Hypotonia in an Infant: The Case of SMA

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Abstract

Spinal Muscular atrophy (SMA) is a rare neuromuscular disorder that affects only 1 in 10,000 births. SMA causes deletions or mutations in the survival motor neuron 2 (SMN2) gene which allows for the maintenance of the motor neurons and mRNA in the development of nerve cells.

In this case report we talk about a 3-month-old Caucasian female infant brought in by parents due to progressive hypotonia in the lower extremities found to have SMA type 1. On physical examination there were reduced reflexes in the lower extremities. Along with that there was increased accessory respiratory muscle use with significant diaphragmatic movement. Laboratory results showed elevated CK and genetic analysis showed SMN protein deletion. With a confirmed SMA type 1 diagnosis our patient was transferred to a major hospital.

Treatment for SMA has advanced in recent years. Current analysis shows that azithromycin does increase the SMN protein in the mouse model, however it does not improve the survival of the mice. Azithromycin in combination with an antisense oligonucleotide that increases SMN2 splicing causing an improvement in the survival and movement of the mice. This study could indicate that just having an increase in the SMN protein may not help resolve the disease rather what helps the most is the increase in splicing of the SMN2 protein. This thought process would show increases of the protein-containing both exons and introns does not actually improve symptoms, rather increases of the SMN2 protein-containing just exons that are ligated does improve symptoms.

INTRODUCTION

Spinal Muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder that affects only 1 in 6,000 to 1 in 10,000 live births, essentially only 0.017% to 0.010% of the population is affected [1,2]. SMA causes deletions or mutations in the survival motor neuron 2 (SMN2) gene located on the 5q13.2 chromosome resulting in deficiencies of this protein. SMN2 is a vital protein found mostly in the spinal cord allowing the maintenance of the motor neurons and mRNA that helps with the development of nerve cells [3]. Thus, having a deficiency of this protein results in a reduction of the motor neurons, ergo hypotonia and impaired axons and dendrites thus, neuronal function.

SMA has three main categories- type 1, type 2, and type 3. SMA type 1 or Werdig-Hoffman disease is the one that our patient presented with and usually presents within the first six months of life [4]. The infant can appear to be developing normally initially, however with time will develop severe hypotonia and will not develop the ability to lift their head or seat unsupported. Further, they may develop a poor cry, poor swallowing reflexes, and an increase in accessory respiratory muscle use resulting in a bell-shaped deformity [5]. Type 2 SMA usually presents at around 3-15 months with a child who never stands without help and type3 SMA or Kugelberg-Welander disease usually presents > 18 months with a child that have proximal weakness- trouble climbing stairs and eventually become wheelchair dependent [5]. To confirm SMA type 1 there usually is a deficiency of SMN2 protein. In this case report, we present a case of a 3-month-old baby girl with SMA whose diagnosis was confirmed after a positive SMN2 protein reduction.

CASE PRESENTATION

A 3-month-old Caucasian female infant was brought in by parents for consultation due to a chief complaint of hypotonia in the lower extremities. Per maternal history she did not have any decrease in fetal movement on any ultrasound at any point in the pregnancy, this is usually indicative of SMA, however there was IUGR (intra-uterine growth restriction). No congenital myopathies or other neuromuscular defects were present on either side of the family, per history. Upon delivery our patient did have lower extremity movement and was kicking. Parents however had noticed a decrease in lower extremity movement over time compared to upper extremity movement with eventual loss of movement in the lower extremity. On physical examination she did present with decrease hypotonia in her lower extremities along with absent/ reduced reflexes in the lower extremities compared to the upper extremities. Along with her lower extremity hypotonia there was increased accessory respiratory muscle use with significant diaphragmatic movement.

The patient had numerous laboratory studies conducted. The CBC, TSH, and BMP all came back negative. The CK however came back elevated. This at the time was not particularly indicative because it could both be elevated or decreased in SMA and is elevated in many myopathies. Further mitochondrial analysis workup conducted was all negative. The final test analyzing the genetics for an SMN protein deletion or defect was found to be positive.

Once this was found the patient was transferred to a higher level medical center for further evaluation likely including...
emergonography (EMG), nerve conduction study (NCS), and muscle biopsy along with more inclusive treatment options.

**DISCUSSION**

In our patient, as in many cases of SMA the patient would require transfer to a major university hospital that is more adept to dealing with such rarities. Treatment for SMA has advanced in recent years significantly. Earlier this year researchers at the University of Missouri examined if Azithromycin could help improve SMA. They were able to find that although azithromycin does increase the SMN protein in the mouse model it did not improve the survival of the mice, however Azithromycin in combination with an antisense oligonucleotide that increases SMN2 splicing causing an overall improvement in the survival and movement of the mice [6]. This study has been very important in terms of further research in SMA treatment because it could indicate that just having an increase in the SMN protein may not help resolve the disease rather what helps the most is the increase in splicing of the SMN2 protein. This thought process would show increases of the protein-containing both exons and introns does not actually improve symptoms, rather increases of the SMN2 protein-containing just exons that are ligated does improve symptoms. This could be suggestive that a problem with SMA is not only that there is a decrease in the SMN2 protein, but also that the introns of the SMN2 proteins in those with SMA have sequences further exacerbating the muscular hypotonia.

Currently, one of the major treatment options for SMA is Spinraza (Nusinersen), this is a 2'-O-methoxymethyl phosphorothioate modified antisense drug. Basically, the goal of this drug is to increase the amount of SMN protein by altering the splicing of the SMN2 pre-mRNA [6,7]. This is a vital study and new treatment opportunity because it shows that 40% of patients that were treated with Nusinersen were able to reach a motor milestone as opposed to those who just received the placebo [7]. This new drug continues to back up the theory that the concern with SMA is both that there is a decrease in SMN2 protein but also that there is an exacerbating factor with the introns of the SMN2 protein causing greater symptomatology.

**CONCLUSION**

Through this case study we explore the importance of considering all causes of hypotonia through a thorough history, physical, and workup. Although, SMA is found very rarely in the population it is vital to be caught early on so the parents and family can be educated on what to expect. Finally, it is vital that future treatments and clinical trials examine further the relationship of SMN2 splicing verses just increases in SMN2 as potential treatment factors in SMA type 1.

**REFERENCES**

5. Bodamer OA. Spinal Muscular Atrophy.