Variants in *HNRNPDL* and *SETX* Not Necessarily Indicate Familial Amyotrophic Lateral Sclerosis or Limb Girdle Muscular Dystrophy 1G in Acute Muscular Respiratory Failure

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Abstract

Genetic work-up is useful for the identification of a primary myopathy. However, even sophisticated genetic methods may fail to detect the underlying cause of myopathy as in the following case. The patient is a 52-year-old female with a history of epilepsy, arterial hypertension, atrial flutter requiring cardioversion, ablation, and anticoagulation, coronary heart disease, hyperlipidemia, and hyper-CKemia. At age 52 years, she was referred for heart failure due to ischemic cardiomyopathy requiring appropriate medication and implantation of an ICD. During hospitalization she developed acute muscular respiratory failure requiring mechanical ventilation. Genetic panels for myopathy, neuropathy, and cardiomyopathy revealed variants of unknown significance in the *HNRNPDL* and *SETX* genes respectively. Clinical presentation and muscle biopsy, however, suggested metabolic myopathy. Acute muscular respiratory failure may require traditional diagnostic work-up for primary myopathy and long-term invasive and non-invasive ventilation. Panel investigations not necessarily lead to a conclusive diagnosis. The multisystem nature of the condition rather suggests a metabolic defect than LGMD-1G or fALS as genetic findings suggested.

Keywords
- amyotrophic lateral sclerosis
- genetics
- mitochondria
- mitochondrial disorders
- neuromuscular disorders

Case Report

The patient is a 52-year-old female, height 160 cm, who was referred for heart failure. Her history included recurrent syncopes/seizures in childhood, pyelonephritis in adolescence, diabetes, arterial hypertension, hyperCKemia, coronary heart disease, atrial flutter requiring cardioversion, ablation, and anticoagulation, non-ST segment myocardial infarction, hyperlipidemia, statin myopathy, and smoking 35 pack/years. The family history was positive for dementia and statin myopathy (mother).

Upon bisoprolol, eplerenone, sacubitril/valsartan, and furosemide, heart failure resolved. Creatine-kinase did not exceed 899U/L (n < 170U/L). Electrocardiogram showed left-anterior hemiblock and right bundle-branch block. Echocardiography revealed systolic and diastolic dysfunction, ventricular hypertrophy, biatrial enlargement, right ventricular dilatation, and noncompaction. Cardiac magnetic resonance imaging confirmed echocardiographic findings and additionally revealed transmural late gadolinium-enhancement. For primary prophylaxis, an implantable cardioverter-defibrillator (ICD) was implanted. ICD-implantation was complicated by a toxic reaction to local anesthetics. Nonalcoholic liver cirrhosis was detected.

On hospital day (hd) 17, she developed acute, muscular respiratory failure under continuous positive airway pressure-assisted spontaneous breathing (CPAP-ASB) requiring

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intubation/mechanical ventilation. Clinical neurologic exam revealed hypermetropia, weakness for head anteflexion (M5-), weakness for elbow extension (M5-), reduced tendon reflexes, and male hair-type. Nerve-conduction studies revealed axonal neuropathy. Muscle biopsy revealed selective type-2 fiber atrophy, occasional COX-negative fibers, and deposition of complement complexes. Genetic panel for myopathy, neuropathy, and cardiomyopathy revealed the variants c.115G>C and c.1327G>T of unknown significance in *HNRNPDL* and *SETX*, respectively.

Extubation was unsuccessful two times and followed by a third intubation on hd 33 and tracheotomy. On hd 110, the patient was released with noninvasive ventilation (NIV) by a home-respirator. After a period of altogether 10 months, she could be weaned off NIV.

Despite a panel for myopathy, neuropathy, and cardiomyopathy, the cause of cardiomyopathy and primary myopathy could not be identified. *HNRNPDL* variants have been associated with autosomal-dominant limb girdle muscular dystrophy-1G and *SETX* variants have been associated with familial amyotrophic lateral sclerosis. However, the clinical presentation was neither compatible with limb girdle muscular dystrophy-1G[1] nor with familial amyotrophic lateral sclerosis.[2] Arguments in favor of a metabolic myopathy are previous reports about acute respiratory failure as a complication of metabolic myopathy,[3,4] the multisystem disease, the mother's history positive for statin-induced myopathy and dementia, deterioration of muscle weakness upon local anesthetics, statin-intolerance, noncompaction, and incompatibility of the variants with the patient's phenotype. Recovery from muscular respiratory failure may be attributed to ventilatory treatment and care,[5] heart failure therapy, exemplary compliance, or the reversible nature of muscle weakness.

This case shows that acute muscular respiratory failure may require traditional diagnostic work-up and long-term invasive/noninvasive ventilation, and that panel investigations not necessarily lead to a conclusive diagnosis.

Authors' Contributions

All authors contributed equally. J.F. and C.S. helped in clinical investigations, design, literature search, discussion, first draft, and critical comments.

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Conflict of Interest

None declared.

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