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Autopsy Case Reports

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Autopsy of a child with Spinal muscular atrophy Type I (Werdnig-Hoffmann disease)

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ABSTRACT

Spinal muscular atrophy (SMA) is a heritable neuromuscular disorder which encompasses a large group of genetic disorders characterized by slowly progressive degeneration of lower motor neurons. The mutation is seen in the *SMN1* gene mapped on chromosome 5. Depending on the age of the onset and the degree of severity, SMA has three subtypes. We discuss the autopsy findings in a case of Type 1 SMA also known by the name Werdnig-Hoffmann disease, to highlight the primary changes in the spinal cord, and skeletal muscle with association changes in the liver and terminal respiratory complications.

Keywords
Gliosis; microvesicular steatosis; neurogenic atrophy; spinal muscular atrophy type I.

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by the degeneration of the anterior motor neurons of the spinal cord manifesting as group atrophy of downstream skeletal muscle fibers.[1] Based on the age at the onset and the severity, it is classified into 3 subtypes – Werdnig-Hoffmann disease (Type I); Intermediate disease (Type II), and Kugelber-Welander disease (Type III).[1] The causative gene – survival motor neuron gene 1 (*SMN1*), has been mapped to the telomeric end of chromosome 5p.[2] We discuss the autopsy findings in a 2-month-old boy, with type I SMA who was detected to have a homozygous deletion in exon 7 and 8 of the *SMN1* gene.

CASE REPORT

A 2-month-old male was brought to the hospital presenting with cough for 3 days, rapid breathing, and poor feeding for 2 days and fever for 1 day. He had an on-and-off fever since day 4 of life associated with dry, non-paroxysmal cough. The antenatal and birth history was uneventful. He had a birth weight of 3000 g and was discharged on day 2 of life. However, during the first week, he was observed to have a weak cry associated with reduced spontaneous movement in all four limbs. The developmental history divulged the absence of neck holding. However, he showed regard to the mother's face, responded to sound, and was following objects. The family history was significant with the pedigree chart showing the child to be the 3rd born in a non-consanguineous marriage, with

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early infantile deaths of two male siblings following a history suggestive of hypotonia and succumbing on day 50 and day 90 of their lives, respectively. On examination, he had tachycardia (heart rate 143/min) and tachypnoea (68/min) with 50% oxygen saturation at room air. The anthropometric measurement revealed a weight of 3.6 kgs (-3 Z score), length of 58 cm (0.88 Z score), and occipitofrontal circumference of 36.2 cm (-2.5 Z score). Muscle weakness was indicated by frog-like posture, jug-handle deformity of upper limbs, bilateral wrist contracture, bell-shaped chest, and poor spontaneous activity. He was awake and alert with the presence of spontaneous eye-opening, extra-ocular movements, absence of ptosis, or facial weakness. However, there was the presence of tongue fasciculations, and flabby skeletal muscles. Hypotonia was indicated by the presence of head lag when pulled to sit, dangling of legs on ventral suspension and head lying below the plane of the body on horizontal suspension. There were minimal spontaneous distal movements with the absence of antigravity movements. The deep tendon reflexes were absent, and bilateral planters were mute. The sensations were preserved with the absence of nystagmus. Respiratory system examination revealed nasal flaring, bell-shaped chest, bilateral suprasternal, intercostal, and subcostal retractions with a seesaw pattern of breathing, indicating intercostal muscle weakness. Auscultation of the chest revealed decreased air entry with bilateral crackles. Investigations revealed normocytic normochromic anemia (haemoglobin-10.7 gm/dl, MCV-88fl, and MCHC-31gm/dl), marginally raised creatinine (1.8 gm/dl) and creatinine kinase level (56 IU/l). Nerve conduction study was indicative of normal sensory nerves with preferential involvement of motor nerves. Electromyography was indicative of denervation. Chest X-ray showed collapse and consolidation of the right lung, while abdominal ultrasound was normal. He soon developed respiratory failure and shock, and his condition worsened despite supportive care. He succumbed to aspiration following an episode of vomiting.

AUTOPSY FINDINGS

At autopsy, multiple muscle groups (deltoid, psoas, and hamstrings) showed features of group atrophy with relative hypertrophy of type I fibers in the absence of inflammation (Figure 1).

The entire length of the spinal cord was dissected (Figure 2A), and representative sections at multiple levels showed the loss of the anterior motor neurons in the ventral horns (Figures 2B, 2C, 2D) with many degenerative forms (Figure 2E). Sections from the motor cortex, basal ganglia, and cranial nerve nuclei did not reveal any pathological alterations.

Lungs were heavy with the presence of fibrinous pleural exudates and predominantly lower lobe consolidation. Representative sections showed presence of dense neutrophil rich infiltration within the alveolar spaces accompanied by fibrin, intra-alveolar hemorrhage, and features of hyaline membrane formation (Figures 3A and 3B). The liver was grossly unremarkable, however microscopically showed pan-acinar microvesicular steatosis (Figures 3C and 3D).

The thymus showed features of stress-induced involution, and the bone marrow revealed maintained trilineage hematopoiesis and occasional hemophagocytosis. With the clinical presentation indicating a possible autosomal recessive pattern of inheritance manifesting as a floppy infant, investigations and autopsy findings localizing the disease to anterior horn cells leading to group atrophy of muscle fibers, the possibility of the type I SMA was high on the differentials. DNA extracted from the antemortem blood sample used to establish molecular diagnosis by demonstration of absence of amplification of probes specific for exons 7 and 8 of *SMN1* gene using a Multiplex Ligation-dependent Probe Amplification

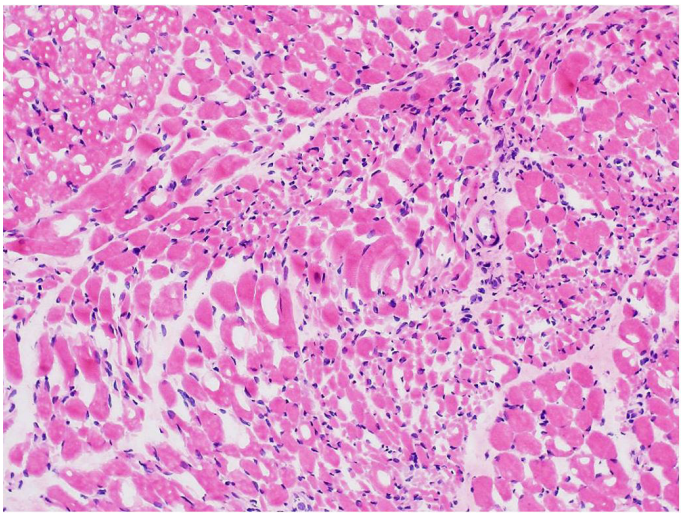

Figure 1. Photomicrograph of the deltoid muscle shows group atrophy of muscle fibers in the background of relatively preserved and apparently hypertrophic muscle fibers (H&E, 200x).

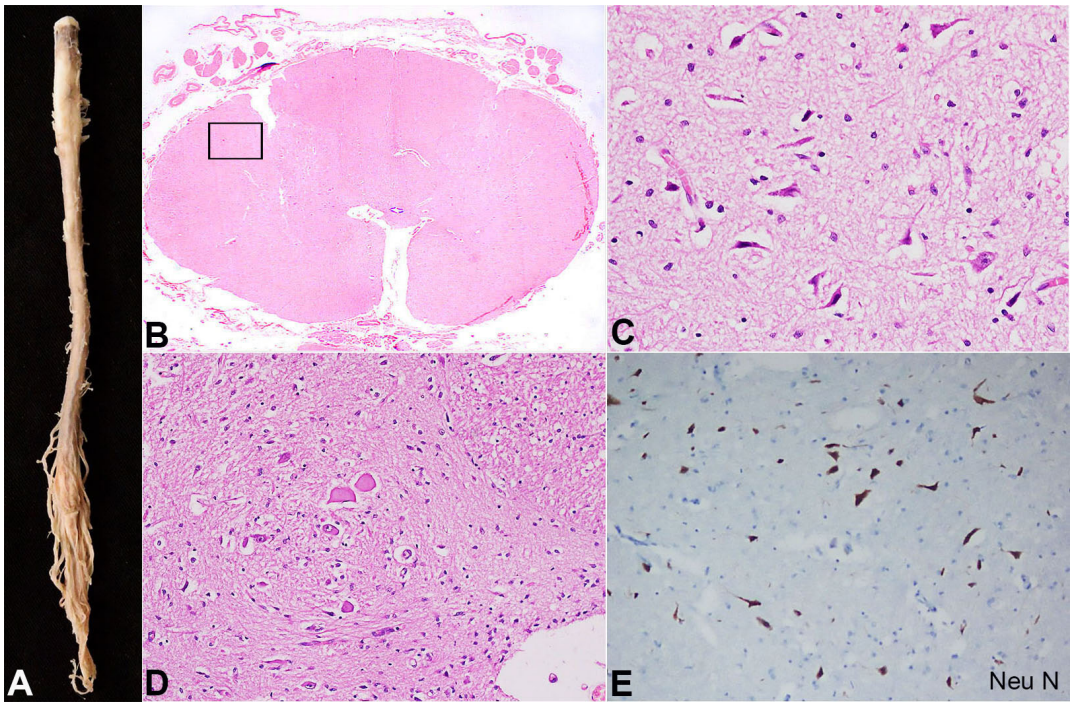

Figure 2. A – Gross view of the dissected spinal cord. B, C, D and E are photomicrographs of the spinal cord; **B –** Transverse section from the spinal cord at the thoracic level without evidence of infarct or inflammation with the rectangle denoting the ventral horn site on one side (H&E, 20x); **C –** Section from the area of ventral horn shows degenerated anterior motor neurons with pyknotic nuclei(H&E, 200x); **D –** Sections from the area of ventral horn shows swollen and pale neurons with loss of Nissl substance (H&E, 200x); **E –** Neu N (Clone EPR12763, 1:1000 dilution, DAKO) highlights reduced density of neurons in the ventral horn of spinal cord (200x).

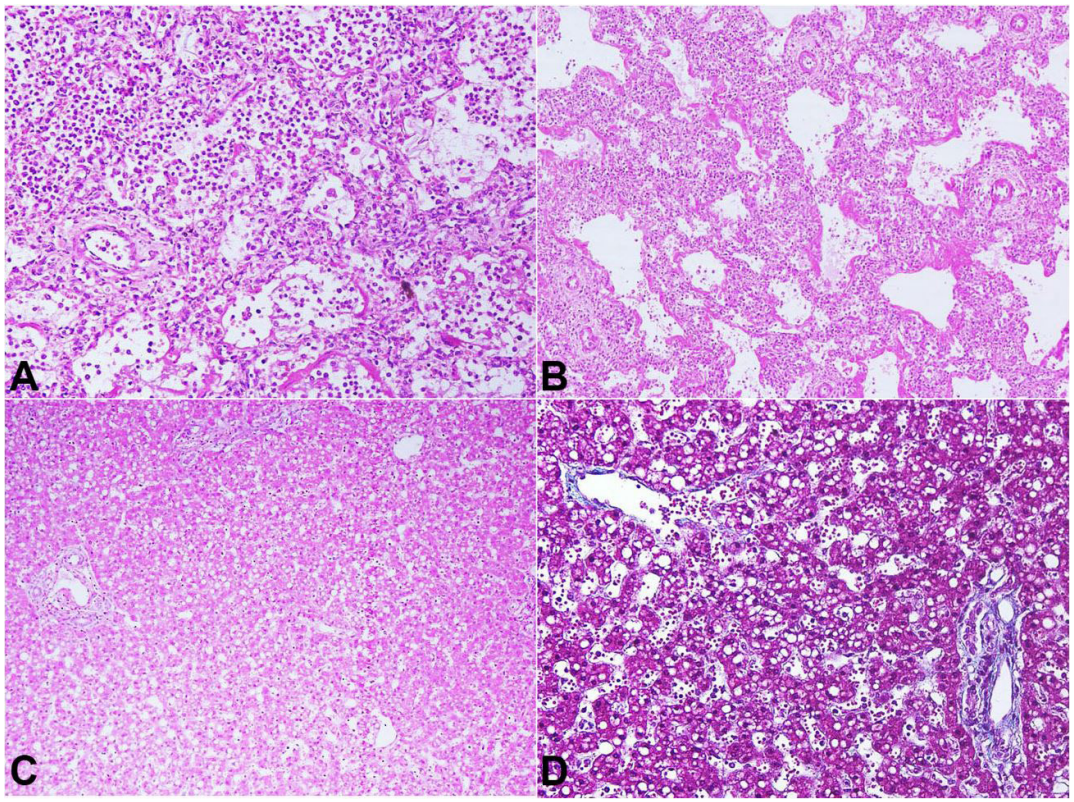

Figure 3. Photomicrographs of the Lung (A and B). **A –** Dense infiltration of alveolar spaces by polymorphs (H&E, 200x); **B –** Alveolar ducts lined by dense eosinophilic hyaline membrane (H&E, 200x). Photomicrographs of the liver (C and D); **C –** Panlobular microvesicular steatosis (H&E, 40x); **D –** Absence of fibrosis and accentuates the panacinar microvesicular steatosis (Masson Trichrome, 100x).

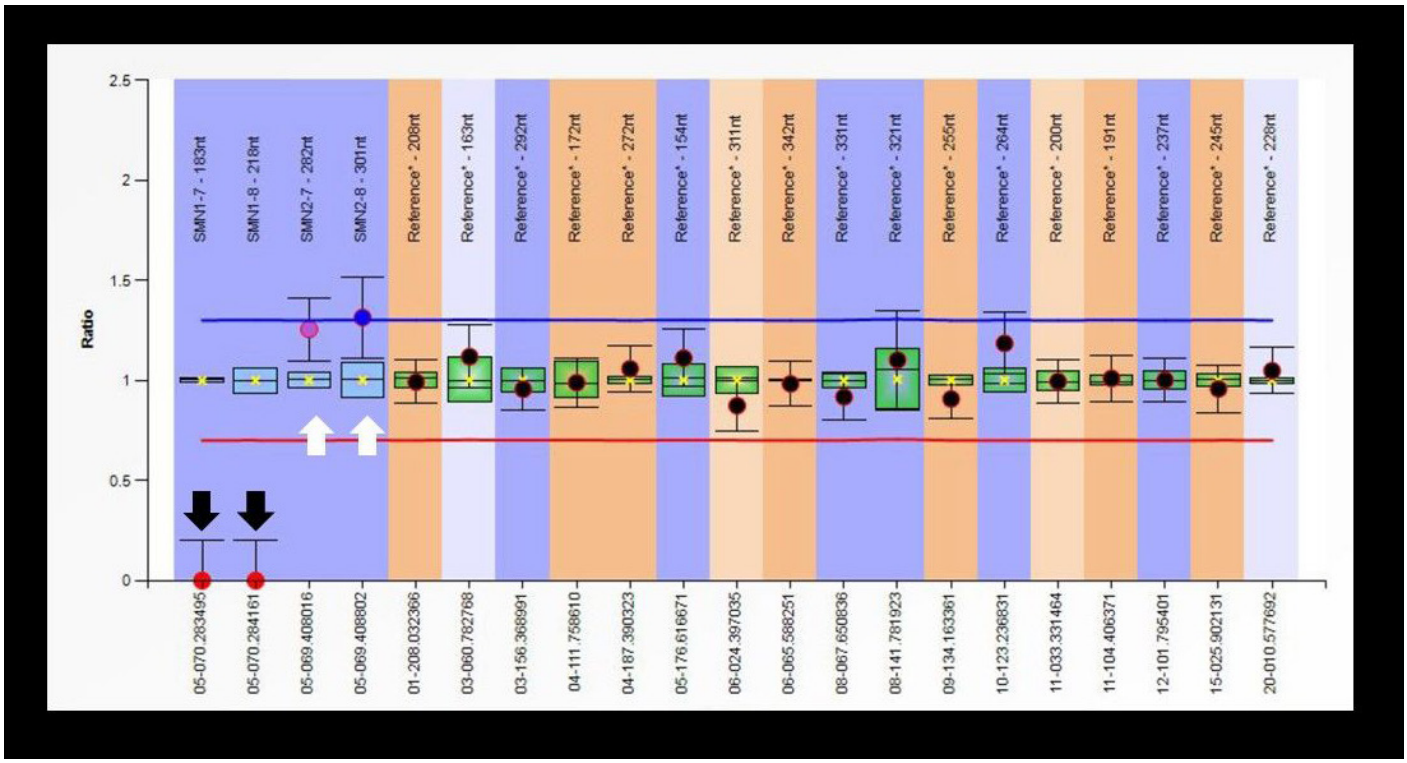

Figure 4. The graphical representation of the sample run on MPLA platform shows zero copies of exons 7 and 8 of *SMN1* gene (black arrows) and three copies of (1.5 x 2 copies) of exons 7 and 8 of *SMN2* gene (white arrows).

(MPLA, *MRC-Holland, Amsterdam, the Netherlands*) platform following standard protocols, which suggests homozygous microdeletion involving at least these two exons (Figure 4).

DISCUSSION

SMA is an autosomal recessive disease characterized by varying degrees of muscle weakness due to degeneration of the anterior horn neurons.[1,3] SMA has an incidence of 1:100000 with a carrier state predicted to have a frequency of one in every 90, making it one of the most prevalent heritable diseases encountered in the routine practice.[4] Type I or Werdnig-Hoffmann disease, the most common and severe subtype, has the onset within the first 6 months and is usually fatal within 24 months.[5] They present as floppy infants with symmetrical hypotonia, lack of head control, and a bell-shaped chest with characteristic paradoxical breathing pattern due to weak intercostal muscles and relatively spared diaphragm.[1,6] In addition, these children show evidence of bulbar weakness with tongue fasciculations and weak suck/swallow maneuvers.[1,7] Thus, predisposing them to aspiration pneumonia which is the leading cause of mortality.[8] Histologically, there is the evidence of degeneration of spinal anterior horn neurons with characteristic denervation patterns of the group atrophy in the corresponding skeletal muscle fascicles.[1,9] The atrophic fibers are small, round, and uniform with interspersed groups of relatively spared hypertrophic fibers.[10,11] The immunocytochemistry study (ATPase or Slow and Fast myosin) demonstrates these large fibers to be of type I phenotype.[1,10] The hypertrophic fibers are hypothesized to be a compensatory phenomenon. The most common genetic aberration is the homozygous loss of the *SMN1* gene by mutation, deletion, or rearrangement.[1,12] These patients have a preserved copy of adjoining *SMN2* gene, which is subjected to mRNA splicing resulting in a non-functional SMN protein that gets degraded.[3,13] Genotype-phenotype studies have shown that the number of copies of SMN2 gene has a bearing on degree of severity of disease, with more than 3 copy numbers is associated with a milder forms of SMA.[14] It has also been shown that the patients with SMA have a concomitant defect in the beta-oxidation, which is seen as microvesicular steatosis or evidenced by a raised fatty acid metabolites.[15] There have also been reports of a Reye-like syndrome in patients with SMA.[16,17]

In summary, this case highlights the protean manifestations in a genetically confirmed case of type I SMA in the form of degeneration of anterior horn neurons, group atrophy of skeletal muscles, concomitant beta-oxidation defect in the form of microvesicular steatosis and cause of death being due to respiratory failure secondary to aspiration pneumonia.

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Authors' contributions: Madakshira MG, Singla S and Gupta K were involved in conducting the autopsy and analysing the autopsy findings. Zahan S, Paria P and Sahu JK actively participated in the ante-mortem clinical management of the child and counselling of the parents. Madakshira MG and Gupta K were involved in preparation of the manuscript. Singla S, Zahan S, Paria P and Sahu JK reviewed and approved the final manuscript.

The authors retain an informed consent signed by the deceased's next of kin, authorizing the autopsy and data publication. The manuscript is approved by the Institutional Ethics committee.

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