The evolving natural history of SMA types II and III

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Disclosures

- Advisory boards for Roche, Ionis, Biogen, Avexis, Novartis for SMA studies
- PI of the ongoing Ionis/Biogen and Roche trials
- Funding from Italian Telethon, Famiglie SMA Italy, SMA Europe,

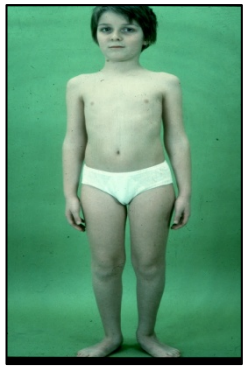
Type	Age at Symptom Onset		Incidence %	Prevalence %	Maximum Motor Function	*SMN2* copy number	Life expectancy
0		Fetal	<1	0	Nil	**1**	Days -Weeks
1	< 6 Months	1A: B-2 Weeks 1B: <3 Months 1C: >3 Months	60	15	Never sits	1, **2**,3	< 2 years
2	6-18 Months		25	70	Never walks	2,**3**,4	20-40 years
3	1.5-10 Years	3A: <3 Years 3B: > 3 Years	15	15	Walks, regression	**3**, **4**, 5	normal
4	>35 Years		<1	1	Slow decline	**4, 5**	normal

SMA 3

walks independently (may be lost)

3a: onset before 3 years

3b: onset after 3 years

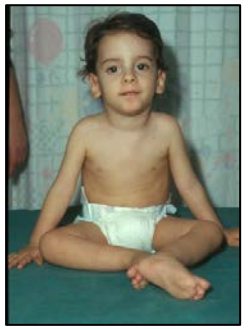


SMA 2

can sit independently

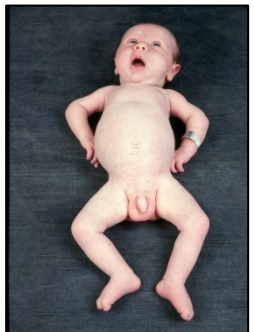
ranging from just able to sit (2.1) to

ability to stand with minimal support (2.9)



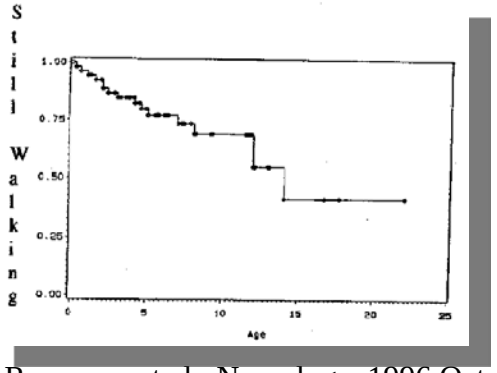
SMA 1

inability to sit unsupported



What was known: natural history data type 2 and 3 SMA are progressive

Still sitting

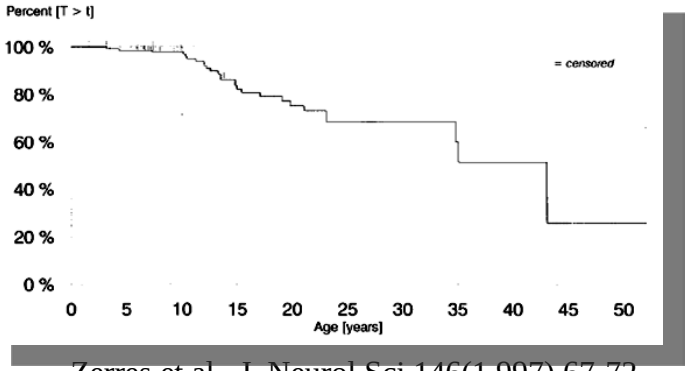


Russman, et al., Neurology. 1996 Oct;47(4):973-6.

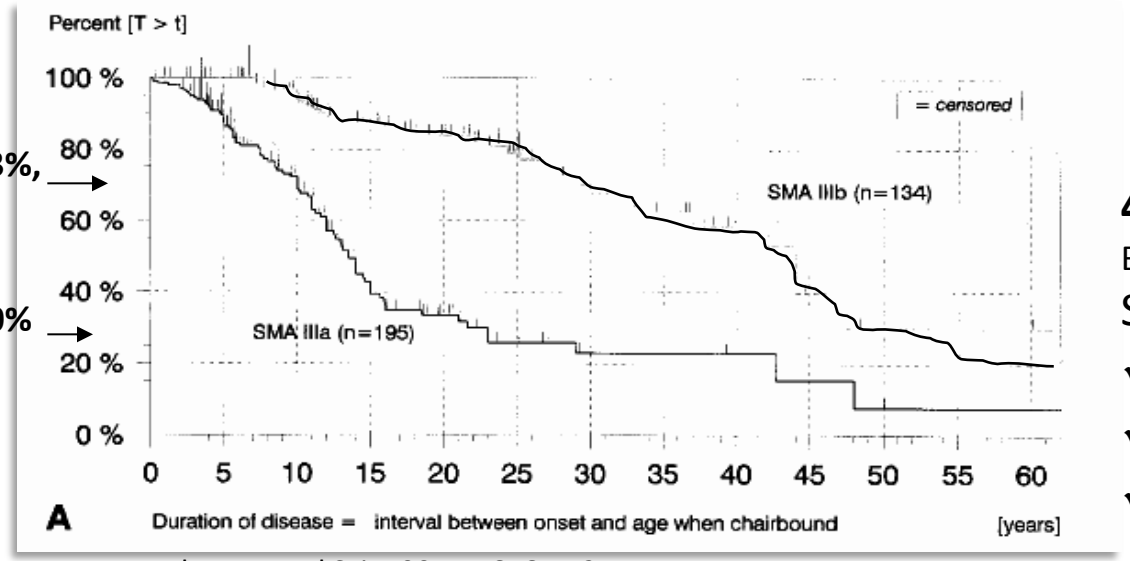
SMA type IIIa

SMA type IIIb

Age at death



Zerres et al., J Neurol Sci 146(1 997) 67-72



Zerres et al., J Neurol Sci. 1997;146: 67-72.

4 y (168 p SMA from 6 centers)

Barois et al., 2005

Significant worsening (~20%)

- ✓ Muscle strength
- ✓ Muscle function index
- ✓ Respiratory index

What we learned in the last decade

- Type 2 (and 3) SMA are less progressive than classically reported
- Very little changes over relatively short intervals (1-2 years)

Natural history studies: MFM

Responsiveness of the Motor Function Measure in Patients With Spinal Muscular Atrophy

Carole Vuillerot, MD, PhD, Christine Payan, MD, Jean Iwaz, PhD, René Ecochard, MD, PhD, Carole Bérard, MD

Archives of Physical Medicine and Rehabilitation
Volume 94, Issue 8, Pages 1555-1561 (August 2013)

Table 1 Patients' characteristics and MFM scores according to SMA types

Variable	SMA Type 1	SMA Type 2	SMA Type 3
Participants	9	44	59
Males	6	24	31
Age (y)	10.2±2.7 (7.4–15.4)	11.5±5.0 (5.7–27)	18.7±12.3 (6.2–59)
Range of follow-up (mo)	3.6–28.8	2–62.4	1.2–66
Follow-up >6mo	1	12	19
Patients with at least 2 MFM	3	14	23
Patients with more than 2 MFM	1 with 3 MFM	9 with 3 MFM 3 with 4 MFM	2 with 3 MFM 1 with 4 MFM
Optimal cooperation	6/6	34/38	38/47
MFM scores			
D1	2.3±2.4 (0–7.7)	3.3±3.8 (0–23.1)	40.2±29.4 (0–100)
D2	30.9±19.5 (5.6–72.2)	57.6±21.0 (13.9–94.4)	87.8±20.0 (11.1–100)
D3	42.9±24.7 (9.5–90.5)	76.6±12.8 (38.1–100)	94.43±9.53 (42.9–100)
Total	21.9±12.8 (7.3–47.9)	40.0±11.4 (14.6–66.7)	70.1±18.8 (14.6–93.8)

NOTE. Values are n, mean ± SD (range), or as otherwise indicated.

- Cross sectional data in 44 type 2 and 59 type 3

- Longitudinal data (more than 2 MFM) 12 type 2 and 3 type 3

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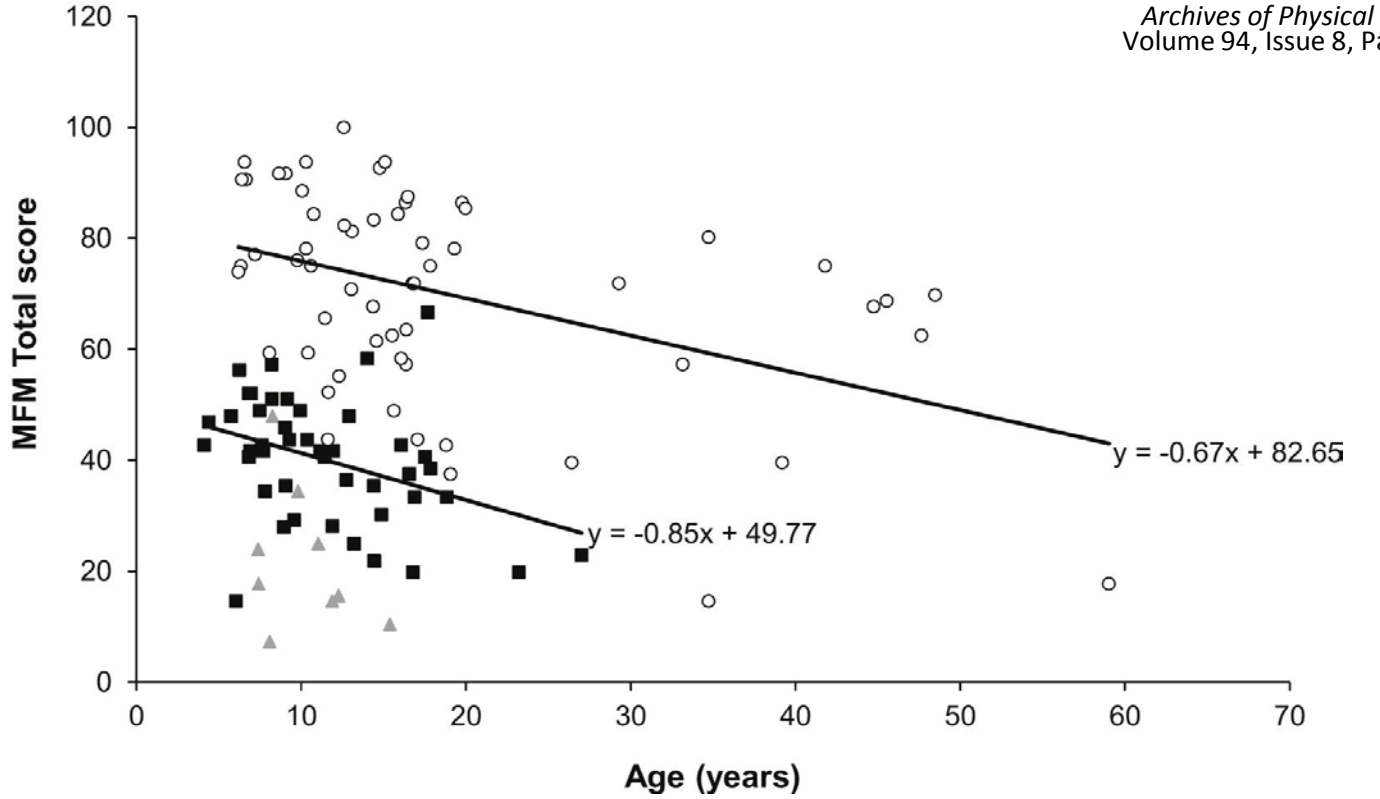


MFM total score according to age in patients with SMA type 2 (dark squares) and type 3 (clear dots). Patients with SMA type 1 (gray triangles) are represented without fitting line.

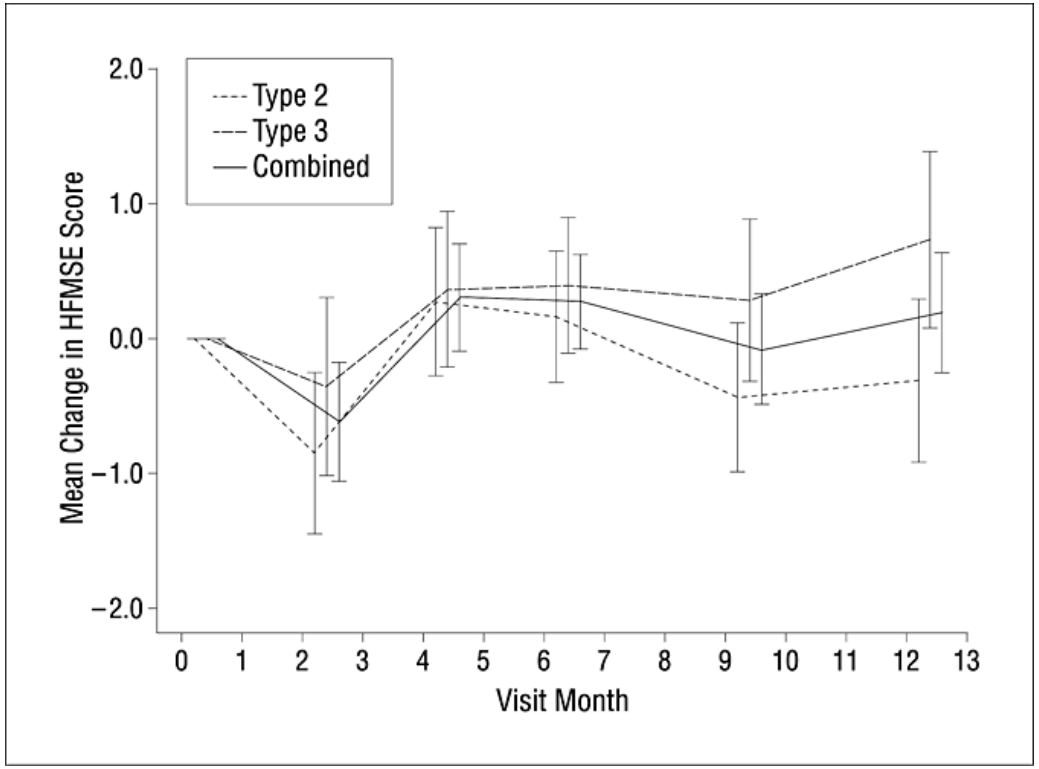
Natural history studies: HMFSE 1 year data

Arch Neurol. 2011 Feb 14. [Epub ahead of print]

Observational Study of Spinal Muscular Atrophy Type 2 and 3: Functional Outcomes Over 1 Year.

Kaufmann P, McDermott MP, Darras BT, Finkel R, Kang P, Oskoui M, Constantinescu A, Sproule DM, Foley AR, Yang M, Tawil R, Chung W, Martens B, Montes J, O'Hagen J, D Flickinger JM, Quigley J, Riley S, Glanzman AM, Benton M, Ryan PA, Irvine C, Annis CL, Butler H, Caracciolo J, Montgomery M, Marra J, Koo B, De Vivo DC; for the Muscle Study Pediatric Neuromuscular Clinical Research Network for Spinal Muscular Atrophy.

- Longitudinal data:
- 65 SMA patients



ARCHIVES OF NEUROLOGY

Natural history studies: HMFSE

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.

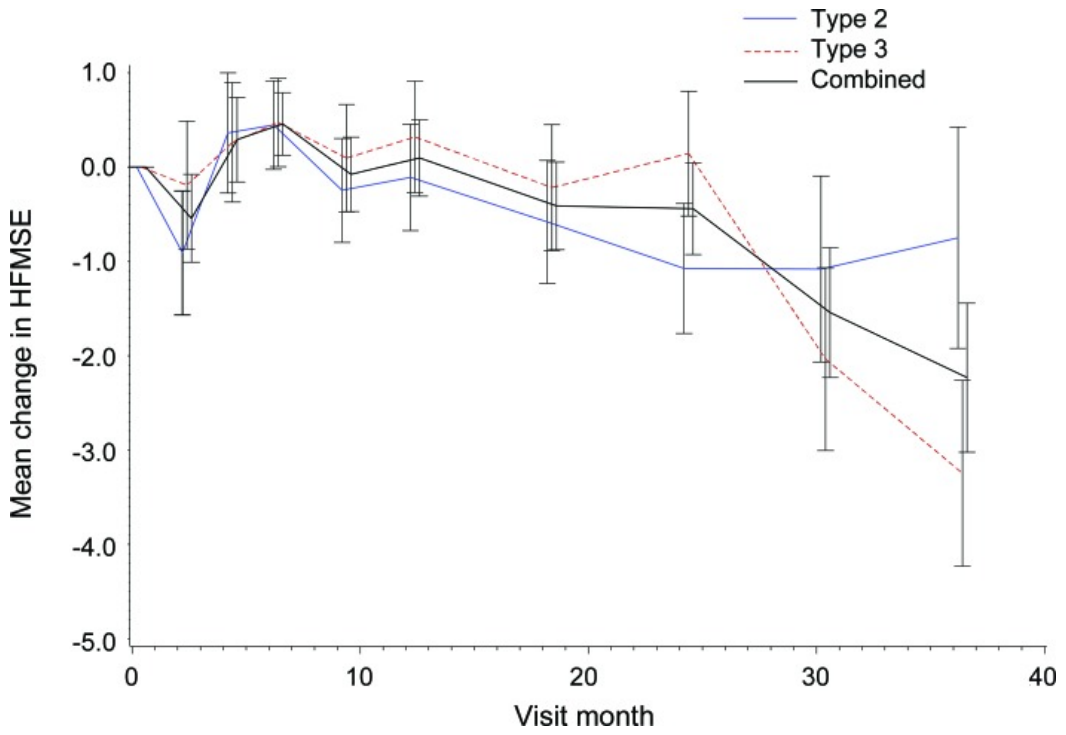
Results: In cross-sectional analyses, certain biological measures (specifically, CMAP, DXA fat-free mass index, and *SMN2* copy number) and muscle strength measures were associated with motor function. Motor and pulmonary function declined over time, particularly at time points beyond 12 months of follow-up.

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

GLOSSARY

AUC = area under the curve; **CMAP** = compound motor action potential; **DXA** = dual x-ray absorptiometry; **FFMI** = fat-free mass index; **GMFM** = Gross Motor Function Measure; **HFMS** = Hammersmith Functional Motor Scale; **HFMSE** = Expanded Hammersmith Functional Motor Scale; **NHANES** = National Health and Nutrition Examination Survey; **FVC** = forced vital capacity; **SMA** = spinal muscular atrophy.

Spinal muscular atrophy (SMA), the second most common recessive lethal pediatric disease,[1] causes proximal muscle weakness, atrophy, and respiratory and orthopedic complications. The severity of the clinical phenotype is heterogeneous with the most severe form (SMA type 1) beginning in infancy. The intermediate (SMA type 2) and mild (SMA type 3) forms cause less severe motor disability.[2]



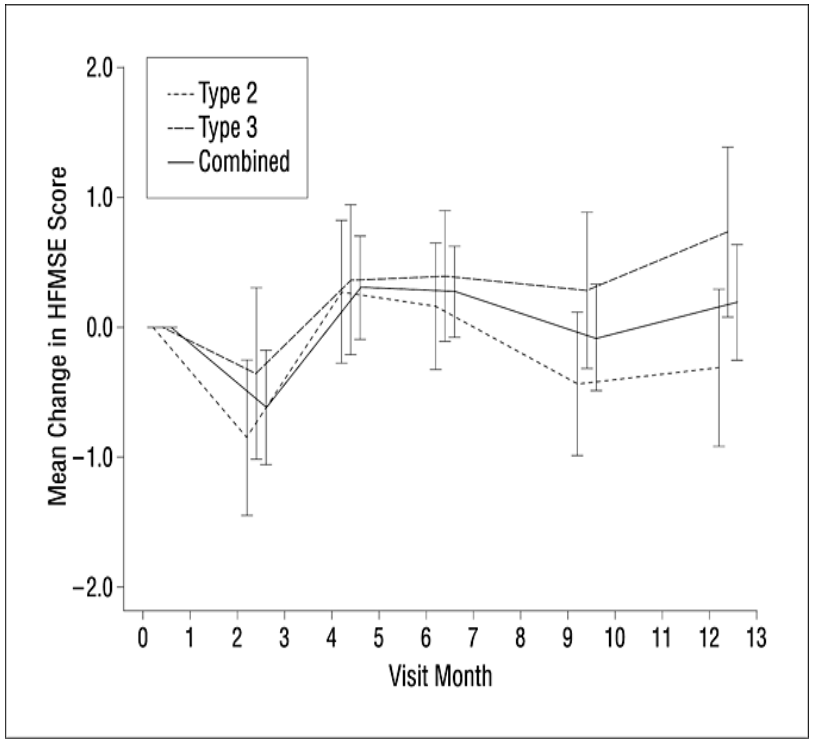
Longitudinal data: 79 type 2 and 3 SMA

Are we measuring the right thing?

- Are the scales not sensitive enough or the small mean changes do not reflect the variability found in individual patients?

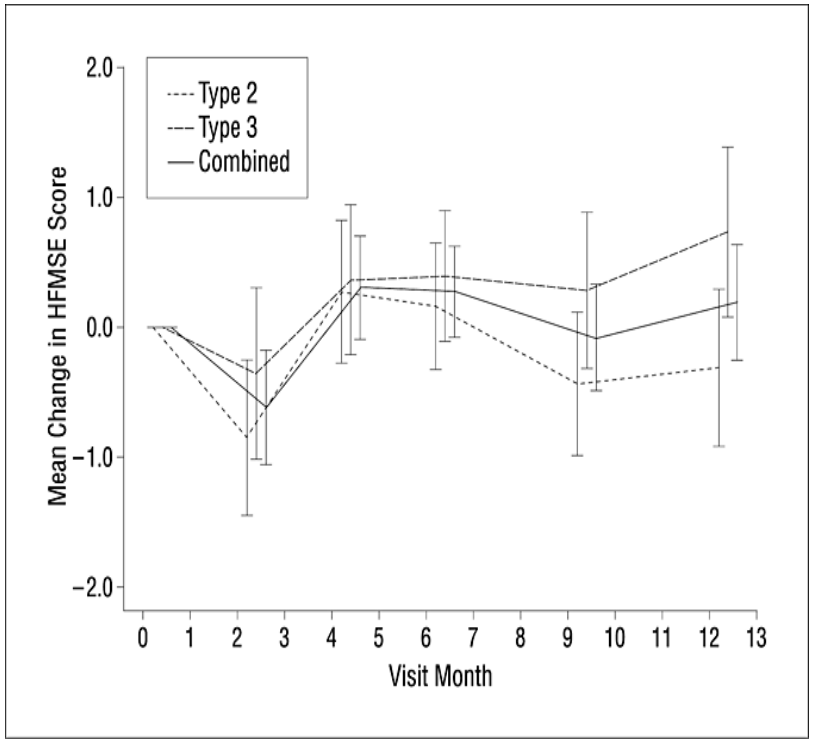
- Is there variability and if yes can we identify prognostic factors or trajectories?

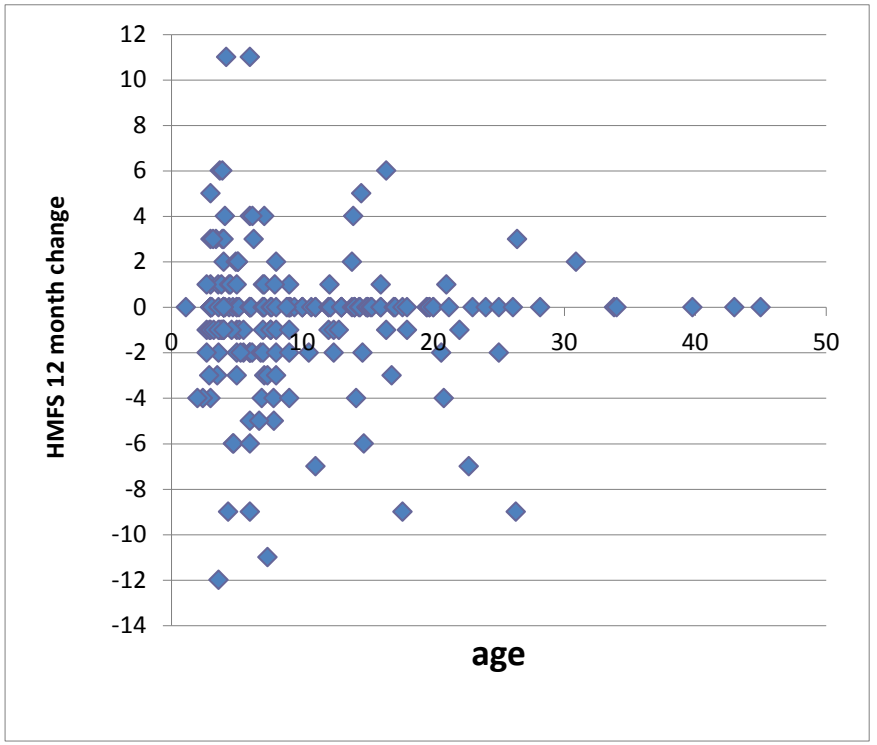
Mean 12 month changes: 0.45



Mean 12 month changes: 0.45

12 month changes: individual changes ranging from -12 to +11





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www.elsevier.com/locate/nmd

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

Eugenio Mercuri [a,l,*], Richard Finkel [b,l], Jacqueline Montes [c], Elena S. Mazzone [a], Maria Pia Sormani [d], Marion Main [e], Danielle Ramsey [e], Anna Mayhew [f], Allan M. Glanzman [g], Sally Dunaway [c], Rachel Salazar [c], Amy Pasternak [h], Janet Quigley [h], Marika Pane [a], Maria Carmela Pera [a], Mariacristina Scoto [e], Sonia Messina [i], Maria Sframeli [i], Gian Luca Vita [i], Adele D'Amico [j], Marleen van den Hauwe [k], Serena Sivo [a], Nathalie Goemans [k], Petra Kaufmann [c], Basil T. Darras [h], Enrico Bertini [j], Francesco Muntoni [e,2], Darryl C. De Vivo [c,2]

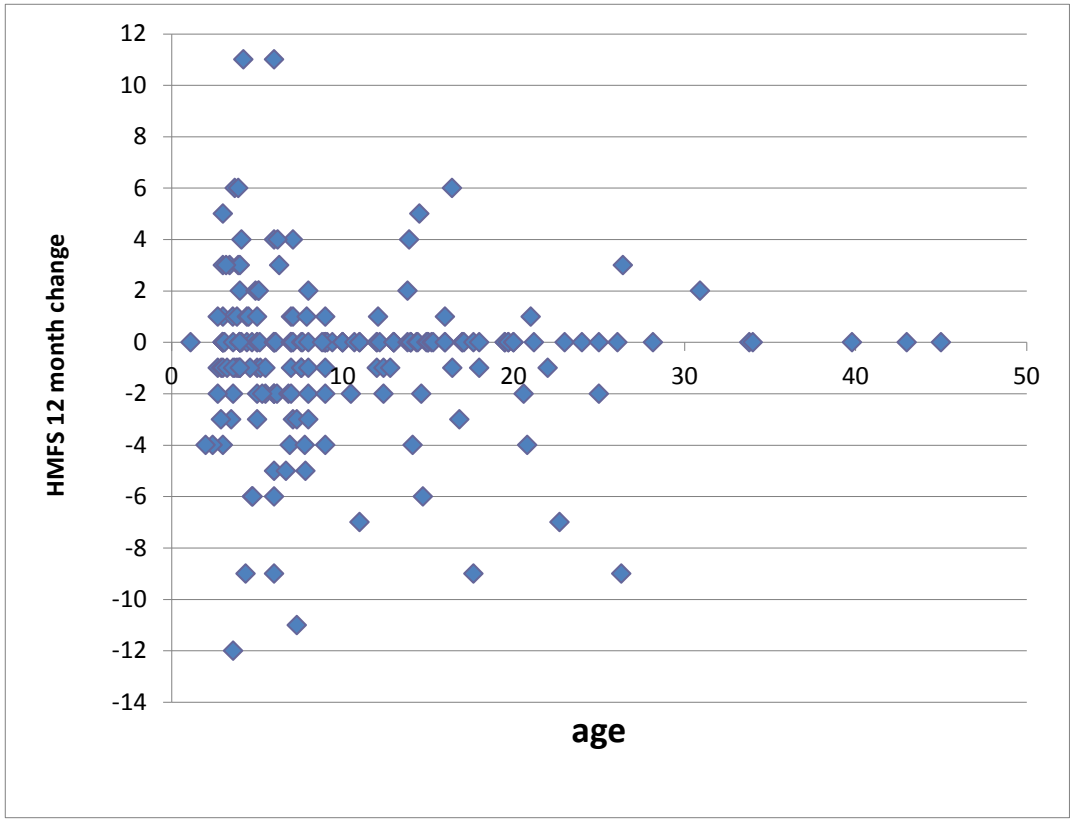
[a] Department of Paediatric Neurology, Catholic University, Rome, Italy

- PNCR (US)
- Italian network for SMA
- SMA Reach UK
- Belgium data (Leuven)

- Largest database available with longitudinal data using the same measure in SMA

- 268 with longitudinal assessments (12 months)
- age ranged between 2.5 and 55.5 years at baseline (mean 10.65).
- 68 were ambulant and 200 non ambulant

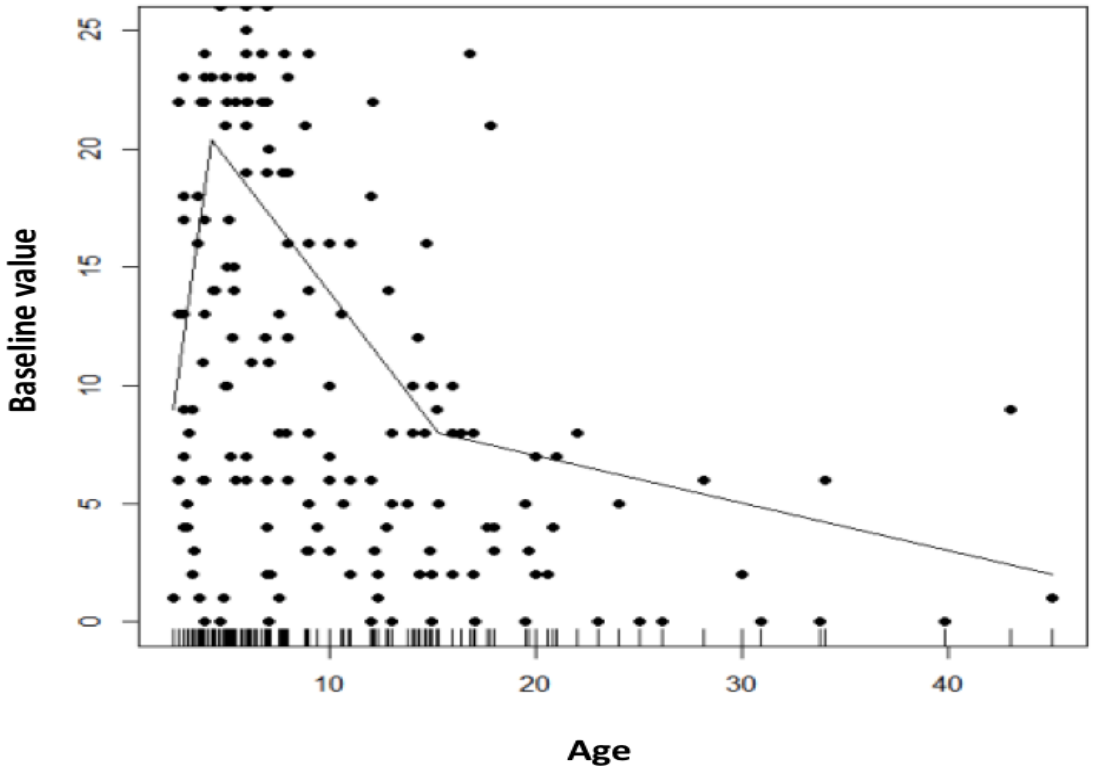
- Mean 12 month changes close to 0 (-o.5 points)
- Most of the changes are within ±2 points,
- Changes can range between -12 and +10.



Mean change : -0,52238806

- 1: different patterns of progression according to age

Baseline values and age



12 month changes and age

12 month changes

	< - 2	+/- 2	> + 2
All (n=268)	41 (15.29%)	206 (76.86%)	21 (7.83%)
<5 (n=61)	6 (9.83%)	47 (77.04%)	8 (13.13%)
5-10 (n=102)	21 (20.58%)	72 (70.58%)	9 (8.84%)
10-15 (n=47)	9 (19.14%)	36 (76.59%)	2 (4.27%)
>15 (n=58)	5 (8.62%)	51 (87.93%)	2 (3.45%)

In the whole cohort most of the negative changes occurred in patients before puberty

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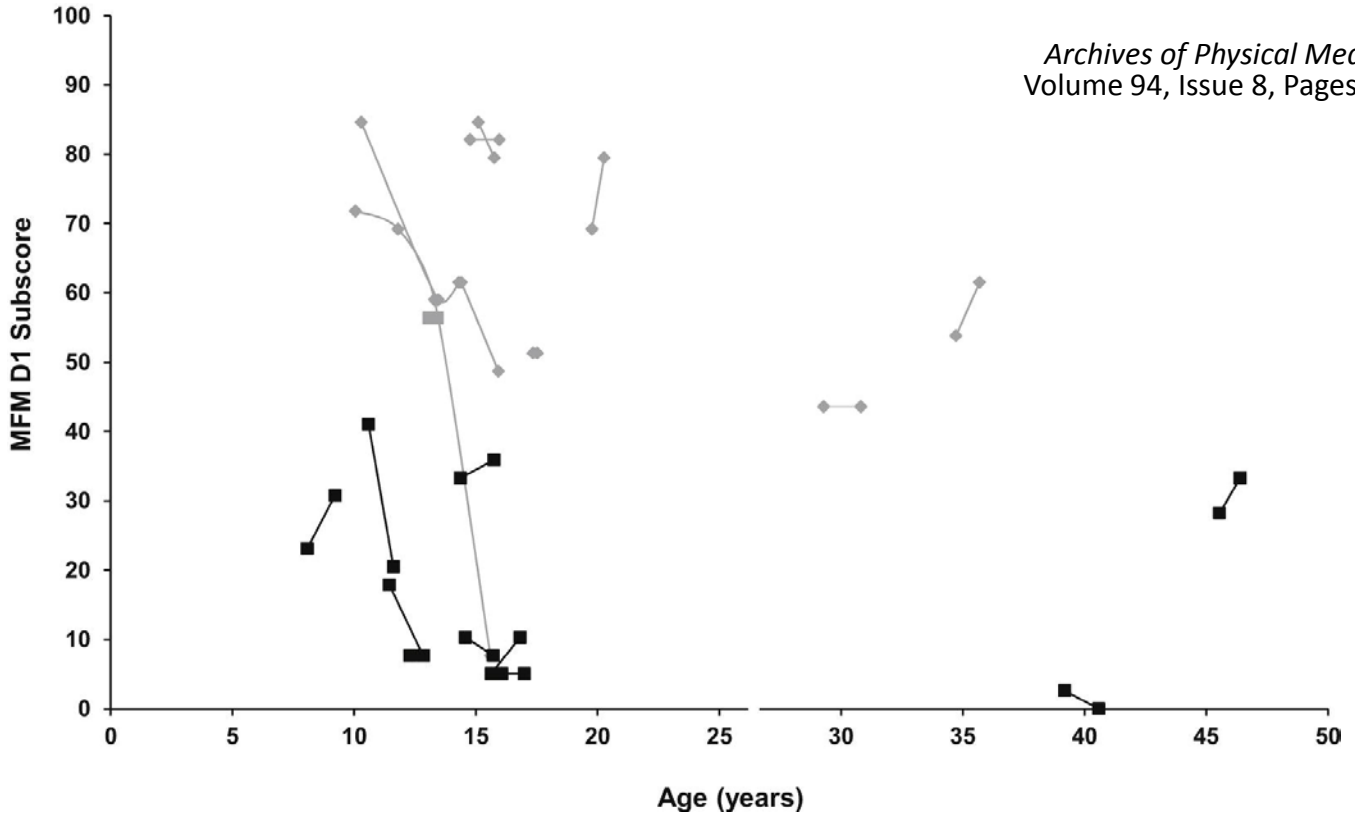
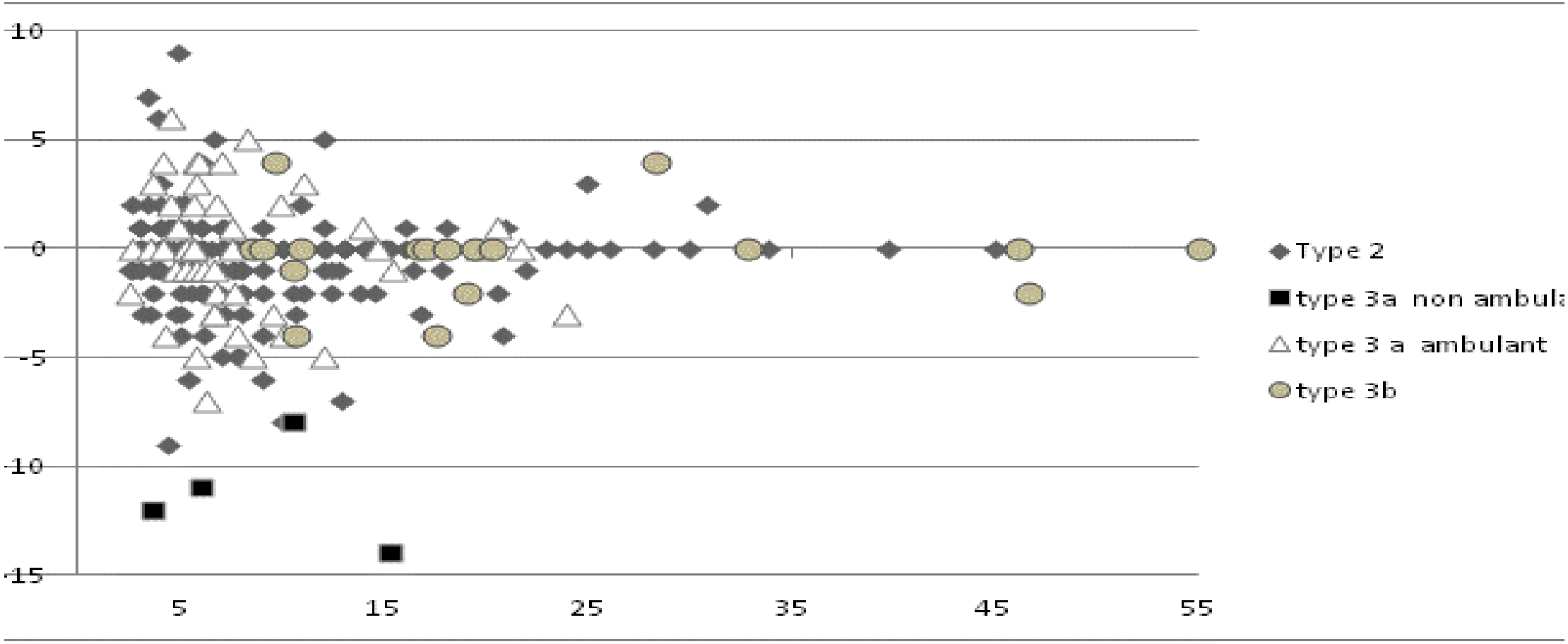


Change in MFM D1 subscore according to age in 23 patients with SMA type 3. Gray lines correspond to ambulant patients and black lines to non ambulant ones.

- 1: different patterns of progression according to age
- 2. different patterns according to type of SMA

12 month changes in type 2 and 3 SMA



Different patterns in type 2 and type 3 but type 3 non ambulant had results more similar to the type 2

- 1: different patterns of progression according to age
- 2. different patterns according to type of SMA
- 3. different patterns in ambulant and non ambulant patients

Different patterns in ambulant and non ambulant

	< - 2	+/- 2	> + 2
NON AMBULANT (n=200)	26 (13%)	164 (82%)	10 (5%)
<5 (n=49)	5 (10.20%)	39 (79.6%)	5 (10.20%)
5-10 (n=73)	14 (19.17%)	56 (76.73%)	3 (4.10%)
10-15 (n=38)	5 (13.15%)	32 (84.21%)	1 (2.64%)
>15 (n=40)	2 (5%)	37 (92.5%)	1 (2.5%)

	< - 2	+/- 2	> + 2
AMBULANT (n=68)	15 (22.05%)	42 (61.78%)	11 (16.17%)
<5 (n=12)	1 (8.3%)	8 (66.70%)	3 (25%)
5-10 (n=29)	7 (24.14%)	16 (55.17%)	6 (20.69%)
10-15 (n=9)	4 (44.44%)	4 (44.44%)	1 (11.12%)
>15 (n=18)	3 (16.66%)	14 (77.77%)	1 (5.57%)

positive changes in ambulant patients occur at 5 to 10 years, later age than in non ambulant

Different patterns in ambulant and non ambulant :

	< - 2	+/- 2	> + 2
NON AMBULANT (n=200)	26 (13%)	164 (82%)	10 (5%)
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10-15 (n=9)	4 (44.44%)	4 (44.44%)	1 (11.12%)
>15 (n=18)	3 (16.66%)	14 (77.77%)	1 (5.57%)

Most negative changes in ambulant patients occur at 10 to 15 years, later age than in non ambulant

What we know now

- Variable progression of the disease
- Ambulant and non ambulant patients have different trajectories
- Age effect different in the two groups

In non ambulant patients

- Some improvement can be observed in younger children (below 5 years)
- Faster decline more frequent from the age of 5

In ambulant patients

- Improvement can also be noted after the age of 5
- More marked decline is observed at the time of reaching puberty

Identification of different trajectories important for

- Clinical practice
- Inclusion criteria/stratification for clinical trials
- Trial design
- Interpretation of results

Work in progress

- Better identify outliers in both ambulant and non ambulant groups
- Other variables possibly affecting trajectories: copy numbers? Scoliosis? Surgery?
- Defining effect of standards of care on trajectories and more generally on natural history
- Consider new methods for identifying trajectories