

Letters to the editor

Steroids in Duchenne muscular dystrophy



In his commentary [1] on our recent publication on glucocorticoids in Duchenne muscular dystrophy (DMD) [2], Professor Dubowitz raises the interesting possibility that the prolonged ambulation in Duchenne boys on continuous therapy in contrast to the intermittent schedule may be related to the marked stunting of growth secondary to the higher dose of corticosteroid in the former therapy.

That height could have an effect on the clinical course of Duchenne muscular dystrophy has been suggested and explored in the past. One of the first observations was from Zatz et al. who reported one patient with congenital growth hormone deficiency in whom the disease course was clearly milder than in his siblings and cousins also affected by DMD but not by the growth hormone deficiency [3]. The same group subsequently published a study showing a significant negative correlation between height vs. motor ability, and weight vs. clinical course, suggesting that heavier patients had poorer performance, and that smaller boys had a slower progression of the disorder [4]. It is however important to highlight that height and weight were reported as actual values and were not converted to standard deviations; additionally their analysis did not take into account the age difference of the 93 patients studied (2–23 years); finally functional scores were not correlated to the BMI.

Another issue, which should be taken into consideration, is that growth in these children occurs alongside muscle destruction, as a continuous phenomenon, and even with the most sophisticated statistical analysis, it may be challenging to interpret when a change occurs over time in relation to each other. In a longitudinal study on the 6-min walk distance (6MWD) test, comparing 18 boys with either Duchenne or Becker muscular dystrophy on steroids and 22 healthy controls, McDonald et al. reported that the major determinant of change in 6MWD was stride length; and changes in stride length in boys with muscular dystrophy were primarily dependent upon age-related disease progression, and not height. In this study, heights increased equally in both muscular dystrophy boys and healthy controls; but while stride length increased in healthy controls, it decreased in boys with dystrophy [5]. However, these boys were followed for a limited time only, which could explain why growth showed a similar pattern to healthy controls. Nevertheless, what this study

shows is that growth occurs at the same time as progressive muscle weakness.

An additional factor, which complicates things further, is the use of steroids. It is unequivocal that long-term daily use of steroids slows the progression of the disorder, but it also has a substantial detrimental effect on growth. A recent study comparing treated and untreated DMD boys with daily deflazacort, showed that by the age of 15 years, boys on treatment were 21 cm shorter, which is a significant growth stunt [6]. Boys on steroids also showed significant preservation of motor and respiratory function over time, and delayed loss of ambulation.

In our manuscript we reported that boys on continuous prednisolone demonstrated a slower decline on the NorthStar Ambulatory Assessment (NSAA). Maximum function was the same for both regimens, which was achieved between 6 and 7 years of age; however once decline started, boys on intermittent prednisolone lost function more rapidly. In our paper for boys over seven years of age we quoted an interaction coefficient between the two regimens of 1.58, (95% CI 1.04, 2.11), meaning that boys treated with an intermittent regimen decline 1.58 NSAA units more every year ($p < 0.001$) than those on daily regimen. For this statistical model we adjusted for duration of treatment. Additionally, adjusting our analysis for standardised BMI, we found a similar interaction coefficient (1.45, 95% CI 0.89, 2.01, $p < 0.001$). We therefore concluded that the overall results were consistent, irrespective of the BMI.

In relation to growth, not surprisingly after a mean duration of four years of treatment, we found that the BMI was significantly higher in boys treated with daily (mean z -score 1.99, 95% CI 1.79, 2.19) than intermittent corticosteroids (mean z -score 1.51, 95% CI 1.27, 1.75) and height restriction was much more severe in boys on daily (mean z score -1.77 , 95% CI -1.79 , -2.19) than intermittent prednisolone (mean z -score -0.70 , 95% CI -0.90 , -0.49). However, even when we adjusted our model taking in consideration the height discrepancy, we came to the same conclusion; in other words that boys on daily steroids are slower to decline in terms of their ambulatory function.

Enthused by Professor Dubowitz' suggestion, we analysed the data further from a different perspective by exploring the relationship between height and motor function, irrespective of steroid regimen. In our analysis we included the whole DMD population previously

studied, and after adjusting our analysis for age and treatment regimen, we found a negative interaction coefficient of -0.42 (95% CI $-0.85, 0.01$; $p = 0.06$) suggesting that as height increases in these boys, the NSAA total score falls, implying a more rapid decline.

We found a similar conclusion for BMI, although the effect for BMI was greater than for height (interaction coefficient -0.73 , 95% CI $-1.19, -0.26$; $p = 0.002$). However, what our analysis supports is that progressive muscle weakness indeed occurs at the same time as growth, but not that one is the direct consequence of the other.

In conclusion, the question remains yet to be answered; what is perhaps required to address this intricate issue is a stratification of patients by height and by steroid profile to analyse their disease progression (including strength) in a more systematic way. Furthermore, what is yet poorly understood is the impact that short stature (and excessively increased BMI) can have on boys and young men with DMD. If on the one hand a daily regimen can preserve muscle function better, the alternative is a body image that can be very discomfoting in some boys. As a consequence, we are now observing an emerging interest for the use of growth hormone as a potential treatment for glucocorticoid-induced growth failure, which of course comes with its side effects [7].

The international clinical trial of different corticosteroids regimens funded by the National Institute of Health (FOR-DMD), with all UK sites now open to recruitment [8], purposely aims at elucidating these yet unexplored areas; including the role that height may play on strength and function, and the implication of different corticosteroid regimens on quality of life. Indeed FOR-DMD will prospectively and systematically assess not only the benefits but also the perceived burdens of different regimens' long-term effects, adding therefore an important perspective to the debate on the optimal corticosteroid regimen.

References

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Response



I am grateful to Dr. Ricotti and her colleagues [1] for their comments and for the further analysis of their data in relation to my hypothesis and look forward to their additional cumulative data in the future.

I am also pleased that the NIH study has included quality of life issues, which have been largely ignored in earlier studies. I personally remain doubtful that there is a holy grail for long-term corticosteroid treatment of Duchenne dystrophy and anticipate that after completion of the NIH study, Duchenne parents will still be faced with weighing the potential benefits against the serious side effects of long-term continuous corticosteroid therapy, which, in addition to stunting of growth, also include suppression of puberty and severe osteoporosis, with painful collapse of vertebrae.

Reference

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