

# Fontan Failure Secondary to Charcot-Marie-Tooth–Induced Phrenic Neuropathy

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*Charcot-Marie-Tooth disease comprises a vast array of defects in myelin integrity that causes progressive peripheral sensorimotor neuropathy. It is the most prevalent inherited peripheral neuropathy, and it can affect the management of coexisting medical conditions. We report the case of a 25-year-old woman who had undergone successful Fontan surgery during childhood, but her Fontan circulation failed as a result of diaphragmatic paresis caused by Charcot-Marie-Tooth disease type 1A. This diagnosis precluded cardiac transplantation. (Tex Heart Inst J 2018;45(4):270-2)*

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**C**harcot-Marie-Tooth (CMT) disease is a heterogeneous group of hereditary motor and sensory neuropathies affecting 1 in 2,500 individuals.<sup>1</sup> Individuals with CMT can experience progressive, symmetric peripheral muscle weakness and atrophy. Manifestations include foot drop with a steppage gait, bilateral hand weakness, and often pes cavus foot deformity.<sup>2,3</sup> Nerve conduction slowing, resulting in sensory defects and skeletal deformities, may also be present.<sup>2</sup> Charcot-Marie-Tooth disease type 1A (CMT1A), the most prevalent subtype, results from a duplication of the peripheral myelin protein 22 (*PMP22*) gene,<sup>2</sup> which disrupts normal myelin synthesis.<sup>4-6</sup> In addition to a progressive ascending neuromyopathy, almost all patients with CMT1A have phrenic nerve conduction abnormalities,<sup>7,8</sup> which can alter the management of concomitant medical disorders.

Functional single ventricle is not generally associated with CMT disease. Most children with a single ventricle undergo the Fontan operation for definitive palliation, after which their pulmonary circulation and cardiac output rely on low-pressure passive flow of systemic venous blood through the lungs.<sup>9,10</sup> Thus, abnormal chest wall mechanics or diaphragmatic function can affect Fontan circulation. We report the case of a young woman who had undergone Fontan surgery during infancy and was diagnosed with CMT1A during her teens. Subsequent diaphragmatic paresis led to failure of her Fontan circulation.

## Case Report

A 25-year-old woman who had been born with pulmonary atresia with intact ventricular septum had undergone atrial septectomy and central aortopulmonary shunt placement shortly after birth. At 13 months of age, she underwent right-sided modified Blalock-Taussig shunt placement, and at 2.5 years of age, she had a fenestrated Fontan procedure with direct anastomosis of the right atrial appendage to the main pulmonary artery. Because of obstruction at the atrial-to-pulmonary connection, she needed urgent enlargement of that anastomosis with the addition of a bidirectional cavopulmonary (Glenn) anastomosis.

The patient also had a strong family history of CMT disease: her brother, father, and paternal grandmother had been diagnosed previously. At 14 years of age, the patient had no phenotypic manifestations but was genetically confirmed to have autosomal dominant CMT1A with *PMP22* duplication.

The patient did well until she was 19 years old, when large bilateral pleural effusions developed; the condition resolved after aggressive treatment with diuresis and paracentesis. Cardiac catheterization at the time revealed elevated right atrial pressure (mean, 17 mmHg), a low cardiac index of 1.8 L/min/m<sup>2</sup>, and a calculated pulmonary vascular

resistance of 5.6 Wood U•m<sup>2</sup>. She did well on outpatient medical management until she was 25 years old, when recurrent and persistent pleural effusions and abdominal ascites developed. On repeat cardiac catheterization, she had an elevated right atrial pressure (mean, 18 mmHg), a mean calculated pulmonary vascular resistance of 10 Wood U•m<sup>2</sup>, a left ventricular end-diastolic pressure of 6 mmHg, and a cardiac index of 1.2 L/min/m<sup>2</sup>. Her albumin (4.2–4.7 g/dL) and total protein (7.7–8.3 g/dL) levels were within normal limits, effectively ruling out protein-losing enteropathy. She underwent aggressive diuresis and was given sildenafil to treat elevated pulmonary vascular resistance. The change in the patient's clinical status prompted her medical team to recommend evaluation for heart transplantation, so she sought a second opinion at our institution.

Upon her initial cardiovascular consultation with us, the patient reported increasing abdominal girth, orthopnea, exertional dyspnea, the need for nocturnal oxygen, and wheelchair dependency. Her physical examination results were notable for obesity, kyphoscoliosis, limited pulmonary air entry bilaterally, peripheral edema, and ascites. A transthoracic echocardiogram revealed normal left ventricular size and function, no substantial valvular regurgitation, and a widely patent cavopulmonary anastomosis. Her right atrium was severely dilated.

The patient returned one month later for continued evaluation. Her examination was notable for an increase in oxygen requirements compared with that at baseline, as well as a concern for abdominal ascites, although ultrasonographic evaluation results showed no substantial fluid collection. Cardiac catheterization was considered; however, the patient's progressive and severe orthopnea would have prevented her from lying supine for the time

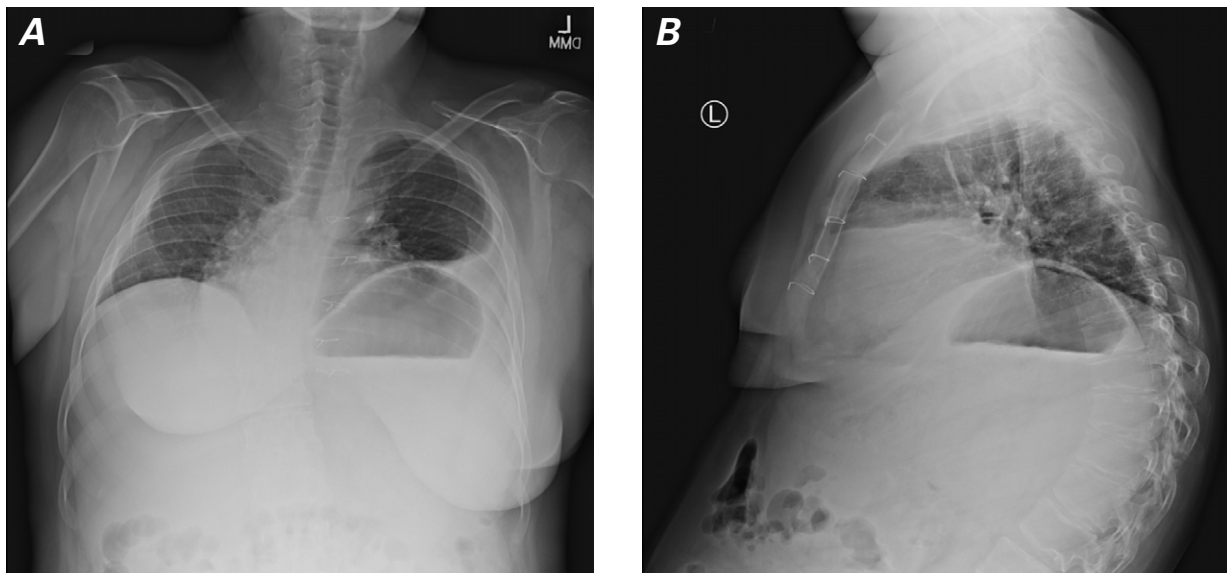
necessary to perform the procedure. A chest radiograph revealed a left pleural effusion with low lung volumes and bilateral hemidiaphragm elevation (Fig. 1). Her diaphragm function was subsequently evaluated through a fluoroscopic gastrointestinal sniff test, which revealed limited hemidiaphragm motion at rest and minimal, nonparadoxical excursion during deep inspiration with concomitant accessory muscle use. Finally, an ultrasound-guided diaphragmatic electromyogram revealed chronic bilateral phrenic neuropathies and atrophic hemidiaphragms, consistent with a demyelinating phrenic neuropathy secondary to CMT disease.

Because the patient's symptoms were caused chiefly by her progressive phrenic neuropathy and by severe CMT-induced diaphragmatic dysfunction, she was not considered a good candidate for cardiac transplantation. She subsequently returned to her referring institution for follow-up.

## Discussion

Unimpeded blood flow, normal systemic ventricular filling pressure, low intrathoracic pressures, and normal respiratory mechanics are important to maintain a functional Fontan physiology. Phrenic nerve paralysis has been identified as a risk factor for suboptimal Fontan hemodynamics.<sup>11</sup> To our knowledge, this is the first report of progressive phrenic nerve paresis caused by CMT1A in a patient with established Fontan circulation.

This case highlights how individual perturbations in basic respiratory mechanics can cumulatively affect Fontan circulation. Our patient's diaphragmatic weakness resulted in elevation and limited downward excursion of the hemidiaphragms, causing a reduction in lung



**Fig. 1** A) Posteroanterior and B) lateral chest radiographs show bilateral hemidiaphragm elevations, diminished lung volumes, bilateral pleural effusions, and kyphoscoliosis.

volumes with decreased alveolar distention, increased pulmonary vascular resistance, elevated Fontan pressures, and reduced cardiac output. Comorbid obesity and kyphoscoliosis further exacerbated the diminished lung volumes in our patient by changing the intrathoracic geometry and limiting chest wall expansion. In situations like this, the respiratory system begins to rely primarily on the accessory muscles of respiration, which may become fatigued over time, giving rise to respiratory failure.<sup>12</sup> Our patient's recurrent ascites and pleural effusions were not caused by protein-losing enteropathy, which is an uncommon but severe sequela of Fontan circulation that produces similar symptoms.<sup>13</sup>

Recognizing patients with diaphragmatic dysfunction may be challenging if the process progresses slowly, as it did in our patient. Regardless of the cause, the hallmark symptom of diaphragmatic paralysis is orthopnea.<sup>12</sup> Other symptoms include paradoxical abdominal movement during inhalation, diminished basilar breath sounds (on the affected side, if unilateral), exertional dyspnea, and fatigue.<sup>12,14</sup> The diagnosis is typically suspected on the basis of clinical presentation and radiographic evidence of at least one elevated hemidiaphragm. Radiographic findings of diaphragmatic paresis, however, are nonspecific and must be confirmed through a gastrointestinal sniff test or through electromyography, which is considered the gold standard.<sup>12</sup> Phrenic nerve conduction abnormalities precede diaphragmatic myopathy and are nearly universal in CMT1A.<sup>8</sup> Although there is no cure for CMT disease, patients with symptomatic diaphragmatic paralysis may benefit from positive-pressure ventilation.<sup>12</sup> In patients with Fontan physiology, however, positive-pressure ventilation impairs antegrade pulmonary blood flow. Other treatment options include diaphragmatic pacing (necessitating an intact phrenic nerve) and surgical plication.<sup>12,14</sup>

Since the description of the Fontan operation in 1971, morbidity and mortality rates have decreased in patients born with various types of single-ventricle physiology.<sup>10</sup> Proper patient selection has been paramount in improving postoperative morbidity and mortality rates,<sup>15</sup> particularly in regard to any comorbid conditions that can have long-term effects. Our patient's case calls attention to the adverse effects of advanced CMT1A-induced phrenic neuropathy and secondary diaphragmatic dysfunction; her progressive, incurable respiratory dysfunction not only caused failure of an established Fontan circulation, but also made her ineligible for cardiac transplantation.

Charcot-Marie-Tooth disease subtypes that result in near-universal progressive phrenic neuropathy may be considered a relative contraindication to the Fontan operation. However, our patient notably lived longer than 20 years without substantial morbidity; only after that time did progressive phrenic neuropathy affect her health. Her quality of life would probably have suffered

considerably in the absence of Fontan completion at a young age. Being aware that progressive phrenic neuropathy negatively affects Fontan homeostasis does not simplify patient selection, because there may be no family history of CMT disease, or the patient may have no signs or symptoms of disease during early childhood. Moreover, the rarity of CMT disease makes routine screening for such ailments before Fontan completion inadvisable.

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