

## RYR1 myopathy complicated by RSV bronchiolitis requiring intubation leading to post-hypoxic leukoencephalopathy in a 4-year-old.

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### Introduction

Mutations in *RYR1* lead to a variety of clinical syndromes including central-core disease: an autosomal dominant or autosomal recessive myopathy which affects skeletal muscles. Baseline respiratory weakness due to central-core disease makes these patients more susceptible to respiratory failure due to what would often be incidental insults—such as bronchiolitis caused by RSV. Despite the frequency of respiratory insult requiring hospitalization in these patients, no specific guidelines exist regarding their respiratory support, largely due to the fact that central-core disease is a rare and vastly heterogeneous condition. We present the intensive care unit (ICU) management of respiratory failure in a patient with central-core disease and outline a unique radiographic finding which to date has not been described in the *RYR1* myopathy literature.

### Case Presentation

A 4-year-old, ex-33 week, medically fragile female with a history of central core disease secondary to autosomal recessive *RYR1* mutation presented to our institution with respiratory distress. Her baseline physical examination was significant for facial elongation and high arching palate. Skeletal muscle involvement of her myopathy included neuromuscular scoliosis, hypotonia, and bilateral hip subluxation. With respect to her activities of daily living, she was gastrostomy tube dependent; she was able to speak and sit on her own but required assistance in standing; she was unable to walk and had a power wheelchair. She was cognitively intact and able to use an iPad. Prior to hospitalization, the patient required nightly nasal BiPAP without oxygen supplementation as well as daily cough assist, albuterol, and glycopyrrolate.

Our patient initially presented to an outside emergency department with a three-day history of cough and hypoxia. Her brother who was ill earlier in the month, was

a notable sick contact. Upon initial evaluation, the patient was afebrile with a temperature of 99.1F, tachycardic with a heart rate of 175, and tachypneic with a respiratory rate of 22. Laboratory workup was significant for a venous blood gas of 7.29/58.3/32/28 on BiPAP with an FiO<sub>2</sub> of 60%. Her complete blood and comprehensive metabolic panel were both unremarkable. Respiratory viral panel was positive for respiratory syncytial virus (RSV). Chest X-ray demonstrated left sided superimposed pneumonia. Blood cultures were drawn and were ultimately negative.

Initial treatment in the emergency department included ceftriaxone and vancomycin. The patient was quickly transferred to our institution due to hypoxemic respiratory failure requiring pediatric ICU care.

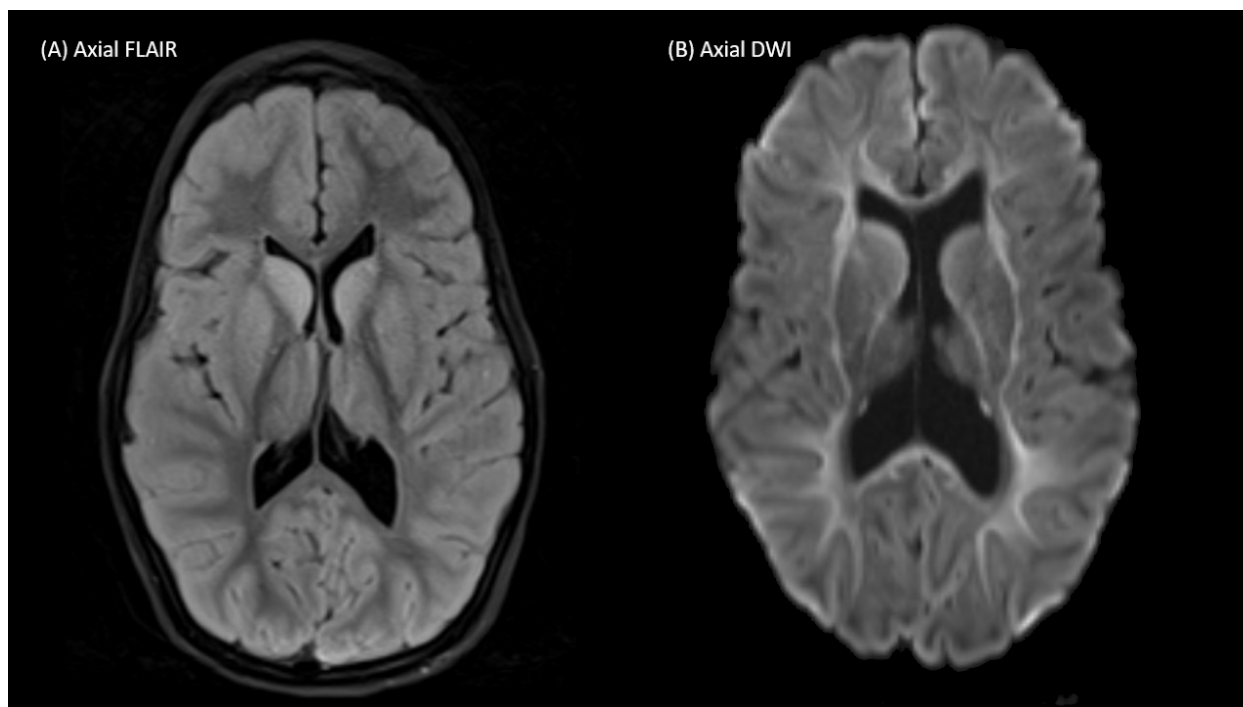
In transit, the patient's respiratory status deteriorated and her respiratory rate rose to the 60s with subcostal and intercostal retractions. Bag mask ventilation required two nurses due to dolichocephaly and elongated facial structure with successful endotracheal intubation.

On hospital day one, the patient required ETT replacement over a bougie due to the cuff on the ETT malfunctioning. The bougie was unable to be advanced fully into the tube due to resistance distal to cords. The patient's oxygen saturation dropped and bag mask ventilation met very high pressures and poor compliance. Eventually, resistance rapidly decreased indicating a likely displacement of a mucous plug. Saturations first improved, and then became unreadable and the patient entered asystole. A code was activated and ROSC was achieved after four minutes following three doses of epinephrine.

Over the next fourteen days, the patient had persistent pneumonitis with worsening infiltrates despite negative blood, urine, and respiratory cultures. Furthermore, the patient remained in relatively deep sedation despite discontinuation of dexmedetomidine. After fourteen days, the patient was deemed stable enough for an MRI to assess for anoxic brain injury following cardiac arrest. MRI and findings depicted in Figure 1.

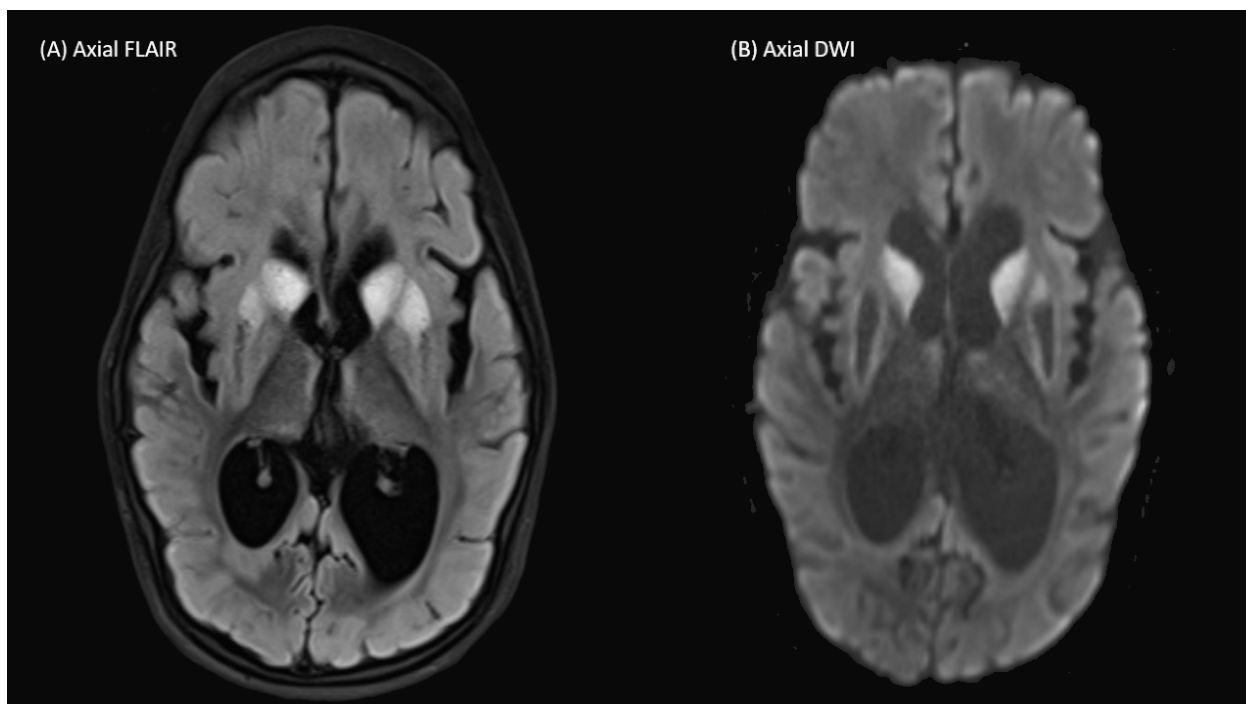
Over the next three months the patient continued to have a protracted ICU course. She developed multiple endotracheal tube-associated pseudomonas infections. She also had multiple failed extubations. She was successfully extubated after three months in the ICU and was eventually transferred to a local children's hospital for closer management from pediatric pulmonology. Prior to transfer, the patient had another MRI performed which is depicted in Figure 2.

At the children's hospital, the patient was gradually weaned down from her BiPAP requirement and eventually was stable on room air during the daytime. Her respiratory cares were gradually weaned and at discharge she was getting cough assist, vest therapy, 3% hypertonic saline, and levalbuterol Q 8 hours. For sialorrhea she was getting 1 mL of atropine per cheek Q 12 hours. Her neurological status was subdued following the hypoxic brain injury, for which



**Figure 1. MRI brain obtained fourteen days following cardiac arrest.**

Axial FLAIR (a) and DWI (b) images through the basal ganglia demonstrates symmetric FLAIR-DWI hyperintense signal abnormality predominantly involving the deep gray nuclei, consistent with sequelae of hypoxic ischemic injury, with extensive confluent DWI hyperintensity and diffusion restriction involving the deep cerebral white matter typical for post anoxic leukoencephalopathy.



**Figure 2. MRI brain obtained two months following cardiac arrest.**

Development of central volume loss with persistent FLAIR (a) and diffusion (b) hyperintense signal abnormality in the bilateral caudate and anterior putamen. New symmetric T1 hyperintensity was present in the striatum (not shown) consistent with superimposed mineralization. While volume loss and mineralization are likely attributable to the previous hypoxic-ischemic insult, persistent FLAIR-DWI signal abnormality is atypical in this timeframe and may reflect cell injury related to clinically reported genetic susceptibility to malignant hyperthermia (RYR1 gene mutation) or other toxic metabolic insult.

**Table 1: Summary of respiratory management.**

Time	Secretion management	Respiratory inhaler	Mechanical respiratory assistance	Humidifiers / nebulizers
Prior to hospitalization	Glycopyrrolate 1 mg/ 5 mL oral; 4 mL by mouth TID	Levalbuterol 45 mcg / inhalation. 2 puffs q6hrs, PRN	BiPAP	3% NaCl inhalation solution. 240 mL via nebulizer 2 times/day.
ICU stay	Dornase alfa 1 drop six times / day. Cough assist six times / day. Vest therapy BID. Atropine 1% ophthalmic solution 1 drop q12 hours.	albuterol (PROVENTIL) oral syrup 0.8 mg, 0.8 mg, Per G Tube, TID	Invasive ventilation => BiPAP	3% NaCl inhalation solution. 240 mL via nebulizer 4 times/day. 7% NaCl inhalation solution. 240 mL via nebulizer 2 times/day.
Upon discharge	Atropine 1% ophthalmic solution q12 hours.	Albuterol 90 mcg / inhalation. 2 puffs p4hrs, PRN	BiPAP	Levalbuterol .63 mg / mL inhalation via nebulizer. 3% NaCl inhalation solution. 240 mL via nebulizer 2 times/day.

she was discharged on amantadine to improve alertness. Two months post hospitalization, the patient had returned to her baseline neurologic function and motor function. A summary of the patient's respiratory management is presented in Table 1.

### Discussion

Central core disease is a congenital myopathy histologically characterized by cores of type I muscle fibers present in the center of myocytes.<sup>1</sup> Central core disease is caused by *RYRI* mutations, can be inherited in either an autosomal dominant or autosomal recessive fashion, and exhibits a relatively large spectrum of phenotypic manifestations.<sup>2,3</sup> Up to one third of patients with central cores due to *RYRI* mutation are asymptomatic and live normal lives.<sup>4</sup> In the mild form, muscular weakness has an adult onset, and patients have normal life expectancy. In more severe autosomal recessive cases, myopathy and weakness develop early in a patient's life.<sup>2</sup> In these cases, weakness accompanies a host of other aberrations including external ophthalmoplegia, bulbar involvement, scoliosis, and hip dislocation. A review of twenty-three patients with central core disease identified respiratory weakness in only 22% of those affected.<sup>5</sup>

Two features of the described case make it useful to the broader literature. First, the specific details of respiratory management utilized in our patients' care may serve as a model for future instances of children with severe *RYRI* myopathy hospitalized with bronchiolitis. Secondly, our case features the unique MRI brain finding of persistent bilateral caudate and putamen hyperintensity which cannot be explained by our patients' post-hypoxic leukoencephalopathy.

Post-hypoxic leukoencephalopathy is an entity characterized by neurological regression following an episode of hypoxia.<sup>6</sup> Diffusion-weighted imaging (DWI)

has allowed for greater characterization of post-hypoxic leukoencephalopathy as extensive restricted diffusion constitutes the most characteristic feature.<sup>6</sup> Our patient's initial MRI represented a typical signal of post-hypoxic leukoencephalopathy; however, persistence of signal abnormality in the deep gray nuclei two months following initial insult is unlikely to be attributable to her hypoxic insult. At the present time, there is not an obvious etiology of her abnormal signal persistence, and it may represent a sequela of her underlying *RYRI* myopathy, although this has not been reported. Comparisons with brain MRI of other children with *RYRI* myopathy may reveal an unreported susceptibility of the deep gray nuclei which would augment the current understanding of this condition.

There are no specific guidelines regarding the respiratory ICU management of patients with autosomal recessive *RYRI* myopathy. Much of the literature regarding ICU management of the neuromuscular patient comes from amyotrophic lateral sclerosis (ALS).<sup>7</sup> The manifestations of muscle weakness from ALS include diaphragmatic respiratory failure, inability to manage respiratory secretions, and bulbar weakness leading to aspiration.<sup>7</sup> Our patient had similar manifestations of muscular weakness. We found a combination of atropine drops and dornase alfa to be effective agents in controlling our patient's oral secretions. While these interventions cannot be directly attributed to our patient's recovery, this instance serves as an example of their successful use.

### Learning Points

1. Hypoxic leukoencephalopathy may have persistent MRI signal abnormalities in patients with *RYRI* myopathy.
2. Amantadine may improve decreased mental status due to hypoxic leukoencephalopathy.

3. Atropine and dornase alfa are agents to consider for management of copious secretions in the context of respiratory failure associated with *RYR1* myopathy.

### Citations

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