

# Cardiac monitoring and treatment for children and adolescents with neuromuscular disorders

Over recent decades, cardiology has evolved into a highly evidence-based specialty. Guided by the results of large, multicentre, randomized trials of patients with common conditions, cardiologists are usually in the happy position of knowing how best to treat patients, once they have been diagnosed with various conditions or are deemed at risk of developing them. This has led to the implementation of standardized approaches to treatment. The progressive uniformity of care has improved outcomes – preserving quality of life and prolonging survival. Arguably, however, cardiologists are now less comfortable in situations of clinical uncertainty, when evidence is inadequate or does not exist to guide decision making. This is well illustrated by the difficulty experienced by many patients in obtaining appropriate care for the cardiac aspects of a neuromuscular disorder. From a patient's perspective, cardiologists seem unfamiliar with their condition and, usually, to favour therapeutic nihilism.

The heart is almost always affected by a progressive cardiomyopathy in Duchenne muscular dystrophy (DMD), the most common form of inherited muscle disease, resulting from the absence of the protein dystrophin on cell membranes.<sup>1–4</sup> Affected individuals typically lose ambulation and become wheelchair-dependent around the age of 12 years and die from cardiorespiratory failure at around 20 years of age.<sup>3</sup> On echocardiography, 25% of patients have evidence of left ventricular dysfunction by age 10 years, and an even higher percentage when more sensitive imaging techniques are used.<sup>2–6</sup> However, symptoms only develop when left ventricular ejection fraction has fallen to between 10 and 15%, around 18 years of age. Although symptoms can be improved by cardio-active treatments, introduced at this late stage, most patients still die within the next year. With a multidisciplinary approach to overall management, over the last 10 years, survival has improved steadily for DMD patients. This has come about, not through any single therapeutic breakthrough, but through the routine use of treatments already available, i.e. nocturnal ventilatory support for respiratory muscle weakness, steroid therapy to bolster muscle strength, and orthopaedic procedures to correct scoliosis.<sup>7</sup> With increased quality of life and prolonged survival, however, heart failure and arrhythmias now contribute more directly to premature death. Yet, most cardiologists are unfamiliar with the nature of cardiac involvement in DMD and its management. Cardiologists would treat similar degrees of left ventricular dysfunction aggressively in other contexts, but concerns about possible side effects seem to dominate therapeutic decisions in DMD, perhaps because of its more obvious outward manifestations.

In the various forms of dilated cardiomyopathy, for

example, initiating therapy at the pre-symptomatic stage of left ventricular dysfunction is known to delay the onset of cardiac failure and improve prognosis.<sup>8–14</sup> Combination therapy with an angiotensin-converting enzyme (ACE) inhibitor<sup>8–10</sup> and non-selective beta-blocker<sup>11–13</sup> has been established management practice for some time. Spironolactone or eplerenone is often added to prevent 'ACE-escape' and reduce fibrosis.<sup>14</sup> Whether the benefits of these cardio-protective therapies will apply equally in cardiac dystrophinopathy has not been established. However, there is some evidence in DMD that the rate of deterioration of heart function can be slowed by ACE-inhibitors<sup>15</sup> and, from rich experience of both ACE-inhibitors and beta-blockers in children with other conditions, they are safe and well tolerated. It seems logical and clinically appropriate, therefore, for cardiologists to discuss the introduction of these therapies routinely, regardless of symptoms, once left ventricular dysfunction is evident in DMD.<sup>16</sup>

Furthermore, based upon current molecular biological understanding of the evolution of cardiomyopathy, the impact of therapies may be even greater, for example, if introduced even before left ventricular dysfunction is evident by echocardiography.<sup>5</sup> In the only clinical trial published to date of prophylactic cardio-active therapy in DMD, Duboc et al. reported that perindopril delayed the onset of cardiac involvement when introduced before any was evident by radionuclide ventriculography.<sup>17</sup> Although subsequently criticized, these results provide the first 'proof of concept' to counterbalance the traditional nihilism surrounding the management of heart involvement in DMD. A larger, randomized, placebo-controlled, UK study is already underway to evaluate the benefits of combined ACE-inhibitor and beta-blocker therapy in a similar DMD cohort. The results of other trials, to determine whether steroid regimes deployed to improve skeletal muscle strength have cardio-protective effects, should be reported over the next few years.

Managing cardiac involvement in neuromuscular disorders is a new frontier in the overlap between cardiology, neuromuscular genetics, and neurology. Cardiologists need to become familiar with these conditions and the implications for their practice. There is much they can offer already, while awaiting the outcome of fundamental research and clinical trials already under way.

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*The references for this Commentary can be found on page 212.*