Paediatric Translational Research Neuromuscular Centre

(CNMPed)

Exploratory outcomes in SMA type 2 and 3

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Conflict of interest

- PI in Roche and Ionis study
- Coordination of Natural History study partially funded by Roche
- SAB of Biogen, Avexis and Roche.
- Patents in Actimyo and myotools, with no financial interest

- Clinical
- MRI
- Electrophysiology

Table 2 Estimated mean changes in motor and pulmonary function outcomes at 2 and 3 years obtained from mixed-effects models with linear and quadratic terms for time[a]

	2 Years			3 Years		
Variable	Mean	95% CI	p Value	Mean	95% CI	p Value
GMFM	−0.70	(−2.84, 1.44)	0.52	−4.39	(−8.38, −0.40)	0.03
HFMS	−0.34	(−1.26, 0.58)	0.46	−1.26	(−2.65, 0.12)	0.07
HFMSE	−0.54	(−1.45, 0.36)	0.24	−1.71	(−3.02, −0.39)	0.01
FVC (% predicted)	−3.14	(−6.01, −0.27)	0.03	−2.92	(−6.50, 0.66)	0.11

Prospective cohort study of spinal muscular atrophy types 2 and 3

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ABSTRACT

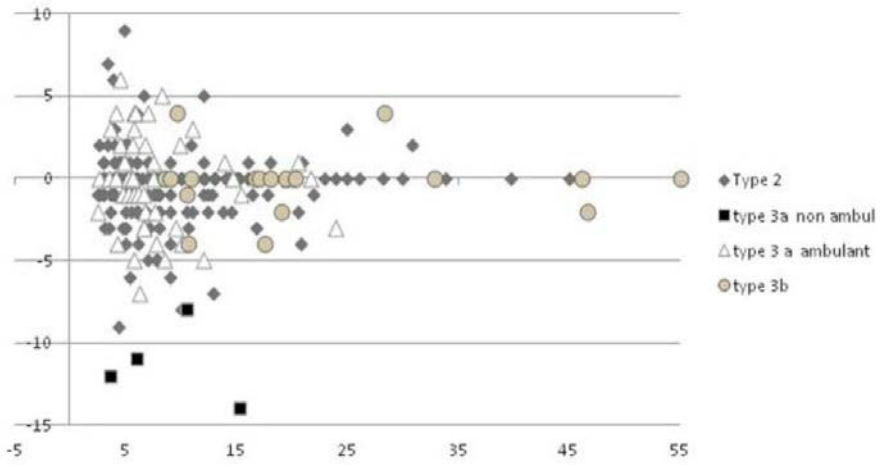
Objective: To characterize the natural history of spinal muscular atrophy type 2 and type 3 (SMA 2/3) beyond 1 year and to report data on clinical and biological outcomes for use in trial planning.

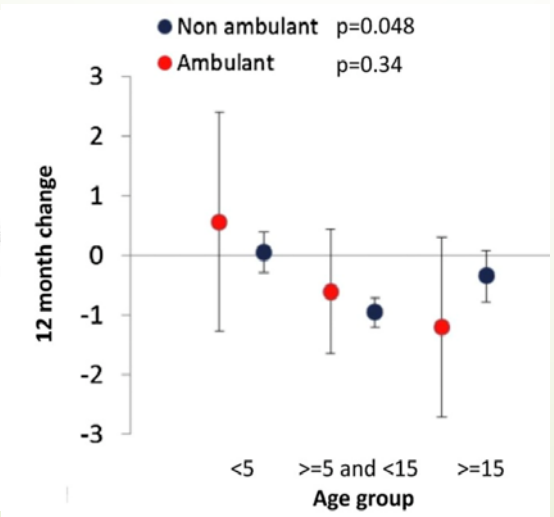
Methods: We conducted a prospective observational cohort study of 79 children and young adults with SMA 2/3 who participated in evaluations for up to 48 months. Clinically, we evaluated motor and pulmonary function, quality of life, and muscle strength. We also measured *SMN2* copy number, hematologic and biochemical profiles, muscle mass by dual x-ray absorptiometry (DXA), and the compound motor action potential (CMAP) in a hand muscle. Data were analyzed for associations between clinical and biological/laboratory characteristics cross-sectionally, and for change over time in outcomes using all available data.

Results: In cross-sectional analyses, certain biological measures (specifically, CMAP, DXA fat-free mass index, and *SMN2* copy number) and muscle strength measures were associated with motor function. Motor and pulmonary function declined over time, particularly at time points beyond 12 months of follow-up.

Conclusion: The intermediate and mild phenotypes of SMA show slow functional declines when observation periods exceed 1 year. Whole body muscle mass, hand muscle compound motor action potentials, and muscle strength are associated with clinical measures of motor function. The data from this study will be useful for clinical trial planning and suggest that CMAP and DXA warrant further evaluation as potential biomarkers. *Neurology*® 2012;79:1889-1897

Rationale : Level and significance of change as captured by current outcome on a 1 year period is low.





NEUROMUSCULAR DISORDERS
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FREE Full-Text Article

Neuromuscul Disord. 2016 Feb; 26(2): 126–131.
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PMCID: PMC4762230

Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials

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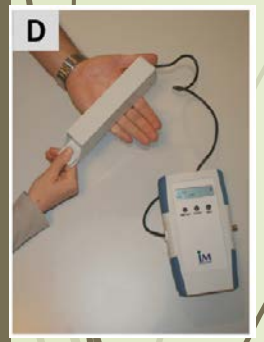
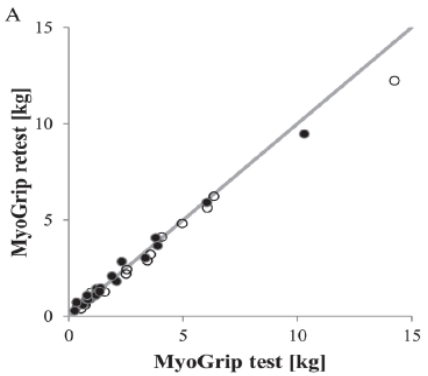
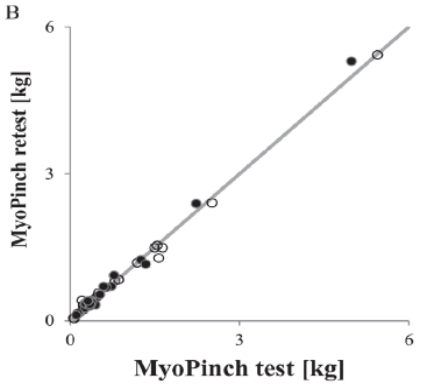
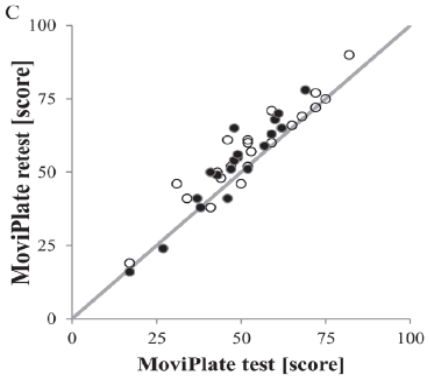
Reliability

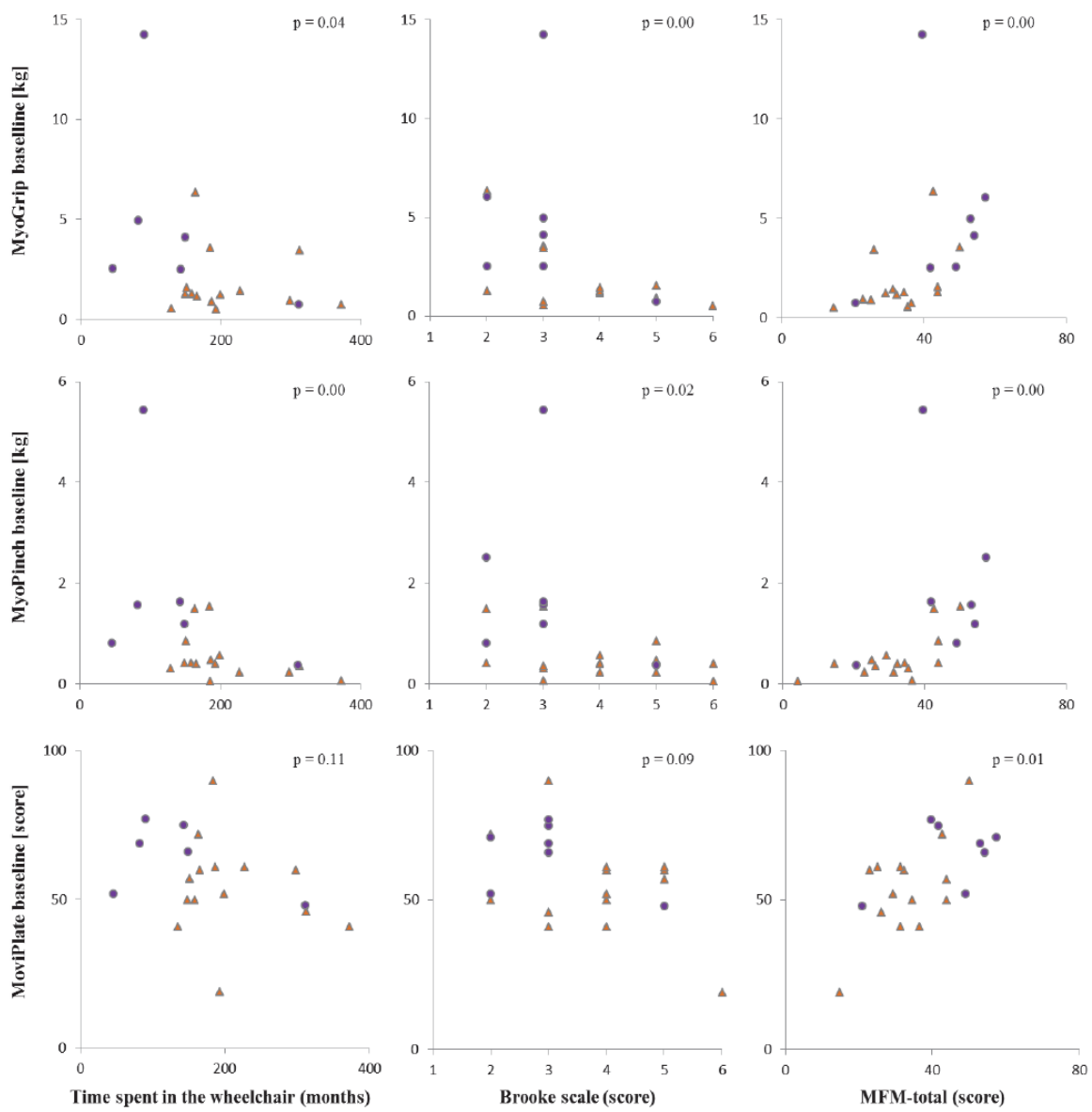








Cross-validation



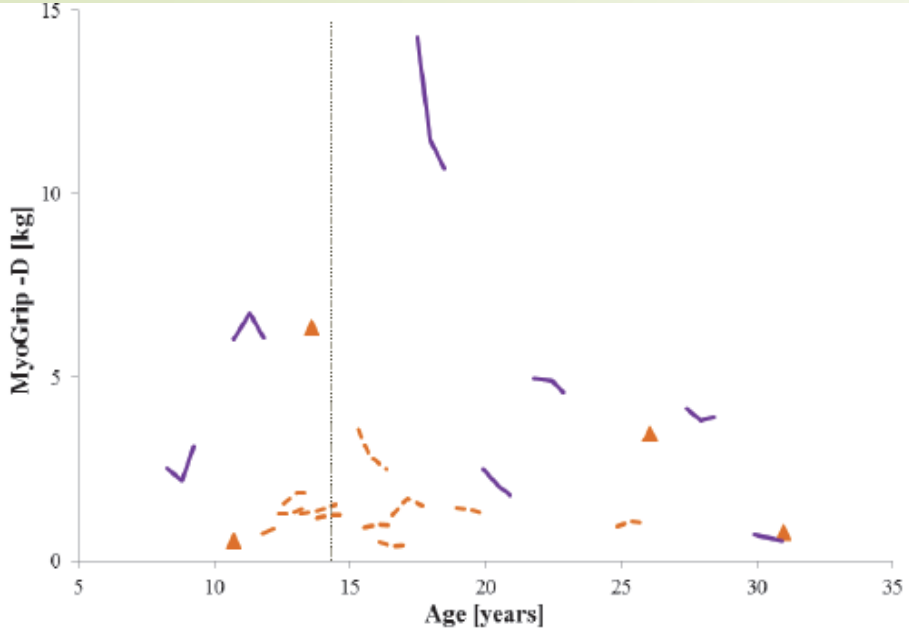
PLOS ONE

RESEARCH ARTICLE

Upper Limb Evaluation and One-Year Follow Up of Non-Ambulant Patients with Spinal Muscular Atrophy: An Observational Multicenter Trial

Andreea Mihaela Seferian[1☯], Amélie Moraux[1☯], Aurélie Canal[1], Valérie Decostre[1], Oumar Diebate[1], Anne Gaëlle Le Moing[1,2], Teresa Gidaro[1], Nicolas Deconinck[3], Frauke Van Parys[3], Wendy Vereecke[3], Sylvia Wittevrongel[3], Mélanie Annoussamy[1], Michèle Mayer[4], Kim Maincent[4], Jean-Marie Cuisset[5], Vincent Tiffreau[6], Severine Denis[7], Virginie Jousten[7], Susana Quijano-Roy[8], Thomas Voit[1,9], Jean-Yves Hogrel[10], Laurent Servais[1,7]*

Sensitivity to change



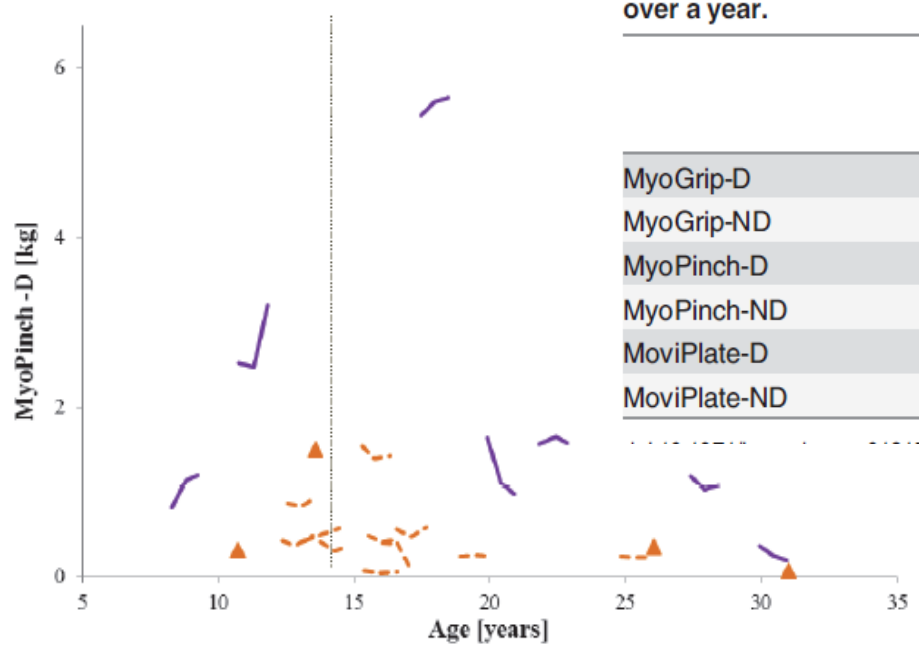


Table 7. Sample size per group to include in a clinical trial to detect a stabilization of motor function on dominant (D) and non-dominant (ND) sides over a year.

	All patients			Patients > 14 years old		
	Total	SMA II	SMA III	Total	SMA II	SMA III
MyoGrip-D	57	56	55	30	36	26
MyoGrip-ND	187	14955	70	60	131	32
MyoPinch-D	15069	168	317	23	26	24
MyoPinch-ND	155404	293	1270	69	36	76
MoviPlate-D	234	501	89	79	93	75
MoviPlate-ND	104	138	65	35	34	47

Baseline data from a European Prospective and Longitudinal Natural History Study of patients with type 2 and 3 Spinal Muscular Atrophy - NatHis-SMA

A. Chabanon[1], A. Daron[2], Y. Péréon[3], C. Cances[4], C. Vuillerot[5], S. Fontaine[5], N. Goemans[6], L. De Waele[6], JM. Cuisset[7], V. Laugel[8], U. Schara[9], A. Gangfuß[9], T. Gidaro[1], E. Gargaun[1], A. Marquet[10], T. Seabrook[11], R. Hermosilla[11], C. Czech[11], G. Ramey[10], P. Jordan[11], O. Khwaja[11], L. Lowes[12], JY. Hogrel[1], A. Jollet[1], M. Villeret[1], A. Phelep[1], M. Annoussamy[1], L. Servais[1, 2]

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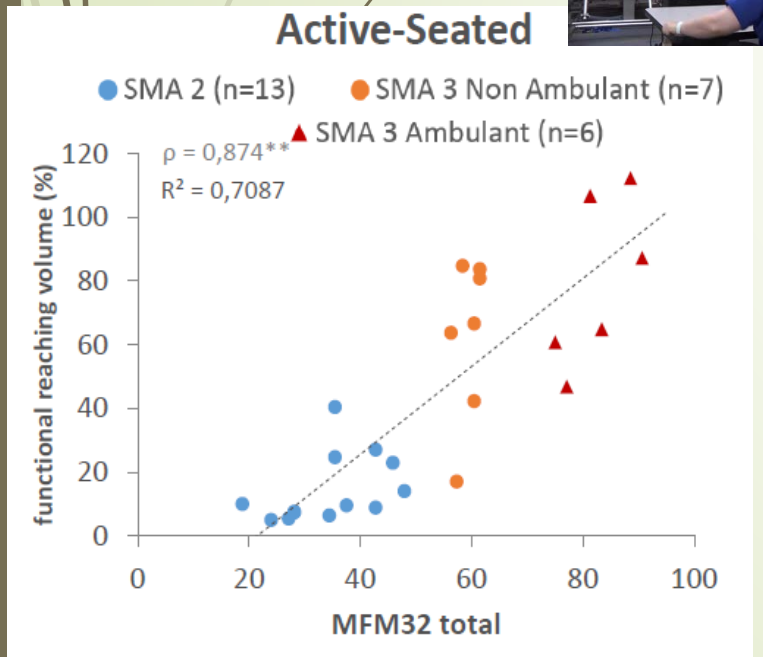
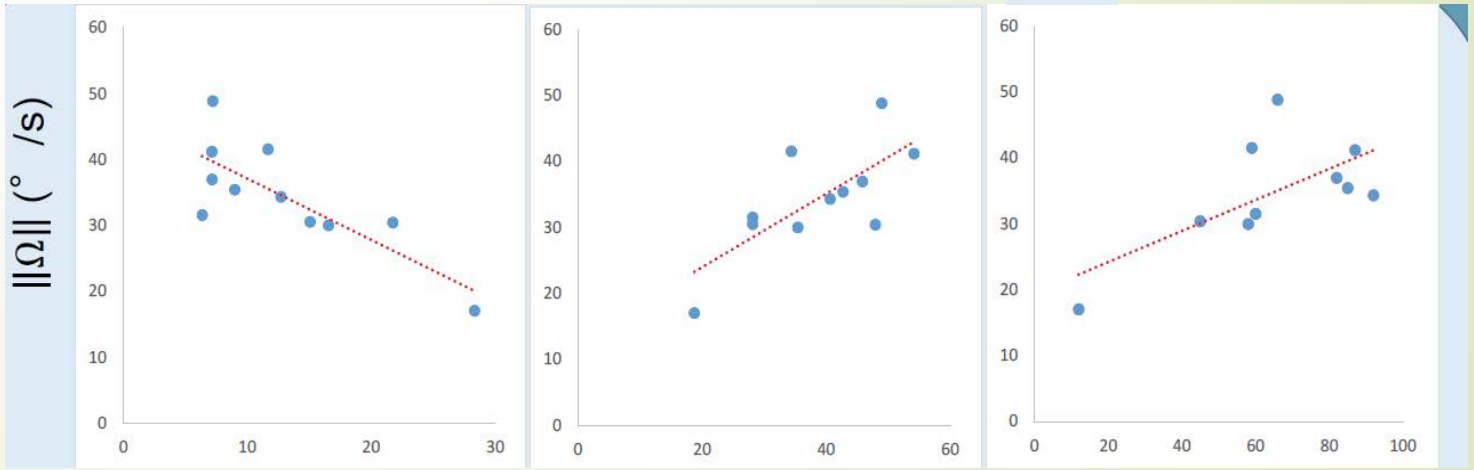
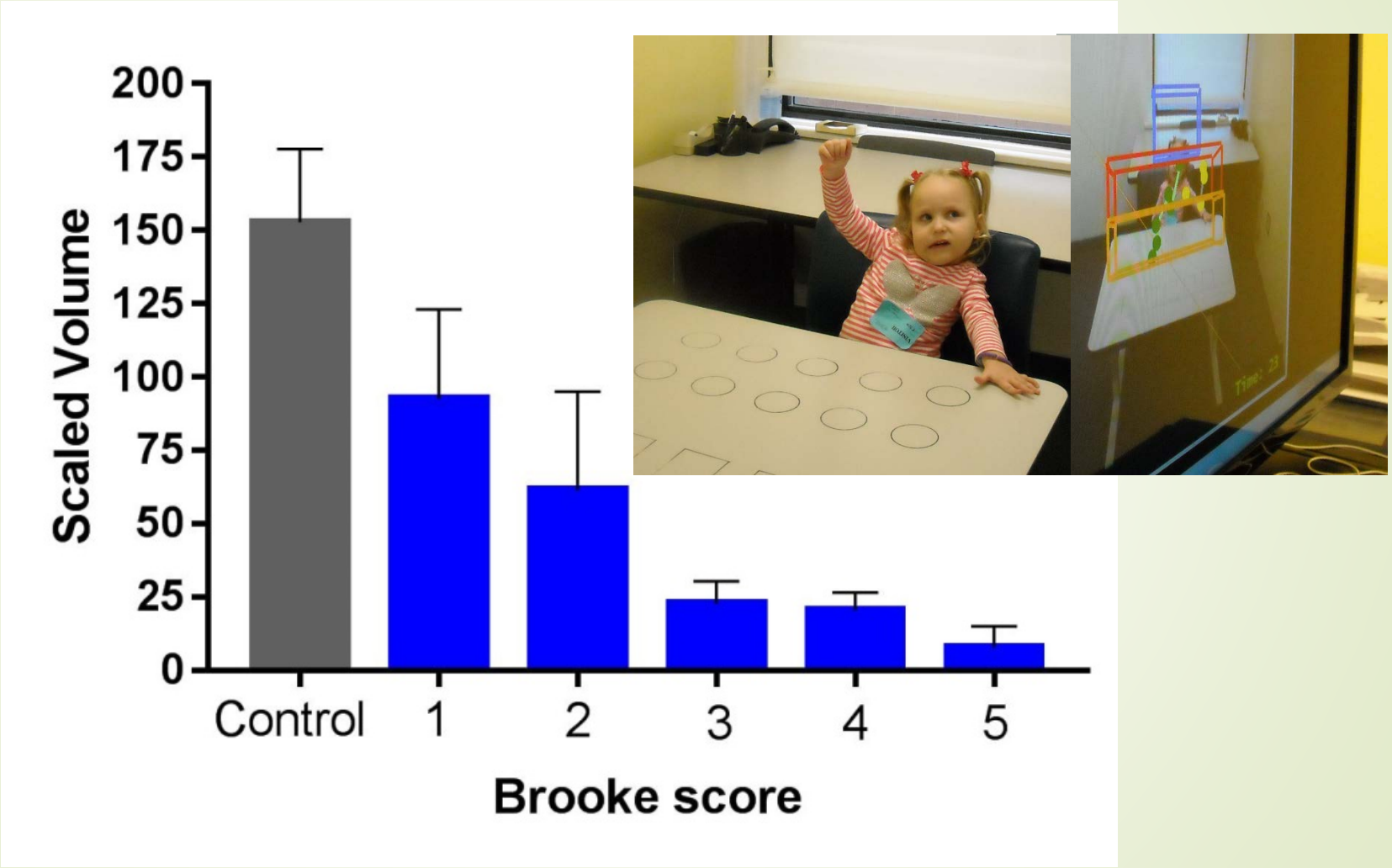
Feasibility of magneto-inertial motion analysis in non-ambulant patients with spinal muscular atrophy

A. Seferian[1¤], E. Gargaun[1¤], G. Quicke[1], T. Gidaro[1], E. Gasnier[r1], A. Moraux[1], Y. Péréon[2], A. Daron[3], C. Cances[4], C. Vuillerot[5], N. Goemans[6], V. Laugel[7], JM. Cuisset[8], U. Schara[9], A. Marquet[10], T. Seabrook[10], R. Hermosilla[10], C. Czech[10], G. Ramey[10], P. Jordan[10], O. Khwaja[10], A. Chabanon[1], M. Annoussamy[1], D. Vissiere[1]1, L. Servais[1]





Scaled Reaching Volume in SMA



Original Article

Muscle Volume Estimation by Magnetic Resonance Imaging in Spinal Muscular Atrophy

Journal of Child Neurology
26(3) 309-317

DOI: 10.1177/0883073810380457
http://jcn.sagepub.com
SAGE

Douglas M. Sproule, MD[1], Mark Punyanitya[2], Wei Shen, MD[2], Stephan Dashnaw[3], Bill Martens[4], Megan Montgomery[1], Jacqueline Montes, PT, MA[1], Vanessa Battista, CPNP[1], Richard Finkel, MD[5], Basil Darras, MD[6], Darryl C. De Vivo, MD[1], and Petra Kaufmann, MD, MSc[1]

14 patients with type1-3 SMA. Muscle volume estimation is highly reliable (r=0.99), and correlated with MUNE, CMAP and HMFSE.

Muscle volume estimation could discriminate between type 2 and 3, but this does not reach statistical significance.

MUSCLE MRI IN SPINAL MUSCULAR ATROPHY 3: SELECTIVE AND PROGRESSIVE INVOLVEMENT

Hacer Durmus MD[1], Ravza Yilmaz MD[2], Yesim Gulsen-Parman MD[1], Piraye Oflazer-Serdaroglu MD[1], Marina Cuttini MD, MS[3], Memduh Dursun MD[2], Feza Deymeer MD, MS[1]

Muscle & Nerve

25 patients with SMA3b (onset from 4-18, median 13) after 10 years (1-13) of evolution

Correlation (r=0.7 for gluteus and 0.54 for triceps) between MRI score and duration of symptoms

SHORT REPORT

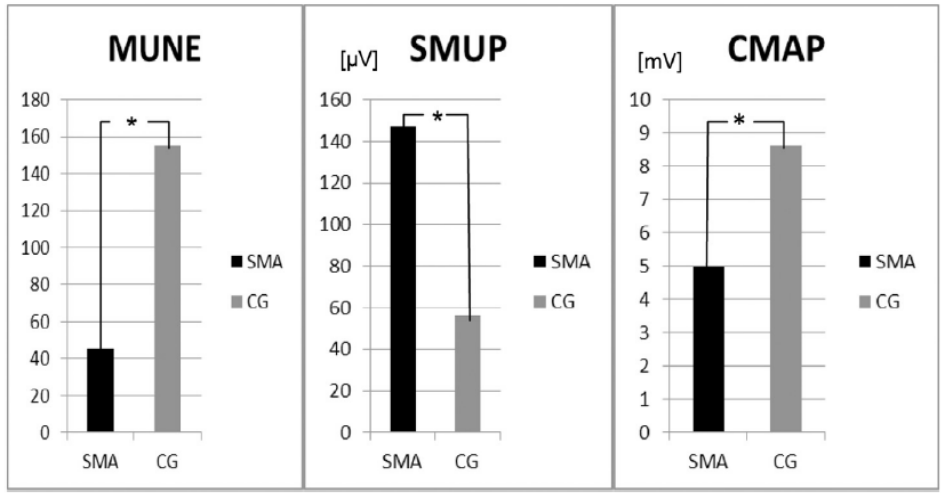
ABSTRACT: Spinal muscular atrophy (SMA) is a disease of lower motor neurons. Motor unit number estimation (MUNE) is an electrophysiologic method to estimate the number of motor neurons innervating a muscle group. We applied the multiple point stimulation technique to the ulnar nerve–hypothenar muscle group to study lower motor neuron loss in 14 SMA subjects, including those presymptomatic, and varying from newborn through 45 years of age. Preliminary data support the value of MUNE to help understand the time course of motor neuron loss in SMA.

 Muscle Nerve **25:** 445–447, 2002

MOTOR UNIT NUMBER ESTIMATION IN INFANTS AND CHILDREN WITH SPINAL MUSCULAR ATROPHY

MARK B. BROMBERG, MD, PhD, and KATHRYN J. SWOBODA, MD

MUNE is highly discriminant between SMA and controls, but is difficult to standardize on a multicenter setting.



Motor unit loss estimation by the multipoint incremental MUNE method in children with spinal muscular atrophy – A preliminary study

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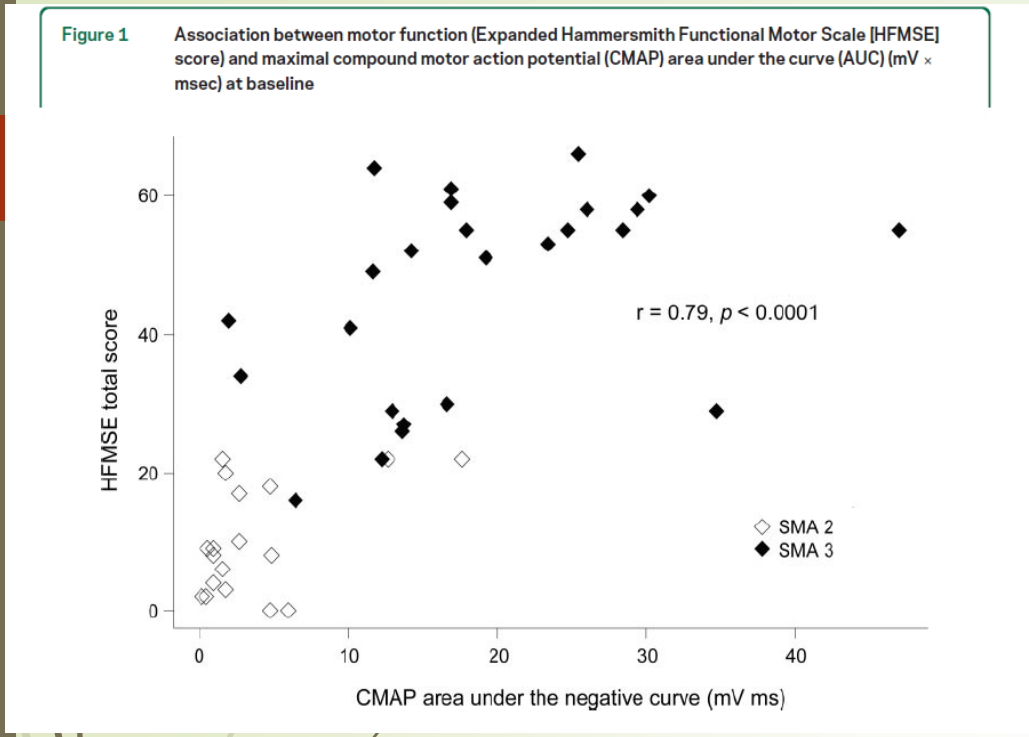
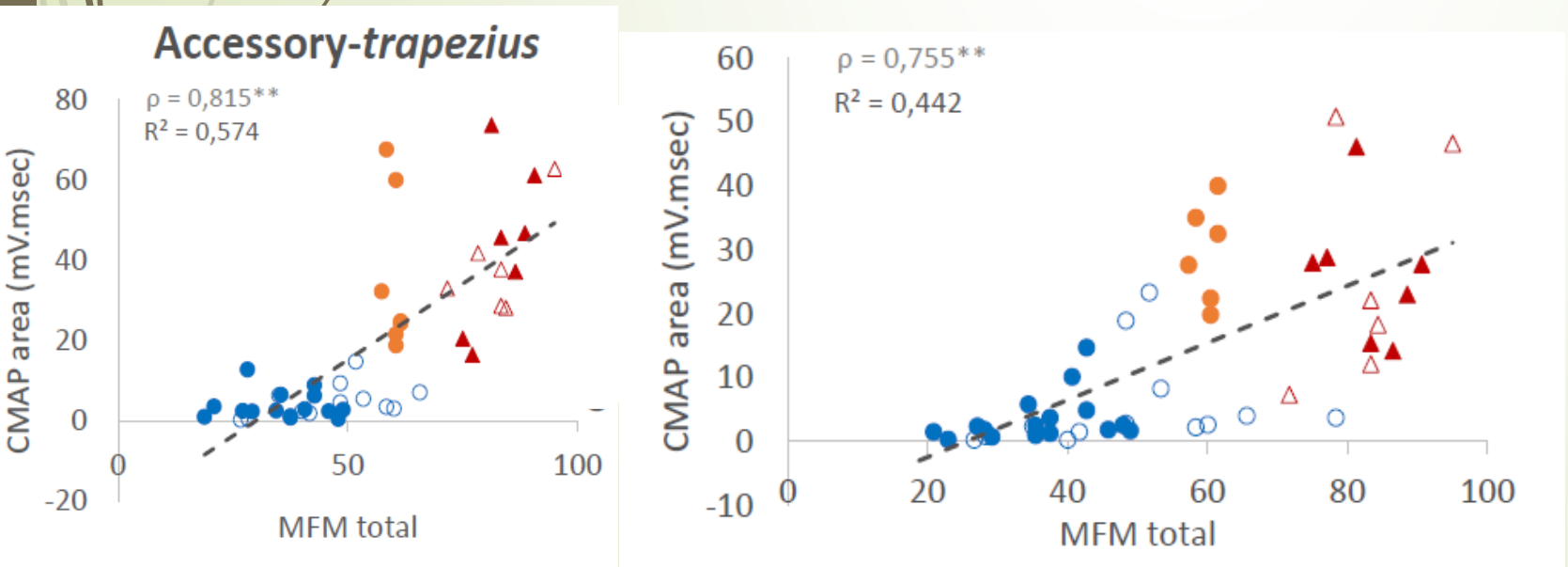


Kaufmann et al. 2012

CMAP is well correlated with HFMSE and MFM, is discriminant between SMA2 and 3, but no change could be pointed out on a three years period.



Chabanon et al. 2016

Summary

- Clinical : -Myotools (Reliable/Cross validated/sensitive to change/clinically meaningfull/normative data)

  -Actimetry (reliable, cross validated, clinically meaningfull, **sensitivity to change to be demonstrated, in progress**)

  -Active seated (reliable, cross validated, clinically meaningfull, **sensitivity to change to be demonstrated, in progress**)

- MRI -Volume and score : reliable, cross validated, but **few sensitivity to change on these parameter**

- Electrophysiology : Moderate reliability and feasibility, cross validated, **no sensitivity to change up to now**