EUROPEAN JOURNAL OF PHYSICAL AND REHABILITATION MEDICINE
EDIZIONI MINERVA MEDICA

Spasticity in disorders of consciousness: A behavioral study

Aurore THIBAUT, Camille CHATELLE, Sarah WANNEZ, Thierry DELTOMBE, Johan STENDER, Caroline SCHNAKERS, Steven LAUREYS, Olivia GOSSERIES

Eur J Phys Rehabil Med 2014 Nov 06 [Epub ahead of print]

EUROPEAN JOURNAL OF PHYSICAL AND REHABILITATION MEDICINE

Rivista di Medicina Fisica e Riabilitativa dopo Eventi Patologici
pISSN 1973-9087 - eISSN 1973-9095
Article type: Original Article

The online version of this article is located at http://www.minervamedica.it

Spasticity in disorders of consciousness: A behavioral study

A. Thibaut Msc[1], C. Chatelle PhD[1,2], S. Wannez Msc[1], T. Deltombe MD[3], J. Stender[4] MD, C. Schnakers[5] PhD, S. Laureys MD PhD[1], O. Gosseries PhD[1,6]

[1] Coma Science Group, Cyclotron Research Centre and Neurology Department, University and University Hospital of Liège, Liège, Belgium

[2] Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, Massachusetts

[3] Physical Medicine and Rehabilitation Department, CHU Dinant – Godinne / UCL Namur (Université Catholique de Louvain), Yvoir, Belgium.

[4] Institute of Neuroscience and Pharmacology, University of Copenhagen, Denmark

[5] Department of Psychology and Department of Neurosurgery, UCLA, Los Angeles, USA.

[6] Center for Sleep and Consciousness and Postle Laboratory, Department of Psychiatry and Psychology, University of Wisconsin, Madison, WI, USA

Congresses: IBIA, 23th March, Edinburg, Scotland, 2012
World Stroke Congress, 11th October, 2012, Brasilia, Brazil
Siz Kine, 14th June 2013, Brussels, Belgium

Conflicts of interest: The authors report no financial relationships or conflicts of interest

Acknowledgements: This research was supported by the Belgian National Funds for Scientific Research (FNRS), James S. McDonnell Foundation, Fonds Léon Fredericq, the Belgian American Educational Foundation (BAEF), the Fédération Wallonie Bruxelles International (WBI), European Commission, European Space Agency, Concerted Research

Action (ARC 06/11-340), Mind Science Foundation, Wallonia-Brussels Federation Concerted Research Action and the Belgian interuniversity attraction pole (IAP). CC is funded by the BAEF and WBI and AT by the IAP. OG received support from NIH grant MH064498 and MH095984 to Bradley R. Postle and from Giulio Tononi. OG is FNRS Postdoctoral Researcher and SL is FNRS Research Director.

Corresponding author:

A.Thibaut

Coma Science Group, Cyclotron Research Centre

University of Liège

Allée du Six Aout, 8

4000 Liège (Sart-Tilman)

Belgium

0032 4 366 80 69

athibaut@ulg.ac.be

ABSTRACT

Background: Spasticity is a frequent complication after severe brain injury, which may impede the rehabilitation process and diminish the patients' quality of life.

Aim: We here investigate the presence of spasticity in a population of non-communicative patients with disorders of consciousness. We also evaluate the correlation between spasticity and potential factors of co-morbidity, frequency of physical therapy, time since insult presence of pain, presence of tendon retraction, etiology and diagnosis.

Design: Cross sectional study.

Setting: University Hospital of Liège, Belgium.

Population: 65 patients with chronic (>3 months post insult) disorders of consciousness were included (22 women; mean age: 44±14y; 40 with traumatic etiology; 40 in a minimally conscious state; time since insult: 39±37months).

Methods: Spasticity was measured with the Modified Ashworth Scale (MAS) and pain was assessed using the Nociception Coma Scale-Revised (NCS-R).

Results: Out of 65 patients, 58 demonstrated signs of spasticity (89%; MAS ≥ 1), including 39 who showed severe spasticity (60%; MAS ≥ 3). Patients with spasticity receiving anti-spastic medication were more spastic than unmedicated patients. A negative correlation was observed between the severity of spasticity and the frequency of physical therapy. MAS scores correlated positively with time since injury and NCS-R scores. We did not observe a difference of spasticity between the diagnostic.

Conclusion: A large proportion of patients with disorders of consciousness develop severe spasticity, possibly affecting their functional recovery and their quality of life. The observed correlation between degrees of spasticity and pain scores highlights the importance of pain management in these patients with altered states of consciousness. Finally, the relationship

between spasticity and treatment (i.e., pharmacological and physical therapy) should be further investigated in order to improve clinical care.

Clinical Rehabilitation Impact: Managing spasticity at first signs could improve rehabilitation of patients with disorders of consciousness and maximize their chances of recovery. In addition, decreasing this trouble could allow a better quality of life for these non-communicative patients.

Keywords: spasticity, pain, treatment, vegetative state/unresponsive wakefulness syndrome, minimally conscious state, severe brain injury, upper motor neuron syndrome, Nociception-Coma Scale-revised, Modified Ashworth scale.

Introduction

Spasticity is defined as a velocity-dependent increase in muscle tone (1). This is a serious complication to brain injury, often accompanied by dyskinesia, spasms or muscle flaccidity (2). Spasticity results from impaired reflex functions and pathological changes in rheologic muscle properties such as atrophy, stiffness and fibrosis (3). In addition to hyper-excitability of the stretch reflex, patients may suffer from spastic dystonia (i.e., muscle constriction in the absence of voluntary movement), and/or spastic co-contraction (i.e., contraction of both agonist and antagonist muscles) (25, 26). These modifications can induce pain and reduce functional autonomy (25, 26). Spasticity has also been reported to be associated with muscle contracture, tendon retraction, fixed equinovarus feet and pain in patients suffering from multiple sclerosis (8) or stroke (25, 26). All these complications increase the clinical impact of spasticity on recovery by impeding the patient's ability to perform activities of daily living and by increasing the cost of treatment (25, 26). Spasticity occurs in approximately 25 to 42% of patients with acquired brain injury (25, 26). Although the onset is usually within the first few days or weeks post-insult, spasticity may appear in the short-, medium-, or long-term period post-insult (2).

The occurrence of spasticity in severe brain damaged patients with disorders of consciousness (DOC) has been poorly explored. DOC includes patients in coma (16), in vegetative/unresponsive wakefulness syndrome (VS/UWS) (25, 26) and in minimally conscious state (MCS) (18). Patients in VS/UWS are characterized by the presence of reflexive responses to external stimuli and are considered unconscious (19). Patients in MCS show reproducible but minimal and fluctuating signs of consciousness (18). By definition, these patients with DOC are unable to express their feelings and cannot communicate about potential discomfort or pain (25, 26). To our knowledge, only a few studies of small sample

size have described motor patterns in patients with DOC. These studies reported the presence of abnormal primitive reflexes, altered tonus, considerable posturing and varied degrees of reduced range of joint motion (25, 26) as well as abnormal cortical excitability of the motor cortex (24). In addition, other studies show that some patients fail to show clinical signs of consciousness due to severe motor impairments including spasticity, thus leaving them vulnerable to misdiagnosis (25, 26). The need to understand and prevent spasticity in this population is therefore urgent.

The aim of our study is to measure the occurrence and clinical impact of spasticity in patients with DOC. We assess the presence of spasticity in a cohort of chronic patients in VS/UWS or MCS. We also evaluate the correlation between spasticity and potential factors of co-morbidity, frequency of physical therapy, time since insult presence of pain, presence of tendon retraction, etiology and diagnosis.

Materials and methods

Population

We enrolled medically stable patients with DOC admitted to the University Hospital of Liège in Belgium for one week of diagnostic assessments. This week includes repeated behavioral examinations with an array of neuroimaging-based examinations such as magnetic resonance imaging, positron emission tomography, and electroencephalography. The aim is the detection of consciousness and possible means of communication. All patients came from their homes, nursing homes or rehabilitation centers. Inclusion criteria were: 1) a diagnosis of VS/UWS or MCS, 2) time since onset of condition more than 3 months, and 3) age 16 years and over. Exclusion criteria were: 1) documented neurological disorders previous to the acquired brain damage, and 2) presence of skin or musculoskeletal lesions (e.g., bedsores, fractures, wounds). The study was approved by the ethical committee of the University Hospital of Liège and written informed consents were obtained from the legal

representatives.

In total, we included 65 patients in this cross sectional study (22 women; mean age: 44±14 years). Forty patients were of traumatic etiology, 14 suffered from anoxia, 6 had a subarachnoid hemorrhage, 4 presented mixed etiology (trauma and anoxia) and 1 patient had an encephalomyelitis. The time since insult varied from 3 months to 12 years with a mean ± SD of 39±37 months. Patients were diagnosed as being in VS/UWS (n=25) or in MCS (n=40) based on repetitive assessments using the Coma Recovery Scale-Revised (CRS-R) (25, 26). We took the highest diagnosis observed during the week of assessments. Anti-spastic medication was classified as oral treatments (baclofen, clonazepam, tizanidine) or intrathecal baclofen therapy. The amount of physical therapy received as part of the usual patient's cares program varied between 0 and 6 sessions per week, including stretching of all limbs for at least 20 minutes. Clinical data are summarized in the supplementary material.

Material

Spasticity was assessed once for each patient with the Modified Ashworth Scale (MAS); a 6-level ordinal scale with documented reliability (31). Higher scores indicate increasing severity of the spasticity (see figure 1 for the description of the scale). All patients were examined by the same physiotherapist to minimize inter-rater variability. Assessment of spasticity followed the guidelines of the scale (i.e., patients assessed in a resting position) and included passive flexion and extension of upper and lower extremity joints (shoulder, elbow, wrist, fingers, hip, knee, and ankle). The mean MAS score of assessable (i.e., without joint total fixation that makes the evaluation impossible) joints of the upper limbs (left and right shoulder, elbow, wrist, fingers) and lower limbs (left and right hip, knee and ankle) were used for our correlation analyses (see supplementary material for clinical data).

Among the 65 studied patients, 48 were also assessed with the Nociception Coma Scale-Revised (NCS-R), a validated and reliable scale assessing behavioral signs of pain in patients

with DOC (32). The scale measures motor, verbal and facial responses to potential pain. Its total score ranges from 0 to 9, with a score of 4 or higher indicating the presence of pain. The assessment was conducted during patient's daily care, on the same day as the spasticity assessment.

Patients were diagnosed using the CRS-R, which consists of 23 hierarchically arranged items and includes 6 subscales assessing auditory, visual, motor, verbal, communication and arousal functions (25, 26). This scale is currently considered the most accurate tool for the detection of consciousness in post-comatose patients (25, 26).

Statistical analyses

MAS data were evaluated on a scale ranging from 0 to 5, assigning the 1+ a value of 2, the 2 a value of 3, and so on. We used the Mann-Whitney U tests to investigate the difference of MAS scores according to the level of consciousness (i.e., VS/UWS vs. MCS), joint deformities (i.e., presence vs. absence of upper limb tendon retraction and equinovarus feet), and medication (i.e., presence vs. absence of pharmacological treatment) (34). We used the Wilcoxon test to assess differences in MAS scores between upper and lower extremities. Correlations between MAS scores and NCS-R total scores, time since insult, and frequency of physical therapy were assessed with Kendall's Tau tests (35, 36). Differences in MAS scores according to the etiology (i.e., anoxic, hemorrhagic, traumatic and mixt) were assessed by Kruskal-Wallis ANOVA.

Results

Out of 65 patients, 58 showed signs of spasticity (89%; MAS ≥ 1). Out of these 65 patients, 39 suffered from severe spasticity (60%; MAS ≥ 4) (see figure 1 and table 1). Eight patients (12%) showed no signs of spasticity (MAS=0) including five patients (8%) who were flaccid. Six patients (9%) had a maximal score of 2, 12 (18.5%) had a maximal score of 3, 12

(18.5%) had a maximal score of 4 and 27 (42%) had a maximal score of 5.

INSERT FIGURE 1 ABOUT HERE

INSERT TABLE 1 ABOUT HERE

We found a significant difference in spasticity between the upper and lower limbs (T=446.5; Z=2.55; p=0.01).

A negative correlation was found between MAS scores and the frequency of physical therapy for both the upper limbs (tau=-0.20, Z=-2.37; p=0.018; figure 2A) and the lower limbs (tau=-0.20; Z=-2.41; p=0.016).

A positive correlation was found between MAS scores and time since insult for both upper limbs (tau=0.23; Z=2.71; p=0.007; figure 2B) and lower limbs (tau=0.21; Z=2.46; p=0.014), and between MAS scores and NCS-R total scores for the upper limbs only (upper limbs, tau= 0.31, Z=3.11; p=0.001; figure 2C; lower limbs: tau=0.18; Z=1.80; p=0.072).

Twenty-seven patients (42%) had tendon retraction in the upper limbs (i.e., metacarporphalangean joint, wrist and elbow) and 37 (57%) fixed equinovarus feet (see table 2). The presence of retraction was associated with higher MAS score for the upper limbs (U=155; Z=4.71; p<0.001) and equinovarus feet were associated with higher MAS scores of the lower limbs (U=139.5; Z=4.89; p<0.001).

Thirty-nine out of 58 patients who showed sign of spasticity (67%) received oral anti-spastic treatment (34 baclofen, 3 tizanidine, 2 clonazepam), 4 patients (7%) received intrathecal baclofen therapy and 15 patients (26%) did not receive any pharmacological treatment (see table 2). Patients on anti-spastic medication (n=43, 74%) showed more spasticity than patients without anti spastic treatment for the lower limbs (U=209.5; Z=2.52; p=0.01) but not for the upper limbs (U=260; Z=1.67; p=0.09).

INSERT TABLE 2 ABOUT HERE

Upper and lower limbs MAS scores did not differ according to the etiology (Chi square 2.05; dl=3; p=0.56 and Chi square 0.71; dl=3; p=0.87, respectively).

No difference was found between MAS score and the level of consciousness (upper limbs: U=459; Z=0.55; p=0.59; lower limbs: U=477.5; Z=-0.30; p=0.76).

INSERT FIGURE 2

Discussion

Current literature reports the presence of spasticity in 25 to 42% of patients after stroke or traumatic brain injury (25, 26). In our cohort of 65 chronic patients with DOC, 88% showed spasticity, of whom 60% to severe degrees. This result suggests that spasticity is even more frequent in patients with DOC than in patients with milder brain injuries. This high rate of spasticity supports previous results from a pilot study conducted by Pilon et al. in 1996, reporting important motor and posturing impairments in 12 patients with DOC (22). Extensive brain lesions, prolonged immobility, as well as weakness, disuse, and absence of movement of muscles in contracted positions are likely to be causative factors, as they are known to increase spasticity and contracture (37).

Our analyses demonstrated a negative correlation between the degree of spasticity and the frequency of physical therapy. This result suggests that frequent physiotherapy may have a positive effect on patient's spasticity. One could, however, argue that patients showing less spasticity might receive more physical therapy as our result is based on a correlation. But in our view, this is less likely to be the case because the amount of physical therapy is not determined by the severity of spasticity, but rather depends on the health system of the country and assurance reimbursement (i.e. in Belgium patients with DOC should receive 30

minutes of physical therapy 5 days a week). On the other hand, it is possible that patients showing more spasticity receive less physical therapy, especially at the chronic stage. Some patients may show signs of pain (e.g., grimace or other facial expressions) during stretching, which may lead the physical therapist to stop or reduce the time of stretching. Another explanation could be that due to high level of tendon retraction or joint fixation, stretching is very limited and the effects of physical therapy being reduced, patients receive less therapy. Overall, we cannot strongly claim from our results that less spasticity is the result of more physical therapy.

Additionally, our findings on physical therapy contradict a recent study reporting no improvement of spasticity after 6 to 36 weeks of physiotherapy (i.e., manual stretching, casting, and pharmacological treatment) in 10 patients in VS/UWS and MCS (25, 26). The small sample size and the absence of a control group in the study likely contribute to this result. Moreover, a recent study showed that a soft splint placed for 30 minutes in the hand of spastic patients with DOC could decrease the severity of spasticity of the flexor hand muscles and increase the patient's hand opening, although the effect was short lasting (39). It is thought that stretching has an immediate positive effect on spasticity and contractures (25, 26). The duration of these effects, however, appears to fluctuate among studies (25, 26). Further investigation focusing on the effect of physical therapy and the type of rehabilitation (e.g., stretching, tilt-table, massage or passive bike movement trainer) should be performed.

In our study, spasticity appeared to increase over time. This result highlights problems of patient management (e.g., mobilizations, stretching) associated with immobility. Spasticity and immobilization induce adaptive anatomical muscles changes and reflexes modifications (e.g., muscle atrophy, loss of sarcomeres and accumulation of connective tissue and fat) (37) constituting a self-reinforcing negative effect.

A positive correlation was observed between MAS of the upper limbs and NCS-R scores

during daily cares. Nursing and mobilization, especially for the upper limbs as they are more spastic, thus appear associated with pain in spastic patients, as previously observed in other patients with neurological disease (e.g., multiple sclerosis) (25, 26). This is critical as patients with DOC are, by definition, unable to communicate potential discomfort (21). Interventions to alleviate potential pain are therefore mandated in this patient group.

Concerning side-effects, about half of our sample suffered from tendon retraction (upper extremity: 42% and equinovarus feet: 57%), the presence of which was associated with higher level of spasticity. This supports the notion that spasticity increases the risk of tendon retraction (25, 26). Immobilization of joints could also be a driving factor in this regard (for a review see Gracies et al 2005) (37). The high proportion of patients with tendon retractions and joint fixations indicates that muscle hyperactivity should be treated at an early stage to minimize the risk of fixation.

Surprisingly, patients without anti-spastic medication showed lower MAS scores, specifically for the lower limbs, than medicated patients. This probably reflects that patients who do not show signs of spasticity do not need anti-spastic medication, while patients who suffer from spasticity certainly need anti-spastic medication to decrease the severity of spasticity but this treatment may not be sufficient enough to completely abolish it. The reason why only the lower limbs showed a significant difference could be due to weaker spasticity intensity in the lower limbs as compare to the upper limbs. This difference could be even more important without the influence of an anti-spastic medication. Therefore, the spasticity of the lower limbs for the un-medicated patients is the less pronounced (see table 3). So far, available treatments can reduce spasticity by inhibiting excitatory pathways (e.g., baclofen), by stimulating inhibitory pathways (e.g., diazepam) or by inducing local muscle paralysis (e.g., botulinum toxin). Until now, no standard treatment is known to totally suppress spasticity (44). Continuous development of pharmacological options for spastic

conditions is clearly warranted.

The absence of correlation between MAS scores and etiology or level of consciousness suggests that the onset of spasticity is not directly associated with specific lesions patterns but may appear across a broad range of brain injuries. The high presence of spasticity could be explained by the severity and the extent of cerebral damages in this population, which may induce motor pathway impairments and paralysis, with flaccidity or spasticity (45). Moreover, motor deficits are associated with immobility, which increases spasticity and accompanying complications (46). In addition to severe brain damage encompassing the pyramidal tracts, other extrapyramidal disorders, such as parkinsonian syndrome (47), could be involved in motor disabilities. Parkinsonian symptoms during recovery from DOC are very common although rarely reported (25, 26). This possibility could be explored with future neuroimaging studies.

In line with recommendations for stroke patients (25, 26), our findings indicate that muscle hyperactivity should be treated early to minimize risk of spasticity and joint fixation, thus improving the prospect of functional recovery. In clinical practice, even at the acute stage, it is therefore highly recommended to apply comprehensive stretching in a daily routine in all patients. Initial treatment of severely brain-injured patients tend to focus on cerebral and cardiopulmonar functions while muscular and motor functions are down-prioritized, as they are not important for the vital prognosis. Antispastic therapy is usually implemented at the sub-acute stage, even if we know that spasticity can occur earlier. Intensivists and medical doctors should therefore give anti spastic drugs as soon as muscle hypertonicity is detected, and physiotherapy sessions should be increased to allow management of respiratory deficiency and movement disorders at the earliest.

At the chronic stage, when patients leave the rehabilitation unit, they should continue to benefit from an adapted care management, including daily mobilizations, several hours on a

chair, raising and braces, as well as appropriate pharmacological treatment to minimize the adverse effects of spasticity and immobility.

This study has important limitations. The first one is the single assessment of spasticity. Future longitudinal studies should assess spasticity several times in the same patients, as spasticity may fluctuate over time. Moreover, prospective studies should be done to provide more easily interpretable results, regarding for example the correlation between physiotherapy and spasticity. Second, our population was heterogeneous with various etiologies and different time since insults, as we enrolled all the patients who were admitted for a week of assessment at the CHU of Liège. We are currently acquiring more data on spasticity in patients with DOC to be able to classified patients according to their specific etiology, brain lesion, rehabilitation and time since insult.

Conclusions

Our study shows an alarmingly high occurrence of spasticity in patients with DOC. As those patients are already limited in their range of movements, spasticity represents one of the most important disabling factors to be treated. Managing spasticity could help this population to initiate and execute movements and may facilitate voluntary gestures, enabling for example a response to command. Complications such as pain or pathological tendon retraction impair these patients' quality of life and functional recovery. Further research should use neurophysiology testing and neuroimaging methods to examine the association between locations of brain lesion and the presence of spasticity, and investigate the possible contribution of an extrapyramidal parkinsonian syndrome. This could give valuable information regarding the physiopathology of spasticity and its onset in both traumatic and non-traumatic etiologies. Additionally, further studies should assess the impact of specific and combined treatments on spasticity or tendon retraction, as well as behavioral signs of

pain. The correlation between spasticity and pain highlights the negative effect of spasticity on quality of life and the importance of rapid action to address this complication. Moreover, as motor impairments have been shown to prevent the expression of signs of consciousness at bedside (25, 26), it is of critical importance to improve the quality of care and rehabilitation for this population. Clear guidelines of therapy are needed and should be established.

REFERENCES

1. Lance J. Spasticity: Disorders Motor Control. Miami, FL: Year Book Medical Publishers: In: Feldman RG, Young RP, Koella WP eds; 1980.
2. Ward AB. A literature review of the pathophysiology and onset of post-stroke spasticity. Eur J Neurol. 2012;19(1):21-7.
3. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007;6(8):725-33.
4. McComas AJ. Human neuromuscular adaptations that accompany changes in activity. Med Sci Sports Exerc. 1994;26(12):1498-509.
5. Sommerfeld DK, Eek EU, Svensson AK, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. Stroke. 2004;35(1):134-9.
6. Gracies JM, Bayle N, Vinti M, Alkandari S, Vu P, Loche CM, et al. Five-step clinical assessment in spastic paresis. Eur J Phys Rehabil Med. 2010;46(3):411-21.
7. Doan QV, Brashear A, Gillard PJ, Varon SF, Vandenburgh AM, Turkel CC, et al. Relationship between disability and health-related quality of life and caregiver burden in patients with upper limb poststroke spasticity. PM R. 2012;4(1):4-10.
8. Svensson J, Borg S, Nilsson P. Costs and quality of life in multiple sclerosis patients with spasticity. Acta Neurol Scand. 2014;129(1):13-20.
9. Ada L, O'Dwyer N, O'Neill E. Relation between spasticity, weakness and contracture of the elbow flexors and upper limb activity after stroke: an observational study. Disabil Rehabil. 2006;28(13-14):891-7.
10. Malhotra S, Pandyan AD, Rosewilliam S, Roffe C, Hermens H. Spasticity and contractures at the wrist after stroke: time course of development and their association with functional recovery of the upper limb. Clin Rehabil. 2011;25(2):184-91.
11. Brainin M. Poststroke spasticity: Treating to the disability. Neurology. 2013;80(3 Suppl 2):S1-4.
12. Zorowitz RD, Gillard PJ, Brainin M. Poststroke spasticity: sequelae and burden on stroke survivors and caregivers. Neurology. 2013;80(3 Suppl 2):S45-52.
13. Wissel J, Schelosky LD, Scott J, Christe W, Faiss JH, Mueller J. Early development of spasticity following stroke: a prospective, observational trial. J Neurol. 2010;257(7):1067-72.
14. Urban P, Wolf T, Uebele M, Marx J, Vogt T, Stoeter P, et al. Occurence and clinical predictors of spasticity after ischemic stroke. Stroke. 2010;41(9):2016-20.
15. Elovic EP, Simone LK, Zafonte R. Outcome assessment for spasticity management in the patient with traumatic brain injury: the state of the art. J Head Trauma Rehabil. 2004;19(2):155-77.
16. Jennett B, Plum F. Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet. 1972;1(7753):734-7.
17. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, Leon-Carrion J, Sannita WG, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 2010;8:68.

18. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58(3):349-53.
19. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. N Engl J Med. 1994;330(21):1499-508.
20. Schnakers C, Zasler ND. Pain assessment and management in disorders of consciousness. Curr Opin Neurol. 2007;20(6):620-6.
21. Chatelle C, Thibaut A, Whyte J, De Val MD, Laureys S, Schnakers C. Pain issues in disorders of consciousness. Brain Injury. 2014;in press.
22. Pilon M, Sullivan SJ. Motor profile of patients in minimally responsive and persistent vegetative states. Brain Injury. 1996;10(6):421-37.
23. Leong B. The vegetative and minimally conscious states in children: spasticity, muscle contracture and issues for physiotherapy treatment. Brain Injury. 2002;16(3):217-30.
24. Lapitskaya N, Gosseries O, De Pasqua V, Pedersen AR, Nielsen JF, de Noordhout AM, et al. Abnormal corticospinal excitability in patients with disorders of consciousness. Brain Stimul. 2013;6(4):590-7.
25. Monti MM, Vanhaudenhuyse A, Coleman MR, Boly M, Pickard JD, Tshibanda L, et al. Willful modulation of brain activity in disorders of consciousness. N Engl J Med. 2010;362(7):579-89.
26. Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernandez-Espejo D, Pickard JD, et al. Bedside detection of awareness in the vegetative state: a cohort study. Lancet. 2011;378(9809):2088-94.
27. Habbal D, Gosseries O, Noirhomme Q, Renaux J, Lesenfants D, Bekinschtein T, et al. Volitional electromyographic responses in disorders of consciousness. Brain Injury. 2014;in press.
28. Stender J, Gosseries O, Bruno MA, Charland-Verville V, vanhaudenhuyse A, Demertzi A, et al. Diagnostic precision of multimodal neuroimaging methods in disorders of consciousness: a clinical validation study. Lancet. 2014;in press.
29. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85(12):2020-9.
30. Schnakers C, Majerus S, Giacino J, Vanhaudenhuyse A, Bruno MA, Boly M, et al. A French validation study of the Coma Recovery Scale-Revised (CRS-R). Brain Injury. 2008;22(10):786-92.
31. Mehrholz J, Wagner K, Meissner D, Grundmann K, Zange C, Koch R, et al. Reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in adult patients with severe brain injury: a comparison study. Clin Rehabil. 2005;19(7):751-9.
32. Chatelle C, Majerus S, Whyte J, Laureys S, Schnakers C. A sensitive scale to assess nociceptive pain in patients with disorders of consciousness. J Neurol Neurosurg Psychiatry. 2012;83(12):1233-7.
33. Seel RT, Sherer M, Whyte J, Katz DI, Giacino JT, Rosenbaum AM, et al. Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. Arch Phys Med Rehabil. 2010;91(12):1795-813.
34. Hart A. Mann-Whitney test is not just a test of medians: differences in spread can be important. BMJ. 2001;323(7309):391-3.

35. Kendall. A new measure of rank correlation. Biometrika. 1938;30:81-9.
36. Brown GW, Hayden GF. Nonparametric methods. Clinical applications. Clin Pediatr (Phila). 1985;24(9):490-8.
37. Gracies JM. Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. Muscle Nerve. 2005;31(5):535-51.
38. Wheatley-Smith L, McGuinness S, Colin Wilson F, Scott G, McCann J, Caldwell S. Intensive physiotherapy for vegetative and minimally conscious state patients: a retrospective audit and analysis of therapy intervention. Disabil Rehabil. 2013;35(12):1006-14.
39. Thibaut A, Deltombe T, Wannez S, Gosseries O, Ziegler E, Dieni C, et al. Impact of soft splints on upper limb spasticity in chronic patients with disorders of consciousness: a randomized, single-blind, controlled trial. 2014;under revision.
40. Ada L, Goddard E, McCully J, Stavrinos T, Bampton J. Thirty minutes of positioning reduces the development of shoulder external rotation contracture after stroke: a randomized controlled trial. Arch Phys Med Rehabil. 2005;86(2):230-4.
41. Yeh CY, Tsai KH, Chen JJ. Effects of prolonged muscle stretching with constant torque or constant angle on hypertonic calf muscles. Arch Phys Med Rehabil. 2005;86(2):235-41.
42. Bovend'Eerdt TJ, Newman M, Barker K, Dawes H, Minelli C, Wade DT. The effects of stretching in spasticity: a systematic review. Arch Phys Med Rehabil. 2008;89(7):1395-406.
43. Kheder A, Nair KP. Spasticity: pathophysiology, evaluation and management. Pract Neurol. 2012;12(5):289-98.
44. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: Physiology, assessment and treatment. Brain Inj. 2013.
45. Brown P. Pathophysiology of spasticity. J Neurol Neurosurg Psychiatry. 1994;57(7):773-7.
46. Gracies JM. Pathophysiology of spastic paresis. II: Emergence of muscle overactivity. Muscle Nerve. 2005;31(5):552-71.
47. Jellinger KA. Parkinsonism and persistent vegetative state after head injury. J Neurol Neurosurg Psychiatry. 2004;75(7):1082; author reply -3.
48. Formisano R, D'Ippolito M, Risetti M, Riccio A, Caravasso CF, Catani S, et al. Vegetative state, minimally conscious state, akinetic mutism and Parkinsonism as a continuum of recovery from disorders of consciousness: an exploratory and preliminary study. Funct Neurol. 2011;26(1):15-24.
49. Formisano R, Zasler ND. Posttraumatic Parkinsonism. J Head Trauma Rehabil. 2014.
50. Hesse S, Mach H, Frohlich S, Behrend S, Werner C, Melzer I. An early botulinum toxin A treatment in subacute stroke patients may prevent a disabling finger flexor stiffness six months later: a randomized controlled trial. Clin Rehabil. 2012;26(3):237-45.

TABLES

Table 1: clinical data for patients in UWS and MCS

Diagnosis	Etiology	Gender	Age (years)	Time since injury (months)	UL– MAS mean±SD	LL – MAS mean±SD
25 UWS/UWS	12 TBI	8 w	39±14	40±41	2.9±1.5	2.3±1.9
40 MCS	28 TBI	14 w	38±14	35±28	2.8±1.3	2.5±1.4

Abbreviations: VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state; TBI: traumatic brain injury, w: women; UL: upper limb; LL: lower limb; MAS: modified ashworth scale

Table 2: Percentage of motor disabilities and medication

Presence of	% of patients – IC 95% (n=65)
Spasticity	88 ± 12%
Severe spasticity (MAS ≥ 3)	60 ± 11.8%
Upper extremity tendon retraction	42 ± 10.8%
Fixed equinovarus feet	57 ± 11.7%
Medication of spastic patients (n=58)	74 ± 12%

Table 3: Results of group comparisons with mean, standard deviation (SD) of the MAS and p value

Test	Limbs		Mean ± SD	p value
UL and LL	Upper limb (UL)		2.9±1.4	p=0.001*
	Lower limb (LL)		2.4±1.5	
Medication	UL	Medicated	3.29±0.95	p=0.09
		Unmedicated	2.77±1.19	
	LL	Medicated	2.93±1.38	p=0.01*
		Unmedicated	1.99±1.21	
Etiology	UL	Trauma	3.15±56	p=0.56
		Anoxia	3±2.07	
		Subarachnoid hemorr.	3.83±0.75	
		Mixed	3.25±1.71	
	LL	Trauma	3.22±1.87	p=0.87
		Anoxia	2.79±2.12	
		Subarachnoid hemorr.	2±1.09	
		Mixed	4±1.41	
Diagnosis	UL	VS/UWS	2.9±1.5	p=0.59
		MCS	2.8±1.3	
	LL	VS/UWS	2.3±1.9	p=0.76
		MCS	2.5±1.4	

Abbreviations: MAS= Modified Ashworth Scale; UL= upper limbs; LL= lower limbs; VS/UWS= vegetative state/unresponsive wakefulness syndrome; MCS= Minimally Conscious State. * indicated a significant result

TITLES OF FIGURES

Figure 1: Proportion of patients with different level of spasticity according to the MAS scores

Figure 2: A. correlation between Modified Ashworth Scale (MAS) mean scores and the frequency of physical therapy per week (tau= -0,20; p=0,018). B. correlation between MAS mean scores and the time since insult (tau=0.23; p=0.006). C. correlation between MAS mean scores and the scores at the Nociception Coma Scale-Revised during cares (tau= 0.31; p=0.001)

Table 1: clinical data for patients in UWS and MCS

Diagnosis	Etiology	Gender	Age (years)	Time since injury (months)	UL– MAS mean±SD	LL – MAS mean±SD
25 UWS/UWS	12 TBI	8 w	39±14	40±41	2.9±1.5	2.3±1.9
40 MCS	28 TBI	14 w	38±14	35±28	2.8±1.3	2.5±1.4

Abbreviations: VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state; TBI: traumatic brain injury, w: women; UL: upper limb; LL: lower limb; MAS: Modified Ashworth Scale

Table 2: Percentage of motor disabilities and medication

Presence of	**% of patients – IC 95%** **(n=65)**
Spasticity	88 ± 12%
Severe spasticity (MAS ≥ 3)	60 ± 11.8%
Upper extremity tendon retraction	42 ± 10.8%
Fixed equinovarus feet	57 ± 11.7%
Medication of spastic patients (n=58)	74 ± 12%

Table 3: Results of group comparisons with mean, standard deviation (SD) of the MAS and p value

Comparison	Limbs		MAS mean ± SD	p value
UL and LL	UL		2.9±1.4	p=0.001 *
	LL		2.4±1.5	
Medication	UL	Medicated	3.29±0.95	p=0.09
		Unmedicated	2.77±1.19	
	LL	Medicated	2.93±1.38	p=0.01*
		Unmedicated	1.99±1.21	
Etiology	UL	Trauma	3.15±56	p=0.56
		Anoxia	3±2.07	
		Subarachnoid hemorr.	3.83±0.75	
		Mixed	3.25±1.71	
	LL	Trauma	3.22±1.87	p=0.87
		Anoxia	2.79±2.12	
		Subarachnoid hemorr.	2±1.09	
		Mixed	4±1.41	
Diagnosis	UL	VS/UWS	2.9±1.5	p=0.59
		MCS	2.8±1.3	
	LL	VS/UWS	2.3±1.9	p=0.76
		MCS	2.5±1.4	

Abbreviations: MAS= Modified Ashworth Scale; UL= upper limbs; LL= lower limbs; VS/UWS= vegetative state/unresponsive wakefulness syndrome; MCS= Minimally Conscious State. * indicated a significant result

Supplementary material: Clinical data

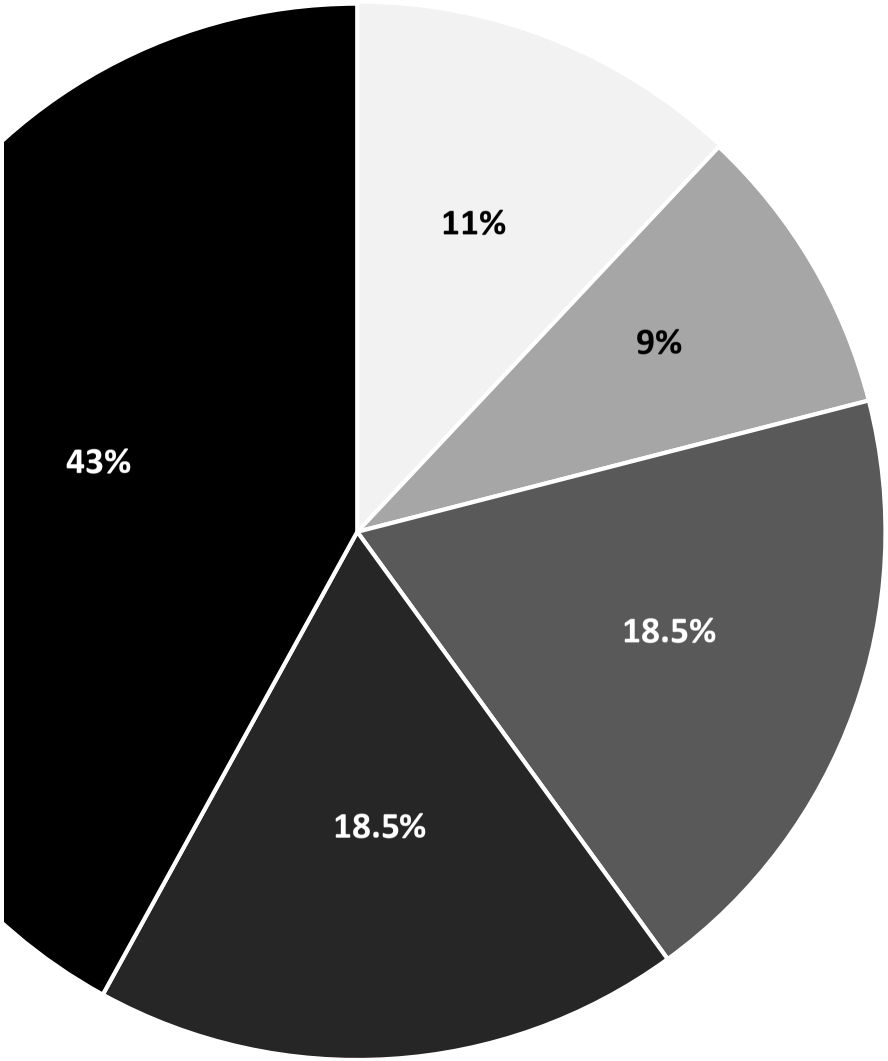
Patient	Diagnosis	Etiology	Age (gender)	TSO (days)	MAS UL	Higher MAS	MAS LL	Higher MAS	Tendon retraction	Equino-varus	CRS-R total score	NCS-R total score	Treatment for spasticity	Frequency of PT
1	MCS	TBI	30 (m)	90	3	EF	4	HS	Elbow	Yes	11	4	No	5
2	MCS	TBI	24 (m)	325	3	EF	3	triceps	Elbow	Yes	8	3	Baclofen	5
3	MCS	TBI	18 (m)	430	3	EF	1+	add	Triple	No	15	/	Baclofen pump	5
4	MCS	TBI	30 (m)	605	3	EF	4	triceps	No	Yes	9	3	Baclofen	5
5	MCS	TBI	50 (m)	240	0	/	0	/	No	No	8	5	Baclofen	5
6	MCS	TBI	27 (m)	545	0	/	0	/	Triple	No	8	/	No	5
7	MCS	TBI	48 (f)	277	3	IHM	1	add	Triple	No	10	6	Baclofen	5
8	MCS	TBI	46 (m)	460	3	EF	4	triceps	Elbow	Yes	9	4	Baclofen	5
9	MCS	TBI	41 (m)	4350	3	EF	3	add	Elbow	Yes	11	2	No	5
10	MCS	Cardiac arrest	48 (f)	210	2	EF	1+	triceps	Triple	Yes	7	/	No	5
11	MCS	Hemorrhagic stroke	40 (m)	2615	4	EF	2	HS	Elbow	Yes	11	3	No	5
12	MCS	Cardiac arrest	63 (f)	120	3	IHM	4	triceps	Elbow	Yes	13	/	Sirdalud	5
13	MCS	TBI	24 (m)	2680	4	EF	4	triceps	Triple	Yes	8	5	Baclofen	0
14	MCS	Subarachnoid hemorrhage	46 (f)	489	2	EF	1+	HS	No	No	17	8	No	3
15	MCS	TBI	31 (f)	150	4	EE	4	triceps	Triple	Yes	9	/	Baclofen	5
16	MCS	Mixed	25(f)	310	2	EF	4	triceps	Triple	Yes	7	/	Baclofen	3
17	MCS	Mixed	22 (m)	3285	3	IHM	3	triceps	Triple	Yes	23	3	Baclofen	5
18	MCS	TBI	29 (m)	239	2	EF	2	add	No	Yes	6	/	No	5

19	MCS	TBI	30 (f)	2705	2	IHM	1+	triceps	No	No	9	/	No	5
20	MCS	TBI	25 (m)	1215	3	IHM	4	HS	Triple	Yes	10	2	Baclofen pump	3
21	MCS	TBI	27 (m)	1094	3	EF	4	triceps	Triple	Yes	9	5	Baclofen pump	3
22	MCS	Anoxia	66 (m)	335	1+	EF	1+	HS	No	No	16	/	No	5
23	MCS	TBI	61 (m)	127	0	/	0	/	No	No	12	2	No	5
24	MCS	TBI	55 (f)	180	2	EF	1+	add	No	No	16	3	No	2
25	MCS	TBI	28(m)	1855	4	EF	3	quadri	Triple	Yes	15	/	Baclofen	3
26	MCS	TBI	22 (m)	2980	2	IHM	3	quadri	No	No	9	2	No	5
27	MCS	Cardiac arrest	51 (m)	1460	4	EF	4	triceps	Triple	Yes	12	3	No	5
28	MCS	Subarachnoid hemorrhage	68 (f)	1430	3	IHM	2	add	Triple	No	7	3	Baclofen	3
29	MCS	TBI	35 (m)	1335	3	WF	4	triceps	Triple	Yes	6	3	Baclofen	3
30	MCS	TBI	23 (m)	2100	2	WF	4	triceps	Triple	Yes	14	/	Baclofen	5
31	MCS	TBI	23 (m)	641	0	/	0	/	No	Yes	7	3	Baclofen pump	5
32	MCS	TBI	22 (m)	1095	3	EF	3	HS	No	No	11	2	Baclofen	5
33	MCS	TBI	30 (m)	3300	2	EF	1+	triceps	No	No	7	2	No	5
34	MCS	Subarachnoid hemorrhage	43 (f)	95	2	EF	1+	HS	No	No	6	2	No	3
35	MCS	TBI	22 (f)	3160	2	EF	2	triceps	Elbow	No	11	3	Baclofen	5
36	MCS	TBI	56 (f)	4320	4	IHM	/	HS	Triple	Yes	15	2	Baclofen	2
37	MCS	Subarachnoid hemorrhage	47 (f)	239	3	EF	1+	add	Elbow	No	10	2	Baclofen	2
38	MCS	TBI	39 (f)	940	3	EF	3	add	No	Yes	9	3	Sirdalud	5

39	MCS	TBI	45 (m)	635	1+	IHM	2	add	No	No	6	5	No	4
40	MCS	Hypoxia	55 (m)	90	2	EF	1	HS	No	No	16	2	No	5
41	VS/UWS	Cardiac arrest	48 (m)	2890	4	EF	4	triceps	Triple	Yes	4	3	Baclofen pump	2
42	VS/UWS	TBI	27 (m)	1544	2	WF	4	triceps	No	Yes	4	3	Baclofen	5
43	VS/UWS	Cardiac arrest	73 (m)	90	0	/	0	/	No	No	6	1	No	5
44	VS/UWS	Cardiac arrest	30 (m)	740	0	EF	1+	triceps	Elbow	Yes	5	1	Baclofen	6
45	VS/UWS	Cardiac arrest	30 (f)	2412	4	EF	4	HS	Triple	Yes	6	/	Baclofen	2
46	VS/UWS	TBI	30 (f)	560	3	EF	4	quadri	Triple	Yes	4	3	Baclofen	3
47	VS/UWS	TBI	28 (m)	2645	4	EF	4	add	Triple	Yes	5	3	Baclofen	5
48	VS/UWS	TBI	22 (m)	200	3	EF	2	HS	No	No	4	5	Baclofen	3
49	VS/UWS	TBI	30 (m)	2555	1+	WF	/	triceps	No	Yes	6	2	Rivotril	5
50	VS/UWS	Cardiac arrest	54 (m)	515	4	EF	0	/	Elbow	No	4	/	Baclofen	5
51	VS/UWS	Cardiac arrest	49 (f)	485	3	IHM	4	triceps	Triple	Yes	4	4	Baclofen	3
52	VS/UWS	Cardiac arrest	64 (m)	790	4	EF	0	/	Elbow	No	6	/	No	5
53	VS/UWS	TBI	30 (m)	850	2	WF	2	add	Triple	Yes	4	2	Baclofen	2
54	VS/UWS	Cardiac arrest	38 (f)	1670	3	EF	4	triceps	Elbow	Yes	5	3	Baclofen	5
55	VS/UWS	TBI	52 (f)	273	0	/	0	/	No	No	4	0	No	1
56	VS/UWS	TBI	21 (m)	314	3	EF	/	triceps	No	No	5	1	No	5
57	VS/UWS	TBI	34 (m)	1000	4	EF	4	quadri	Triple	Yes	5	6	Rivotril	3
58	VS/UWS	Encephalomyelitis	28 (m)	775	0	IHM	1+	triceps	No	Yes	4	3	Baclofen	3

59	VS/UWS	Mixed	30 (m)	605	1	WF	1+	triceps	Elbow	Yes	6	/	Baclofen	5
60	VS/UWS	Subarachnoid hemorrhage	51 (m)	360	3	WF	0	/	Elbow	No	6	4	Sirdalud	4
61	VS/UWS	Cardiac arrest	41 (f)	1750	0	IHM	/	triceps	No	Yes	5	3	No	5
62	VS/UWS	Mixed	31 (m)	1975	4	EF	4	HS	Triple	Yes	6	/	Baclofen	5
63	VS/UWS	TBI	45 (f)	240	0	/	0	/	No	No	6	0	No	5
64	VS/UWS	TBI	25 (m)	485	3	WF	4	triceps	Triple	Yes	6	3	Baclofen	3
65	VS/UWS	TBI	66 (m)	665	1+	EF	1	triceps	No	No	7	/	Baclofen	5

Abbreviations: VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state; TBI: traumatic brain injury; TSO; time since onset; MAS: modified ashworth scale; UL: upper limb; LL: lower limb; CRS-R total scores: the highest total scores obtained at the coma recovery scale-revised; NCS-R total scores: total scores at the nociception coma scale-revised; PT: physical therapy; EF: elbow flexors; EE: elbow extensor; WF: wrist flexor; IHM: intrinsic hand muscles; HS: hamstring; add: adductor; a slash in LL column means that spasticity could not be assessed due to joint fixation. Triple tendon retraction means tendon retraction of the metacarpophalagean articulation, wrist and elbow.



0 : no increase in muscle tone

1 : slight increase in muscle tone, manifested by a catch or by minimal resistance at the end of the range of motion (ROM) when the affected part(s) is (are) moved in flexion or extension)

2 : slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM

3 : more marked increase in muscle tone through most of the ROM, but affected part(s) easily moved

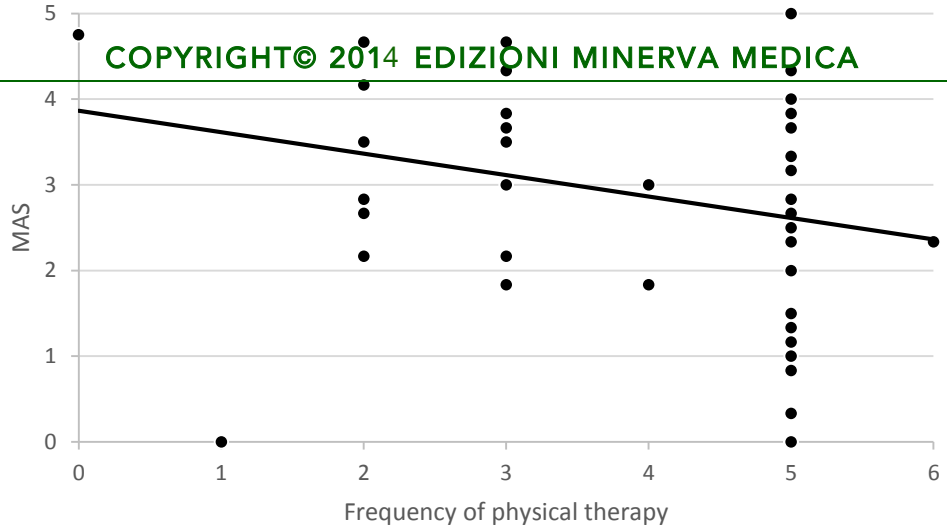
4 : considerable increase in muscle tone, passive movement difficult

5 : Affected part(s) rigid in flexion or extension

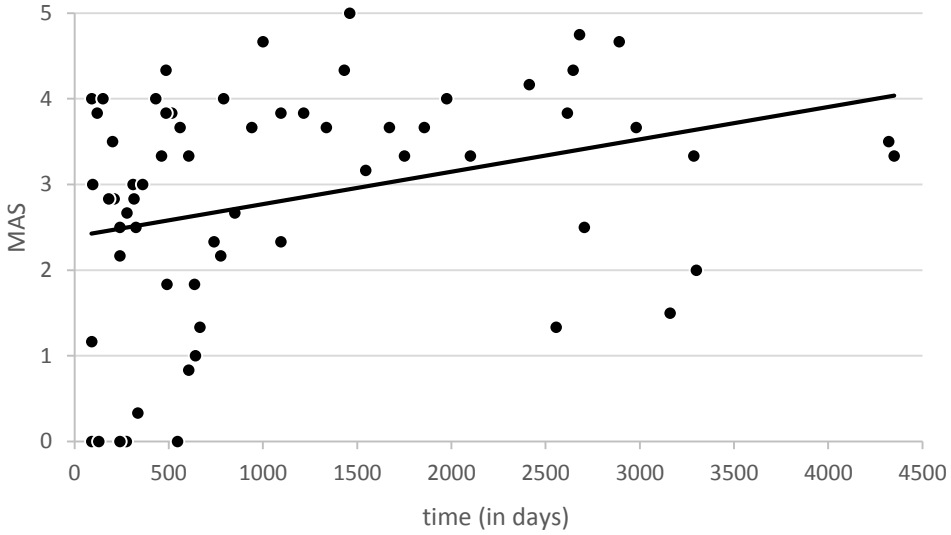
Moderate sp

Severe spast

A.



B.



C.