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Case Report

Acute Liver Failure Due to Acute Heart Failure in Becker Muscular Dystrophy- A Case Report and Review of Acute Cardiac Failure in Liver Disease and the Dystrophin Deficient Cardiomyopathies

Shaun J Drabble[1] and David E Clarke[2]*

[1]*Department of Medicine, Dunedin Public Hospital, Dunedin, New Zealand*
[2]*Department of Hospital Medicine, VA Mather Medical Center, USA*

***Corresponding author**
David E. Clarke, VA Mather Medical Center, Department of Hospital Medicine, 10535 Hospital Parkway, Mather CA 95655, Assistant Clinical Professor of Medicine, UC Davis School of Medicine, Davis, CA, USA

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Abstract

A 34-year-old man with a history of Becker Muscular Dystrophy presented because of near syncope and with signs and symptoms of acute liver failure. He was subsequently found to be in acute heart failure with an estimated left ventricular ejection fraction (LVEF) of 10-15%. We discuss the rare presentation that is acute liver failure precipitated by acute heart failure, and we discuss the ongoing development in understanding of the pathophysiology of this occurrence. A review of the dystrophin deficient cardiomyopathies (primarily Duchene and Becker muscular dystrophy) is presented along with general guidelines for the treatment of these conditions.

CASE PRESENTATION

A 34-year-old man was admitted to hospital because of near syncope. He had a two week history of shortness of breath, chest pain, diarrhea, and vomiting. Four weeks previously he had presented to the emergency department of the same hospital complaining of increasing dyspnea with moderate exertion of two weeks' duration. The emergency department physician noted the patient's history of Becker muscular dystrophy (BMD). The evaluation of the patient in the Emergency department included a brain natriuretic peptide level (NT proBNP) which was elevated to 302 pmol/L (ref range <40), and the patient was advised he should be admitted to hospital for further evaluation and treatment of suspected congestive heart failure. The patient, likely not understanding the potential severity of the situation and feeling well after treatment in the ED, declined the admission and instead chose to follow up with an outpatient evaluation at a later date. The patient felt well for the following two weeks, but then two weeks prior to his current admission he began to experience nausea, vomiting, diarrhea, and shortness of breath. His stools became loose and pale and his urine became dark and foul smelling. He began to experience paroxysmal nocturnal dyspnea, and on several occasion felt very light headed and said he thought he was going to pass out. These symptoms prompted him to present to the Emergency Department. On examination in the Emergency Department on the day of his current admission he appeared unwell. His vital signs were: Glasgow Coma Scale (GCS) of 15, respiratory rate (RR) of 22 breaths per minute, oxygen saturation 96% breathing room air, blood pressure (BP) 109/72 mmHg, and temperature 36.4C. His tongue was dry. His jugular venous pressure (JVP) was elevated (though a measurement was not recorded). His chest had reduced air entry at the bases but no added sounds on auscultation, and his heart rhythm was regular with no murmurs or 4th heart sound present. His abdomen was soft, but he had generalized diffuse tenderness particularly in the right upper quadrant and epigastric regions. He had trace lower extremity edema. His past medical history was significant for congenital spondylolisthesis, an inguinal hernia and hydrocele repair at age two, and a diagnosis of BMD at age five (though signs and symptoms of the disease were present for a year or two before diagnosis). Laboratory studies (see table one) revealed an elevated troponin, White blood cell (WBC) Neutrophil count and C-reactive peptide protein (CRP), and his liver function tests demonstrated markedly elevated transaminases (ALT and AST), and he had acute kidney injury (AKI). The patient was admitted to the general medicine department.

Blood tests the next day revealed a marked increase in the transaminase and bilirubin levels (Table 1).

His International normalized ratio (INR) was also raised.

Table 1: Blood test results

Blood test	ED 4 weeks prior to admission	Admission to hospital	Day 1 of admission	Day before discharge	Units / Reference range
WBC	11.4	15.4	15.6	12.0	x 10^9/L (4.0 - 11.0)
Neutrophils	8.1	11.5	12.5	8.5	x 10^9/L (1.9 - 7.5)
NT proBNP	302	675		222	pmol/L (< 40)
CRP	4	31	33	11	mg/L (< 5)
hsTroponin T		54	43		ng/L (<15)
Bilirubin		48	66	33	umol/L (2 - 20)
GGT		63	67	87	U/L (10 - 50)
ALT		967	3046	60	U/L (0 - 40)
AST		529	2982		U/L (10 - 50)
Sodium	140	133	133	133	mmol/L (135 - 145)
Potassium	4.4	4.4	4.7	4.1	mmol/L (3.5 - 5.2)
Urea	4.7	9.7	12.6	5.6	mmol/L (3.2 - 7.7)
Creatinine	77	128	149	80	umol/L (50 - 110)
Estimated GFR	>90	63		>90	mL/min/1.73m2
INR			2.1	1.2	(2.0 - 3.0)

Hepatitis A, B and C serology results were negative and his paracetamol level was <33 umol/L. The patient denied taking any medication other than bisoprolol, including any over the counter medications, nor had he consumed any wild mushrooms. A point of care (POC) echocardiogram was performed which revealed a very poorly contracting left ventricle with an estimated ejection fraction of 10-20%. A formal echocardiogram was completed later that same day which demonstrated severe global left ventricular impairment, with an estimated left ventricular ejection fraction of 15-20% as well as severe right ventricular impairment. The patient was transferred to the intensive care unit (ICU) due to the worsening liver function tests and a rising lactate level (reaching 4.5 mmol/L). The patient was treated with Vitamin K, N-acetyl cysteine (NAC) infusion for an elevated paracetamol level of 82 umol/L (< 33), an ace inhibitor, and diurectics. This was followed by an infusion of dobutamine and levosimendan. Significant improvement in his clinical condition was noted over the next week, and his liver function tests had nearly normalized by hospital discharge one week later (Table 1).

Acute liver failure as the presentation of acute heart failure

Acute liver failure (ALF) is defined as the abrupt onset of severe hepatic injury with evidence of encephalopathy and impaired hepatic synthetic function [1,2]. It is rare, with an estimated incidence of between 1 and 6 cases per million persons per year [3]. Although it has a high mortality rate, survival from this devastating illness has been significantly improved with modern supportive treatment and liver transplantation [4]. In North America the majority of presentations are due to acetaminophen overdose (46%), as opposed to in Africa and Asia, where viral hepatitis predominates [4]. Ischemic hepatitis is responsible for only a minority (<5%) of acute liver failure [4]. Congestive heart failure as the cause for acute liver failure is exceedingly rare, with few documented cases [5]. Saner et al., in 2009 found that across a five year period 107 patients were admitted to their ICU in Germany for ALF, with congestive heart failure being the cause in only 13 of those cases. The mortality rate for these 13 patients was 54% [5].

The mechanism of exactly how congestive heart failure causes ALF is not well understood, but recent evidence suggests it is multifactorial in nature [6]. Prior to the year 2000, the main hypothesis was that a reduction in systemic blood flow (as seen in circulatory shock) induced ischemic hepatitis. In the year 2000, Seeto et al., demonstrated that a reduction in systemic blood flow alone was unlikely to induce the degree of ischemic hepatitis that would cause acute liver failure, and that the majority of patients who experienced severe ischemic hepatitis and acute liver failure also had significant venous congestion caused by congestive heart failure [7]. Recent literature supports this hypothesis; that right-sided congestive heart failure leads to hepatic venous congestion leaving the liver vulnerable to subsequent episodes of hypoperfusion [5,6,8].

Cardiac Disease in the Muscular Dystrophies

The muscular dystrophies are a group of related diseases characterized by weakness in the skeletal muscles [9]. They are caused by various types of mutations in the *DMD* gene resulting in abnormal quantity (or complete loss) or size of the protein dystrophin [10-12]. The dystrophin protein is located within the plasma membrane of skeletal and cardiac muscle cells, and functions to stabilize the plasma membrane by transmitting forces generated by the sarcomeric contraction to the extracellular matrix [12,13]. The most common form of the disease is Duchenne muscular dystrophy (DMD), an x-linked recessive disorder, in which mutations result in the loss of the protein dystrophin [11-13]. Becker Muscular Dystrophy is a less pronounced version of the disease and includes mutations which produce only a semi-functional dystrophin protein and like DMD it is X-linked recessive [11,12]. The dystrophin deficient muscular cells are weaker, and contraction of them causes membrane damage eventually leading to cell death. This skeletal and cardiac muscle cell death is the cause of progressive weakness and cardiac disease and leads to the eventual death of patients with DMD and BMD [13]. Patients with DMD commonly develop muscle weakness at an early age and most have lost the ability to ambulate by age 10-12 years of age. Many will begin

to develop cardiomyopathies by age 10, and most will have cardiomyopathies by their second decade.[10,13] Whereas in the past, death was most commonly the result of respiratory failure, with current respiratory supportive measures cardiac failure is now the most common cause of death [9,13]. Patients with BMD often do not present with muscle weakness until later in life, compared with patients who have DMD [13]. The incidence of cardiac involvement in patients with BMD is also high, and as with DMD cardiac failure is the most common cause of death [9,13].

Consensus guidelines currently recommend referral to a cardiologist at the time of diagnosis of a muscular dystrophy, and then regular surveillance for cardiac disease with yearly cardiac echocardiograms and electrocardiograms [13,14]. Treatment of DMD and BMD cardiomyopathies often begins with corticosteroids, which since the 1980's were believed to have significant benefits in DMD and BMD [15]. In the early 2000's more conclusive evidence emerged demonstrating corticosteroids improved skeletal muscle function as well as cardiac function and delayed the onset of cardiomyopathy in patients with DMD [13]. ACE inhibitors prevent the progression of cardiac disease in muscular dystrophies, and it is recommended they be commenced from age 10 in asymptomatic individuals, or even earlier in symptomatic individuals [13,14,16]. Additional treatment with an aldosterone inhibitor is recommended in patients with a reduced LVEF <35%, but may also be beneficial to DMD and BMD patients before they reach this point [13]. The use of beta-blockers in the treatment of dystrophin-deficient cardiomyopathies is controversial, with some studies suggesting a benefit to their use, and others demonstrating no difference when added to ACE inhibitor therapy [17,18]. Although more definitive evidence is needed, in patients with DMD and BMD who have impaired left ventricular function, beta-blockers are recommended along with the aforementioned ACE inhibitors, steroids, and aldosterone inhibitors [13]. Patients with DMD and BMD who have symptomatic congestive heart failure are treated in the same manner as patients with heart failure from other (for example, ischemic) etiologies. Ultimately, cardiac transplantation is a viable option and the definitive treatment particularly in patients with BMD with less skeletal muscle weakness [19].

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