRNA. It has been shown to be efficacious in improving motor milestones in infants with SMA Type 1 in the *ENDEAR* trial[16], and in children with SMA Type 2, aged 2 to 12 years, in the *CHERISH* trial[17].

Although these new medications show great promise in improving motor function, they also represent an important financial cost for our healthcare system. For instance, the annual cost of Nusinersen averages $700,000 per patient in the first year and $350,000 in subsequent years. A one-time injection of Onasemnogene abeparvovec costs nearly $3 million per patient.[18] Moreover, caregivers of patients with SMA often face significant additional expenses related to accessing these therapies. Even when caregivers are able to secure coverage through private or public reimbursement plans, travel expenses to treatment facilities are often not covered, creating an additional barrier to care for some families[19].

<u>Multidisciplinary Care</u>

While disease modifying treatments have played a significant role in improving prognosis and life expectancy in patients with SMA, a multidisciplinary approach to the management of SMA patients remains crucial given the multiple comorbidities associated with SMA.

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Rehabilitation
Rehabilitation aims at optimizing function and minimizing impairment. It includes stretching with orthoses, splints and passive techniques to improve range of motion. Thoracic and cervical bracing is also recommended for postural. Chest physiotherapy during illness may be considered to promote airway clearance. Aquatic therapy and general conditioning exercises with and without resistance can be used to improve mobility in people who can sit and people who can walk.[10]

Orthopedic Management
Scoliosis is very common in children with SMA, hence the importance of spine inspection during routine clinical examination. When scoliosis is suspected, a spinal X-ray should be performed to determine if thoracic bracing or surgery is necessary. Hip subluxation or dislocation is also common in children with SMA, especially those who are non-ambulant. When it causes significant pain, surgical management should be considered.[10]

Nutritional Management
During routine visit of children with SMA, it is important to inquire about gastrointestinal symptoms such as gastroesophageal reflux, constipation, and vomiting. Moreover, it is important to assess for safe swallowing mechanism, as bulbar dysfunction can result in aspiration and pulmonary infections. If a swallowing study is failed or if there is growth failure, short-term nasogastric tube is recommended until a long-term gastrostomy tube can be placed.[10]

In brief, a multidisciplinary team approach is central to the management of SMA patients, including neurology, respirology, nutrition, physical and occupational therapy as well as orthopedics.

Conclusion

That's all for today! Let's review the main learning points from this episode:

1. Spinal muscular atrophy is defined as a group of inherited disorders causing degeneration of the anterior horn cells of the spinal cord during fetal development and the postnatal period. It is characterized by progressive muscle weakness and muscle atrophy[1].
2. About 95% of cases of 5q SMA are due to homozygous deletions of exon 7, exon 8 or both, in the *SMN1* gene, leading to loss of function of the SMN protein [1].
3. There are 5 types of SMA that range from type 0, the most severe form, to type 4, the milder phenotype.
4. The combination of gross motor delay, hypotonia, weakness, fasciculations and areflexia should raise our suspicion for SMA and should prompt genetic testing.
5. While disease modifying treatments have played a significant role in improving prognosis and life expectancy in patients with SMA, a multidisciplinary approach to the management of SMA patients remain crucial given the multiple comorbidities associated with SMA.

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Thanks for listening!

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