Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 24 (2014) 201–206

www.elsevier.com/locate/nmd

Reliability of the Performance of Upper Limb assessment in Duchenne muscular dystrophy

Marika Pane [a], Elena S. Mazzone [a], Lavinia Fanelli [a], Roberto De Sanctis [a], Flaviana Bianco [a], Serena Sivo [a], Adele D'Amico [b], Sonia Messina [c], Roberta Battini [e], Marianna Scutifero [d], Roberta Petillo [d], Silvia Frosini [e], Roberta Scalise [a], Gianluca Vita [c], Claudio Bruno [f], Marina Pedemonte [f], Tiziana Mongini [g], Elena Pegoraro [h], Francesca Brustia [i], Alice Gardani [i], Angela Berardinelli [i], Valentina Lanzillotta [g], Emanuela Viggiano [d], Filippo Cavallaro [c], Maria Sframeli [c], Luca Bello [j], Andrea Barp [j], Serena Bonfiglio [k], Enrica Rolle [l], Giulia Colia [b], Michela Catteruccia [b], Concetta Palermo [a], Grazia D'Angelo [j], Antonella Pini [k], Elena Iotti [m], Ksenija Gorni [l], Giovanni Baranello [m], Lucia Morandi [m], Enrico Bertini [b], Luisa Politano [d], MariaPia Sormani [n], Eugenio Mercuri [a,*]

[a] *Child Neurology and Psychiatry Unit, Rome, Italy*
[b] *Unit of Neuromuscular and Neurodegenerative Diseases, Department of Neurosciences, Bambino Gesù Childrens Hospital, Rome, Italy*
[c] *Department of Neurosciences, Psychiatry and Anaesthesiology, University of Messina, Italy*
[d] *Department of Experimental Medicine, University of Naples, Italy*
[e] *Department of Developmental Neuroscience, Stella Maris Institute, Italy*
[f] *Neuromuscular Disease Unit, G. Gaslini Institute, Genoa, Italy*
[g] *Neuromuscular Center, SG. Battista Hospital, University of Turin, Italy*
[h] *Department of Neurosciences, University of Padua, Italy*
[i] *IRCCS "C. Mondino" Foundation, Pavia, Italy*
[j] *IRCCS Eugenio Medea, Bosisio Parini, Italy*
[k] *Child Neurology and Psychiatry Unit, IRCCS Institute of Neurological Sciences, Bellaria Hospital, Bologna, Italy*
[l] *Centro Clinico Nemo, Milan, Italy*
[m] *Pediatric Neurology and Neuroradiology Units, Neurological Institute C. Besta, Milan, Italy*
[n] *Biostatistics Unit, Department of Health Sciences, University of Genoa, Italy*

Received 18 October 2013; received in revised form 15 November 2013; accepted 25 November 2013

Abstract

The Performance of Upper Limb was specifically designed to assess upper limb function in Duchenne muscular dystrophy. The aim of this study was to assess (1) a cohort of typically developing children from the age of 3 years onwards in order to identify the age when the activities assessed in the individual items are consistently achieved, and (2) a cohort of 322 Duchenne children and young adults to establish the range of findings at different ages. We collected normative data for the scale validation on 277 typically developing subjects from 3 to 25 years old. A full score was consistently achieved by the age of 5 years. In the Duchenne cohort there was early involvement of the proximal muscles and a proximal to distal progressive involvement. The scale was capable of measuring small distal movements, related to activities of daily living, even in the oldest and weakest patients. Our data suggest that the assessment can be reliably used in both ambulant and non ambulant Duchenne patients in a multicentric setting and could therefore be considered as an outcome measure for future trials.

Keywords: Upper limb; Duchenne muscular dystrophy

* Corresponding author. Address: Department of Child Neurology, Policlinico Gemelli, Largo Gemelli 00168, Rome, Italy. Tel.: +39 06 30155340; fax: +39 06 30154363.
E-mail address: mercuri@rm.unicatt.it (E. Mercuri).

0960-8966
http://dx.doi.org/10.1016/j.nmd.2013.11.014

1. Introduction

In the last few years a number of therapeutical approaches have become available for Duchenne muscular dystrophy (DMD). The rapidly increasing number of ongoing or planned clinical trials has highlighted the need to identify reliable outcome measures [1,2]. So far the trials have mainly targeted young ambulant DMD boys [3,4], using the 6 min walk test (6MWT) [5,6] or other functional measures such as timed tests or the North Star Ambulatory Assessment (NSAA). In order to have the possibility to also include non ambulant DMD boys and adults in the forthcoming trials, and, more generally, to have measures that could be used across spectrum of abilities, allowing to follow the boys who may lose ambulation during a trial, there has been increasing attention on assessments of upper limb function [7]. An international Clinical Outcomes Group consisting of clinicians, scientists, patient advocacy groups and industries worked together to develop the Performance of the Upper Limb (PUL), a tool specifically designed for assessing upper limb function in ambulant and non-ambulant DMD patients [8–10]. The development of the PUL was based on a conceptual framework reflecting the progression of weakness and natural history of functional decline in DMD. The DMD boys and their families were involved iteratively throughout the process, providing comments on the relevance of individual PUL items to abilities of daily living and on their clinical meaningfulness. Modern psychometric methods (Rasch analysis) were used to improve robust internal reliability, validity, and hierarchical scalability [10].

All the tasks included in the PUL were selected including activities of daily living that should be performed even by preschool children. We were postulating that typically developing children of 3–4 years of age would pass all the items and complete the scale with a plateau of scores in older children. In order to avoid ceiling effect we also included timed items evaluating the speed to perform some tasks such as stacking cans.

The aim of this cross sectional study was to perform PUL in DMD boys and adults and in typically developing boys and male adults in order to observe the distribution of scores and the suitability of the scale at different ages. More specifically we wished to establish (a) the age when typically developing children are able to complete the assessment (b) the profile of scores in DMD boys and adults at different ages and their relationship with the scores found in typically developing subjects. We also wished to investigate whether the timed items could provide additional value to the scale avoiding possible ceiling effect.

2. Subjects and methods

The study is part of a longitudinal multicentric study aimed at establishing changes in upper limb function in DMD. The study was approved by the Ethics committee in each centre. As part of this study all the Italian tertiary care centers for neuromuscular disorders consecutively enrolled 322 DMD patients (mean age 12.7; range 4.1–35.1) attending their routine follow up clinics between September 2012 and April 2013.

In order to establish the earliest age when the PUL can be completed, 277 typically developing boys and young adults were also examined by six examiners from 3 centers (Rome, Milan, Pisa) involved in the DMD study. In the first phase we systematically assessed children up to the age of 5, assessing 47 children between 3 and 5 years. Following the observation that there was already a plateau of full scores by 5 years, we also performed the PUL in 230 boys and young adults between the age of 5 and 25 in order to confirm the plateau in subjects older than 5 years and observe possible variations of the timed items with age.

2.1. PUL

The PUL includes 22 items (online appendix) with an entry item to define the starting functional level, and 21 items subdivided into shoulder level (4 items), middle level (9 items) and distal level (8 items) dimension [10]. For weaker patients a low score on the entry item means high level items do not need to be performed. Scoring options vary across the scale between 0–1 and 0–6 according to performance. Each dimension can be scored separately with a maximum score of 16 for the shoulder level, 34 for the middle level, and 24 for the distal level. A total score can be achieved by adding the three level scores (max global score 74).

2.2. Training sessions

At least one therapist from each group attended a first training session where a senior physiotherapist (ESM) presented the PUL with item description, scoring system and demonstrated scale administration through patient videos to outline any scoring shortcomings or issues. All participants were subsequently asked to video a patient assessment. After a review with the senior physiotherapist and the resolution of possible scale administration issues, the 14 clinical evaluators were then asked to score three more videos to outline any difficulties and possible lack of agreement in scores and to determine inter-rater reliability. The results showed an ICC of 0.96.

Three examiners (ESM, LF, RDS) also assessed six children twice with intervals ranging from 1 h to 1 week with identical results between the first and the second assessment in all six.

2.3. Statistical analysis

Non-linear relationships with age were preliminarily assessed by a visual inspection of the plots and then analyzed using a piecewise linear regression. A piecewise

regression model allows for changes in slope and consists of two or more straight line segments.

Following recent evidence that when examined on the 6MWT, the NSAA and timed items, the slope of deterioration in DMD boys occurs after the age of 7 [11,12], we also arbitrarily subdivided the cohort in very young boys (<5), 5–7.9, 8–12.9, 13–21 and above 21 years.

3. Results

3.1. Typically developing boys and young adults

In this cohort all were able to complete the assessment and none refused to perform it. All but 27 (>90%) had a full score or one point less (73 or 74 out of 74). The 27 boys who had a score lower than 73 were all younger than 5 years and the items that did not have a full score were stacking cans as the children were too short to stack the last cans remaining seated and holding the bigger weights, opening a Ziploc container or tearing a piece of paper because of the small hand size. The sub scores of typically developing and DMD subjects subdivided according to functional levels (shoulder, middle and distal) are shown in Fig. 1.

3.2. DMD patients

The total scores ranged between 0 and 74 with a progressive decrease after the age of 8. (Fig. 2 and Table 1).

3.3. Shoulder level

The results of the piecewise regression analysis showed an improvement of scores in the younger DMD children. The point of slope change was between 9 and 10 years with and a sharp decline after that with very low scores (2 or less) by the age of 16 years (Fig. 1a).

3.4. Middle level

There was an improvement of scores in the younger children and the point of slope change was between 8

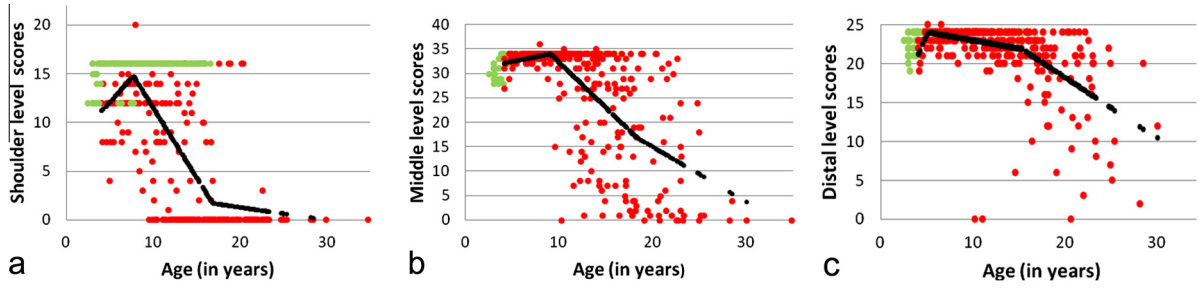

Fig. 1. Distribution of scores in typically developing (green) and DMD (red) subjects at shoulder (a), middle (b) and distal (c) level.

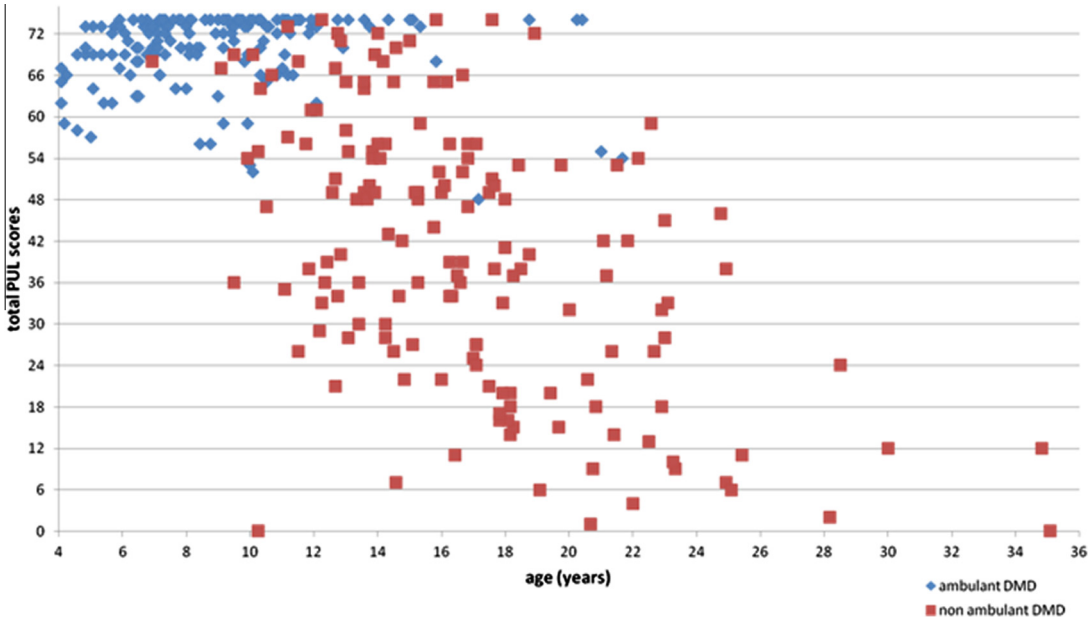

Fig. 2. Total scores in ambulant (blue) and non ambulant (red) DMD patients plotted according to age.

and 9 years, with a subsequent progressive decline (Fig. 1b).

3.5. Distal level

There was an improvement of scores in the younger children with a first point of slope change around 6 years, followed by a mild decline and a second point change associated with a sharper decline around 16 years (Fig. 1c).

3.6. Timed items

Fig. 3 shows the distribution of the time spent to perform the individual items (I, J, K, L) in typically

Table 1
Distribution of total scores and of the subscores in the three levels subdivided according to age groups in typically developing and DMD subjects.

Age (yrs)		Shoulder		Mid level		Distal		Total	
		Control ($n = 277$)	DMD ($n = 322$)	Control	DMD	Control	DMD	Control	DMD
<5		($n = 47$)	($n = 11$)	($n = 47$)	($n = 11$)	($n = 47$)	($n = 11$)	($n = 47$)	($n = 11$)
	Range	12–16	8–16	28–34	27–34	19–24	19–24	60–74	58–73
	Mean (SD)	14.8 (1.72)	11.81 (2.27)	31.8 (1.9)	32.09 (2.3)	23 (1.35)	22.27 (1.67)	69.68 (4.23)	66.18 (4.79)
5–7, 9		($n = 66$)	($n = 62$)	($n = 66$)	($n = 62$)	($n = 66$)	($n = 62$)	($n = 66$)	($n = 62$)
	Range	16	3–16	33–34	24–34	23–24	19–24	73–74	56–74
	Mean (SD)	15.81 (0.83)	13.69 (2.71)	33.8 (0.85)	33.08 (1.41)	23.92 (0.26)	23.46 (0.88)	73.36 (1.21)	70.27 (3.79)
8–12, 9		($n = 107$)	($n = 112$)	($n = 107$)	($n = 112$)	($n = 107$)	($n = 112$)	($n = 107$)	($n = 112$)
	Range	16	0–16	34	0–34	23–24	0–24	73–74	0–74
	Mean (SD)	16 (0)	11.01 (5.92)	34 (0)	30.79 (7.21)	23.96 (0.19)	22.99 (2.5)	73.96 (0.25)	64.81 (13.94)
13–21, 9		($n = 42$)	($n = 115$)	($n = 42$)	($n = 115$)	($n = 42$)	($n = 115$)	($n = 42$)	($n = 115$)
	Range	16	0–16	34	0–34	23–24	0–24	73–74	1–74
	Mean (SD)	16 (0)	3.2 (5.79)	34 (0)	20.77 (12.05)	23.82 (0.38)	20.45 (4.28)	73.82 (0.38)	44.43 (19.47)
>21		($n = 15$)	($n = 22$)	($n = 15$)	($n = 22$)	($n = 15$)	($n = 22$)	($n = 15$)	($n = 22$)
	Range	16	0–3	34	0–33	24	0–24	74	0–54
	Mean (SD)	16 (0)	0.13 (0.63)	34 (0)	8.31 (10.88)	24 (0)	13.77 (7.34)	74 (0)	22.22 (17.52)

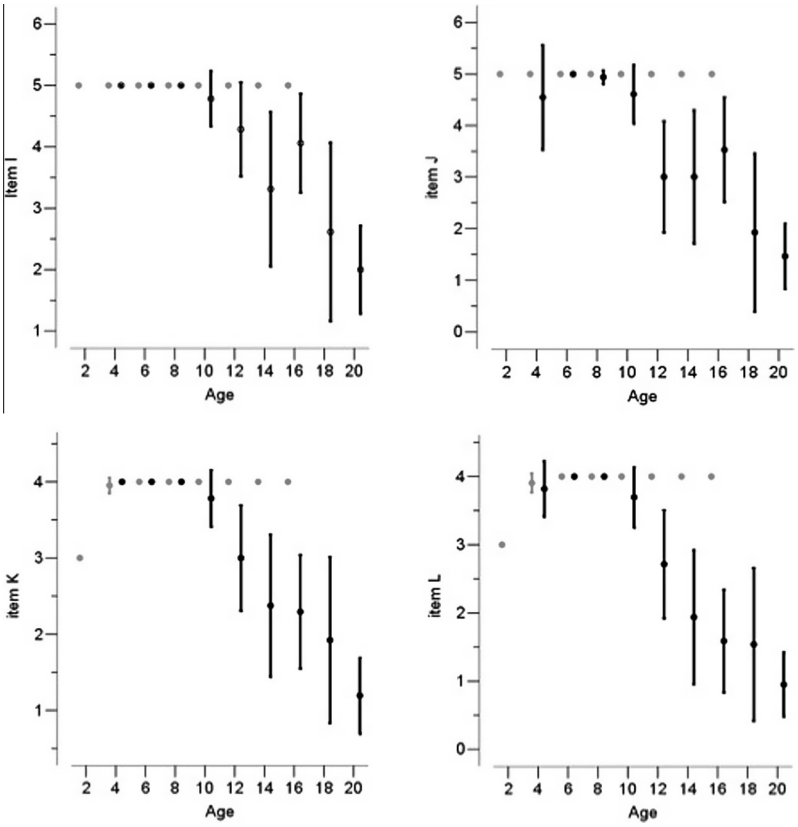

Fig. 3. Mean and 95% confidence intervals of timed activities (in seconds) in typically developing (grey) and DMD (black) subjects in the items I, J, K and L. Note the overlap in the younger subjects and a more obvious divergence of the results after the age of 10.

developing and in DMD boys and young adults. For items I, J and K, there was a marked overlap between the typically developing and DMD cohort until after the age of 10 years.

4. Discussion

One of the aims of this cross sectional study was to evaluate the reliability of the PUL in a multicentric setting. Our results showed that, following standardized training, the PUL has excellent interobserver and intraobserver reliability.

We also wished to establish the earliest age when both typically developing and DMD boys were able to complete the assessment. Performing the PUL in preschool boys, we confirmed that the items included in the assessment could be easily administered. Typically developing children were consistently able to perform the full scale with full total scores or one point less (73 or 74 out of 74) by the age of 5 years. In contrast, a proportion of those younger than 5 had difficulties in completing some items because of their hand and arm size that restricted reaching and holding the bigger weights or stacking cans from sitting. In the DMD cohort the assessment was also easily completed by all the boys with the ones younger than 5 also having the same difficulties met by their peers because of hand and arm size. These results would therefore suggest that the PUL is more appropriate from the age of 5 years.

Not surprisingly, while in the typically developing cohort the scores remained stable after the age of 5, in the DMD cohort there was a steady deterioration. The difference between the two cohorts was minimal before the age of 8 and became wider with increasing age. In the younger group the difference was mainly obvious at shoulder level dimension, as DMD boys generally did not achieve the same scores of their typically developing peers and some proximal weakness could already be detected even in a proportion of the patients who were still ambulant. There was a steep fall in the shoulder level scores between the ages of 9–16, with only a few boys being able to achieve a score of 3 after this age.

As expected the changes at elbow and distal level appeared at a later age, reflecting the proximal to distal gradient of weakness observed in DMD.

In a previous study assessing the suitability of existing measures, such as the Jebsen or the 9 hole peg test or other measures not specifically devised for DMD, we observed that a large proportion of boys older than 15 years had a clear floor effect, scoring 0 on all the items [8–10]. In the present study we were able to demonstrate that the PUL is instead capable of measuring small distal movements even in the older weaker DMD subjects. These items assess the functional use of fingers such as lifting small weights or pointing, that relate to activities of daily living, such as using a mobile phone, a computer mouse or the wheel chair joystick that are very relevant for this age group.

At the time of developing this version of the PUL we decided to keep a number of items assessing different finger pinches as we wished to establish possible differences in their scores due to different levels of weakness or contractures. In the DMD cohort some of these items had similar scores (e.g. two and three finger pinch, data not shown) or were passed in over 90% of the cohort (e.g. place the finger on a diagram). A larger data collection is in progress to perform Rasch analysis in order to explore possible co-dependency and reduce the number of distal items.

Another aim of this study was to establish the value of timed items to avoid ceiling effect. In the younger age group however the timed results were similar in both DMD and typically developing cohorts. The difference was more obvious in the second decade but in that age range there is no risk of ceiling effect as few DMD boys have full total PUL scores. The only timed item that appeared to show some differences already in younger boys was stacking heavy cans.

Our study provides for the first time cross sectional data using the PUL in a relatively large cohort of DMD with a wide age range. The results suggest that the PUL can be reliably used in a multicentric setting and is suitable in patients from the age of 5 until adulthood, as it did not show an obvious floor effect even in the older patients. As observed in other tests assessing other aspects of function in DMD, such as the 6MWT, we also found a wide variability in scores that was particularly true in the 8–14 years age range. The variability in this age range is partly reflected by the level of ambulation with ambulant boys having better scores than the non-ambulant ones who are overall weaker. This however did not always held true for individual cases as a number of non-ambulant boys had similar PUL scores to the ambulant patients.

The total scores allowed to observe the progressive decrease in the whole cohort with age while the subscores assessing the three major level dimensions clearly indicated the proximal to distal gradient of loss of function at different ages. The timed items in contrast did not appear to provide additional information.

Our data suggest that the assessment can be reliably used in both ambulant and non ambulant Duchenne patients in a multicentric setting and could therefore be considered as an outcome measure for future trials. Further studies collecting data in larger cohorts will provide a better understanding of possible changes over time and collect natural history data.

Acknowledgments

The study was funded by a Telethon UILDM grant (GUP 11002). Elena Mazzone is the TREAT NMD research fellow funded by Telethon, Italy. The authors

are also grateful to Parent Project, the Netherlands and Italy for their help in the development of the scale.

References

[1] Mercuri E, Mazzone E. Choosing the right clinical outcome measure: from the patient to the statistician and back. Neuromuscul Disord 2011;21:16–9.
[2] McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. Muscle Nerve 2010;41:500–10.
[3] Goemans NM, Tulinius M, van den Akker JT, et al. Systemic administration of PRO051 in Duchenne's muscular dystrophy. N Engl J Med 2011;364:1513–22.
[4] Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. Lancet 2011;378:595–605.
[5] McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other clinical endpoints in duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study. Muscle Nerve 2013;48:357–68.
[6] McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study. Muscle Nerve 2013;48:343–56.
[7] Mazzone E, Bianco F, Martinelli D, et al. Assessing upper limb function in nonambulant SMA patients: development of a new module. Neuromuscul Disord 2011;21:406–12.
[8] Mercuri E, McDonald C, Mayhew A, et al. International workshop on assessment of upper limb function in Duchenne muscular dystrophy: Rome, 15–16 February 2012. Neuromuscul Disord 2012;22:1025–8.
[9] Mazzone ES, Vasco G, Palermo C, et al. A critical review of functional assessment tools for upper limbs in Duchenne muscular dystrophy. Dev Med Child Neurol 2012;54:879–85.
[10] Mayhew A, Mazzone ES, Eagle M, et al. Development of the Performance of the Upper Limb module for Duchenne muscular dystrophy. Dev Med Child Neurol 2013;55:1038–45.
[11] Bushby K, Connor E. Clinical outcome measures for trials in Duchenne muscular dystrophy: report from International Working Group meetings. Clin Invest 2011;1:1217–35.
[12] Mazzone E, Vasco G, Sormani MP, et al. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. Neurology 2011;77:250–6.