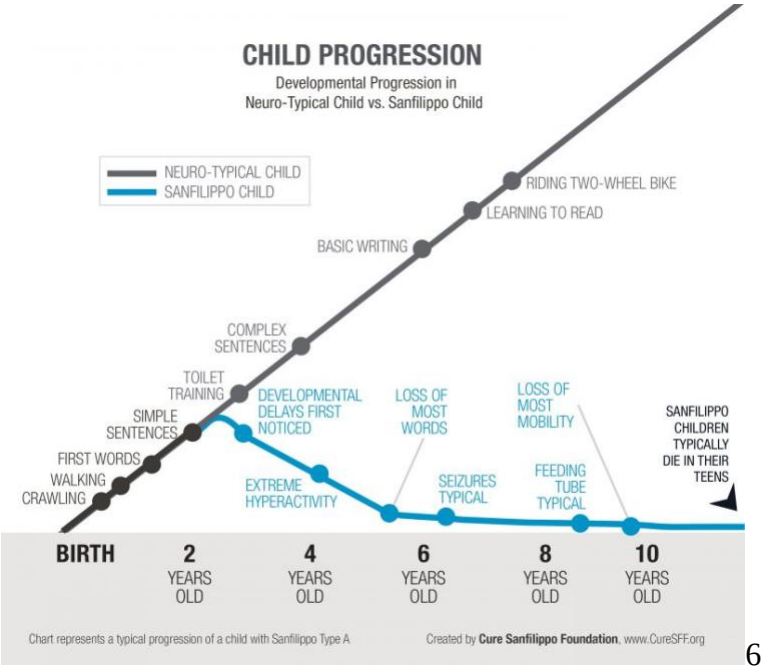
Stem Cells for Childhood Alzheimer's: A Cure for Sanfilippo

By Sabrina Noritake

Can you imagine having a child with Alzheimer's? Unfortunately, this is the reality for children affected by Sanfilippo Syndrome—also called Mucopolysaccharidosis III (MPS III). MPS III is a recessive genetic disease that primarily affects the nervous system. The fact that it is recessive means two healthy people can be carriers and have a child with this disease. MPS III occurs in 1 of 100,000 births. There are different subtypes of this disease, and children with subtype A tend to have the most severe disease progression (Figure 1). MPS IIIA patients have normal development until about two years of age when they begin to experience developmental delay. Afflicted children go on to develop symptoms ranging from behavioral problems, sleep problems, hyperactivity, extreme aggression, and anxiety. The final stage of this disease is immobility, dementia, difficulty swallowing, and an early death in teenage years. Sadly, there is no cure.



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(Figure 1)

The symptoms of MPS IIIA are due to a buildup of a protein called heparin sulfate. Normally, heparin sulfate binds signaling proteins and promotes the immune response in wound healing. Although the exact mechanisms are unknown, the symptoms of MPS IIIA arise from elevated levels of heparin sulfate interfering with normal heparin sulfate functions. Heparin sulfate is degraded by special units in the cell called lysosomes. Inside the lysosome, each step of breaking down heparin sulfate is done by different proteins called enzymes. The "A" in MPS IIIA refers to a deficiency in sulfamidase enzyme, which normally performs the first step in the heparin sulfate

degradation process. Without this sulfamidase, patients' lysosomes enlarge and accumulate heparin sulfate, causing patients to develop signs of neurodegeneration.

All of this can be confusing, so to put it simply: neurons are like office workers and the nervous system is like a company. As the workers do important work, they create trash, heparin sulfate. Patients with MPS IIIA however, don't have any janitorial staff. There are still large dumpsters outside of the building, and the trash collectors still come by, but no janitors take the trash to the dumpsters. So, what do the office workers do? They keep working. Eventually, the trash cans overflow and start cluttering up their workspace. As trash accumulates, it becomes difficult to work and productivity declines. At that point, the company can no longer function and goes under.

So, why isn't there a cure for MPS IIIA? Shouldn't we just give these patients the missing enzyme? A big problem to finding a cure for MPS IIIA is the blood-brain barrier. The blood-brain barrier is a membrane that separates spinal fluid from blood to help protect the brain and spinal cord from infection. This barrier also prevents proteins in blood from entering the spinal fluid, so sulfamidase can't just be administered intravenously like other treatments. Thankfully, scientists are working on different ways to get around this problem.

One approach is using stem cells. Stem cells are unspecialized cells that have the ability to become specialized. It's similar to how children can grow up and choose any profession. Neural stem cells are even more specific in that they can become any type of neural cell. A proposed treatment for MPS IIIA is neural stem cells engineered to overexpress sulfamidase that could be directly injected into the brain. This is likely to be successful because injected neural stem cells can integrate into brain tissues and produce sulfamidase from within the blood-brain barrier. These neural stem cells are designed in collaboration with a company called Neuralstem and are shown to be long-lasting in brain tissues. Going back to the analogy, this would be like adding back the missing janitors so that the trash can be taken out.

A study to test this concept is currently underway at UC Davis' Institute of Regenerative Cures. If this procedure works, patients may only need to be treated once, and the transplanted neural stem cells will continue to make sulfamidase for them for the rest of their lives. Children diagnosed early enough, can undergo one procedure and need no other intervention to grow and develop normally. Before long, we may have a way to help children with MPS IIIA live long healthy lives.

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