

# Treatment of the heart in Duchenne muscular dystrophy

Duchenne muscular dystrophy is the most common life-limiting muscle disorder of childhood. Survival has improved, largely due to more effective orthopaedic and respiratory management. However, abnormal cardiac muscle function (cardiomyopathy) develops in most patients by the age of 18 years and can cause heart failure, leading to 10–40% of deaths. This percentage may be increasing as management of the respiratory complications becomes more successful.<sup>1</sup> As a result, in 2003 a European group recommended an ECG and echocardiogram at diagnosis, then every 2 years until the age of 10, and annually thereafter. If progressive abnormalities occurred they recommended treatment with angiotensin-converting enzymes (ACE) inhibitors and, if needed, beta-blockers. They commented that there was no evidence behind these recommendations and called for multicentre trials.<sup>2</sup> At the end of 2005, the Cardiology section of the American Academy of Pediatrics published similar recommendations and commented on the minimal evidence base.<sup>1</sup> However, as shown by the review article by English and Gibbs in this issue, not all cardiologists agree with these guidelines.

In 2005 several studies were published on different aspects of treatment and prevention. In patients with abnormal echocardiograms, a retrospective uncontrolled study with an average follow-up of 3 years reported significant improvements in a range of echocardiographic parameters during treatment with several ACE inhibitors.<sup>3</sup> Using a different technique, radionuclide ventriculography, in younger males with initially normal cardiac function, a prospective randomized double-blind trial of another ACE inhibitor against placebo over 3 years found no difference in outcome between the two groups. Over the next 2 years in an extension open label study, all the participants received active treatment. At the end there was no significant difference in mean values between the two groups, but significantly more males in the initially untreated group had abnormally poor results and after a further year's follow-up three of the latter died from heart failure. The investigators, who were partially supported by the drug manufacturer, concluded that early treatment delayed the onset and progression of prominent left ventricular dysfunction in children with Duchenne muscular dystrophy.<sup>4</sup> Unfortunately, there are a number of shortcomings in statistical terms which render interpretation difficult (McGuigan, 2006 personal communication). Finally, neither of these papers mention steroid therapy, but a large retrospective survey with a control group, using another echocardiographic measure, reported significant benefits. Intriguingly, a small subgroup treated for an average of 4 years, who then discontinued steroids due to side effects, still had normal values an average of 6 years later, which were no different from those who had continued with treatment.<sup>5</sup> Could a period of prophylactic therapy with either ACE inhibitors or steroids at a critical period in childhood have benefits later on?

The situation is confusing, not least between treatment

and prevention. Guidelines for screening and treatment have been proposed, and promoted by at least one patient group,<sup>6</sup> without an evidence base. Screening will demonstrate abnormalities in a high percentage of patients, which may create anxiety and has resource implications. Different studies use different tests of cardiac function, and our reviewers recommend another, but it is unclear if these are all equivalent in clinical terms. Classically, screening is only justified if there is an effective treatment, but we do not know if ACE inhibitors are or are not effective. In terms of prevention, McGuigan comments that a more appropriate statistical analysis of the randomized trial phase of ACE inhibitors might allow a more reliable conclusion. If ACE inhibitors or steroids do help, the guidelines need rewriting.

Clearly there are several important issues that need proper trials for answers. In the meantime, patients and their families need sufficient information to decide whether or not to accept screening. It reinforces the need for guidelines to specify the level of evidence on which they are based in a prominent position adjacent to their recommendations, as for example in the SIGN guidelines. In addition, SIGN emphasizes the need for consultation and consensus before guidelines are agreed, to avoid dominant groups or individuals having a disproportionate influence.<sup>7</sup> Is it now time that just as the raw evidence is graded according to formal criteria, guidelines should be too?

Peter Baxter

DOI: 10.1017/S0012162206000351

## References

- American Academy of Pediatrics Section on Cardiology and Cardiac Surgery. (2005) Cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy. *Pediatrics* **116**: 1569–1573.
- Bushby K, Muntoni F, Bourke JP. (2003) 107th ENMC International Workshop: the management of cardiac involvement in muscular dystrophy and myotonic dystrophy. 7th–9th June 2002, Naarden, the Netherlands. *Neuromuscul Disord* **13**: 166–172.
- Jefferies JL, Eidem BW, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. (2005) Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy. *Circulation* **112**: 2799–2804.
- Duboc D, Meune C, Lerebours G, Devaux JY, Vaksman G, Becane HM. (2005) Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol* **45**: 855–857.
- Markham LW, Spicer RL, Khoury PR, Wong BL, Mathews KD, Cripe LH. (2005) Steroid therapy and cardiac function in Duchenne Muscular Dystrophy Pediatric Cardiology; July 4 (Epub ahead of print).
- PPUK Muscular dystrophy. Heart difficulties. <http://www.ppek.org/site.php?action=page&pageID=109> (accessed January 2006).
- SIGN. (2001) Sign 50: A guideline developers' handbook. <http://www.sign.ac.uk/guidelines/fulltext/50/> (accessed January 2006).