



A NEW COMPLICATION OF LYME DISEASE; SPINAL MUSCULAR ATROPHY (SMA)

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ABSTRACT

Lyme borreliosis is well known multisystem disease and can produce a wide array of neurological abnormalities in humans. It can effect both the central and peripheral nervous system. Spinal muscular atrophy (SMA) a leading genetic cause of infant death, is a neurodegenerative disease characterised by the selective loss of particular groups of motor neurones in the anterior horn of the spinal cord with concomitant muscle weakness. Spinal muscular atrophy (SMA) is also a neuromuscular disease caused by abnormally low cellular levels of the ubiquitous protein SMN. Recent study finds connection between ALS and SMA. Respiratory failure due to bilateral diaphragm palsy as an early manifestation of ALS. Diaphragmatic paralysis and respiratory failure as a complication of Lyme disease. Lyme –associated diaphragm weakness from phrenic nerve palsy is rare. One of the rarest manifestations of phrenic nerve disorder is neuroborreliosis. I report two cases. **1-**When she was 2 months baby, she had diagnosed with SMA. After three years, her LTT-*Borrelia* test result is positive. CD57+/CD3-(NK cells) % 0.48, (20 mm³), very low. C3 Compleman test result is low. Her mother's (38 years old), LTT-*Borrelia* test result also positive. *It is documented that transplacental transmission of the spirochete from mother to fetus is possible.* **2-** 13 years old son. He had diagnosed Emery-Dreifuss muscular dystrophy (EDMD), when he was 6 years old. He had, LTT-*Borrelia* positive test result, after 5 years. His father Lyme test result was positive, when he was 57 years old. Eventually, these results reveal the need for consideration of Lyme borreliosis in patients diagnosed with SMA for the first time. People who are diagnosed with SMA, DMD, ALS and similar neurodegenerative diseases have a great benefit in performing Lyme tests.

KEYWORDS: Spinal Muscular Atrophy (SMA), Lyme borreliosis, Turkey.

INTRODUCTION

Spinal muscular atrophy (SMA) a leading genetic cause of infant death, is a neurodegenerative disease characterised by the selective loss of particular groups of motor neurones in the anterior horn of the spinal cord with concomitant muscle weakness. To date, no effective treatment is available. However, there remains an ongoing problem in trying to link a single gene loss to motor neurone degeneration.^[1]

Type 1 (Werdnig Hoffman disease), the most severe type is also the most common genetic cause of infant mortality. The molecular basis for disease severity is associated with both the quality and quantity of SMN protein. The SMN1 mutation primarily affects lower neurones, the resulting motor neurone loss causing paralysis and early death due to respiratory failure. However, the reason why loss of a ubiquitously expressed protein causes motor neurones to be particularly more vulnerable than other cell types is an intriguing subject.

SMA was first reported by Werdnig in 1891 and then by others who recognized variability of muscle weakness severity. A century later, a consensus classification scheme outlining three SMA types was adopted, and in 2007 a Standard of care document formalized the clinical treatment of patients with SMA.^[2]

All patients with SMA lack a functioning SMN1 gene and are thus dependent on their SMN2 gene, however inefficient, to produce the SMN protein necessary for survival. Thus, SMA is caused by a deficiency in the SMN protein that, reason still unknown, results in selective motor neuron loss. The SMN protein has also been detected in the axons of motor neurons.^[2]

Despite recent data on the cellular function of the survival motor neuron (SMN) gene, the spinal muscular atrophy (SMA) disease gene, the role of the SMN protein in motor neurons and hence in the pathogenesis of SMA is still unclear.^[3]

The mechanism underlying selective motor neuron (MN) death remains an essential question in the MN disease

field. The MN disease spinal muscular atrophy (SMA) is attributable to reduced levels of the ubiquitous protein SMN. Here, we report that SMN levels are widely variable in MNs within a single genetic background and that this heterogeneity is seen not only in SMA MNs, *but also in MNs derived from controls and amyotrophic lateral sclerosis (ALS) patients.*^[4]

Although the genetic cause of SMA has been mapped to the *Survival Motor Neuron1(SMN1)* gene, mechanisms underlying selective motor neuron degeneration in SMA remain largely unknown. SMN is expressed ubiquitously in all somatic cells; however, reduced SMN levels make spinal motor neurons particularly vulnerable to degeneration. The underlying reasons are not understood, though some hypotheses regarding SMA disease mechanism may begin to explain.^[5]

The molecular basis for disease severity is associated with both the quality and quantity of *SMN* protein. In man, a unique gene called *SMN2*, which is a duplication of *SMN1* and can be present in multiple copies. Also, some mutation in *SMN1* do not cause complete loss of its function (Burghes & Beattie, 2009). As a result, the disease severity is determined by both the preserved function of mutated *SMN1* and the number of copies of *SMN2* found in the patient genome.

The *SMN1* mutation primarily affects lower motor neurones, the resulting motor neuron loss causing paralysis and early death due to respiratory failure. However, the reason why loss of a ubiquitously expressed protein causes motor neurons to be particularly more vulnerable than other cell types is an intriguing subject.

Recent studies have identified a number of cells and tissues that are pathological targets according to the neuromuscular system traditionally examined, which suggest that SMA is a multisystemic disease.

Although there is no direct link between motor neuron death and SMN malfunction in any kind of glial cells, a conclusion that can be drawn is that the interplays between motor-neuron and glial cells may largely contribute to the clinical manifestations, *suggesting SMA is multi-system disorder.*

Interestingly, prenatal immunoblast studies on SMA type 1 fetuses showed that SMN protein was greatly reduced in all tissues examined, i.e. skeletal muscle, heart, brain, kidney, thymus, pancreas and lung (Burlet et al. 1998), (1).

Although it is clear that the primary pathology in SMA is neurodegeneration, there is increasing evidence from clinical reports and animal studies that other tissues are involved in the overall phenotype, especially in the most severe forms of the disease. Additional complications in patients include autonomic nervous system involvement,

congenital heart defects, liver, pancreas and intestinal dysfunction, and metabolic deficiencies.^[1]

On the other hand, recent scientific studies have shown; between ALS and SMA is a link found; mutations in the RNA binding protein FUS cause Amyotrophic lateral sclerosis (ALS), a fatal adult motor neuron disease. Decreased expression of SMN causes the fatal childhood motor neuron disorder spinal muscular atrophy (SMA). *The physical and functional interactions among SMN, FUS, TDP-43, and Gems indicate that ALS and SMA share a biochemical pathway, providing strong support for the view that these motor neuron diseases are related.*^[6]

In 2018 study, Binkai Chi et al., “*The neurodegenerative diseases ALS and SMA are linked at the molecular level via the ASC-1 complex*”. According to this study results; remarkably, mutations in the ASC-1 complex are known to cause a severe form of Spinal Muscular Atrophy (SMA), and we show that an SMA-causative mutation in an ASC-1 component or an ALS-causative mutation in FUS disrupts association between the ASC-1 complex and the RNAP II/U1 snRNP machinery. We conclude that ALS and SMA are more intimately tied to one another than previously thought, being linked via the ASC-1 complex.^[7]

There is a link between ALS and Lyme neuroborreliosis. One of the diseases that Lyme disease secretly imitates is ALS. The *Borrelia burgdorferi* spirochete bacterium can cause the typical symptoms of ALS disease, as it causes deterioration of vital functions of the central nervous system by secreting neurotoxins (a kind of poison). The pathological feature of ALS is motor neuron degeneration and death. This is going until the patient's death.

Lyme borreliosis is a well-known multisystem disease caused by the spirochete *Borrelia burgdorferi* and can produce a wide array of neurological abnormalities in humans. It can be speculated that the Lyme spirochete has the ability to induce an immune reaction that specifically affects motor neurons. This reaction may mimic different, non-curable diseases, such as Spastic spinal paralysis, Amyotrophic lateral sclerosis (ALS), and Spinal muscle atrophy (SMA).

The neurotoxins of the spirochete bacteria are concentrated in the brain fat tissue and the peripheral nervous system. Elements of the central nervous system cause muscle weakening, cognitive impairment, chronic pain and severe inflammation of the spinal cord and brainstem.^[10-39]

Due to the loss of motor neurons in SMA disease, paralysis and respiratory failure occur. **Diaphragmatic paralysis and phrenic nerve palsy is a phenomenon seen in SMA patients.** One of the most essential respiratory muscles is the diaphragm, which is

innervated by cervical motor neurons C3-4-5 via the phrenic nerve. Diaphragmatic paralysis can involve either the entire diaphragm (bilateral) or only one leaflet (unilateral). The functions of the diaphragm do not stop locally in its anatomy but affect the whole body system. The respiratory rhythm, directly and indirectly, affects the central nervous system (CNS).

The phrenic nerve begins in the brain and then continues down to the first few vertebrae of the spine, where it then splits. The two nerves then continue through each side of the body, with the right side coming in contact with the windpipe and heart, while passing the lungs. The left side also comes in close contact with the heart, with both sides eventually ending up in the diaphragm.

The **phrenic nerve** provides the primary motor supply to the **diaphragm**, the major respiratory muscle. This nerve controls the diaphragm muscle, which controls the breathing process. When the phrenic nerve is damaged, it can prevent the normal breathing processes and impact your health.

In recent years, scientific studies have shown that Lyme borreliosis is associated with autonomic nervous system dysfunction, phrenic nerve paralysis, respiratory failure, unilateral and bilateral diaphragmatic dysfunction.^[40-65]

RESULTS

I report two cases. **1-**When she was 2 months baby, she had diagnosed with SMA. After tree years, her LTT-*Borrelia* test result is positive. CD57+/CD3-(NK cells) %0.48, (20 mm³), very low. C3 Compleman test result is low. Her mother's (38 years old), LTT-*Borrelia* test result also positive. *It is documented that transplacental transmission of the spirochete from mother to fetus is possible.* **2-** 13 years old son. He had diagnosed Emery-Dreifuss Muscular Dystrophy (EDMD), when he was 6 years old. He had, LTT-*Borrelia* positive test result, after 5 years. His father lyme test result was positive, when he was 57 years old.

Eventually, These results reveal the need for consideration of Lyme borreliosis in patients diagnosed with SMA for the first time. People who are diagnosed with SMA, DMD, ALS and similar neurodegenerative diseases have a great benefit in performing Lyme tests. It's clear that further and detailed researchs about SMA-LYME Disease connection are needed emergency.

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