25th International Symposium on ALS/MND

5 -7 December 2014

Brussels, Belgium

ALS: Einblicke
Neuigkeiten

Dr. Kathi Schweikert

11.12.2014

Neuigkeiten 2014

- Genetik
- Pathophysiologie
- Klinik: Symptome
- Diagnostik: MRI
- Todesursachen
- Copeing
- Advanced Care Planning/End of life Care
- Therapie/Hilfsmittel

Genetik

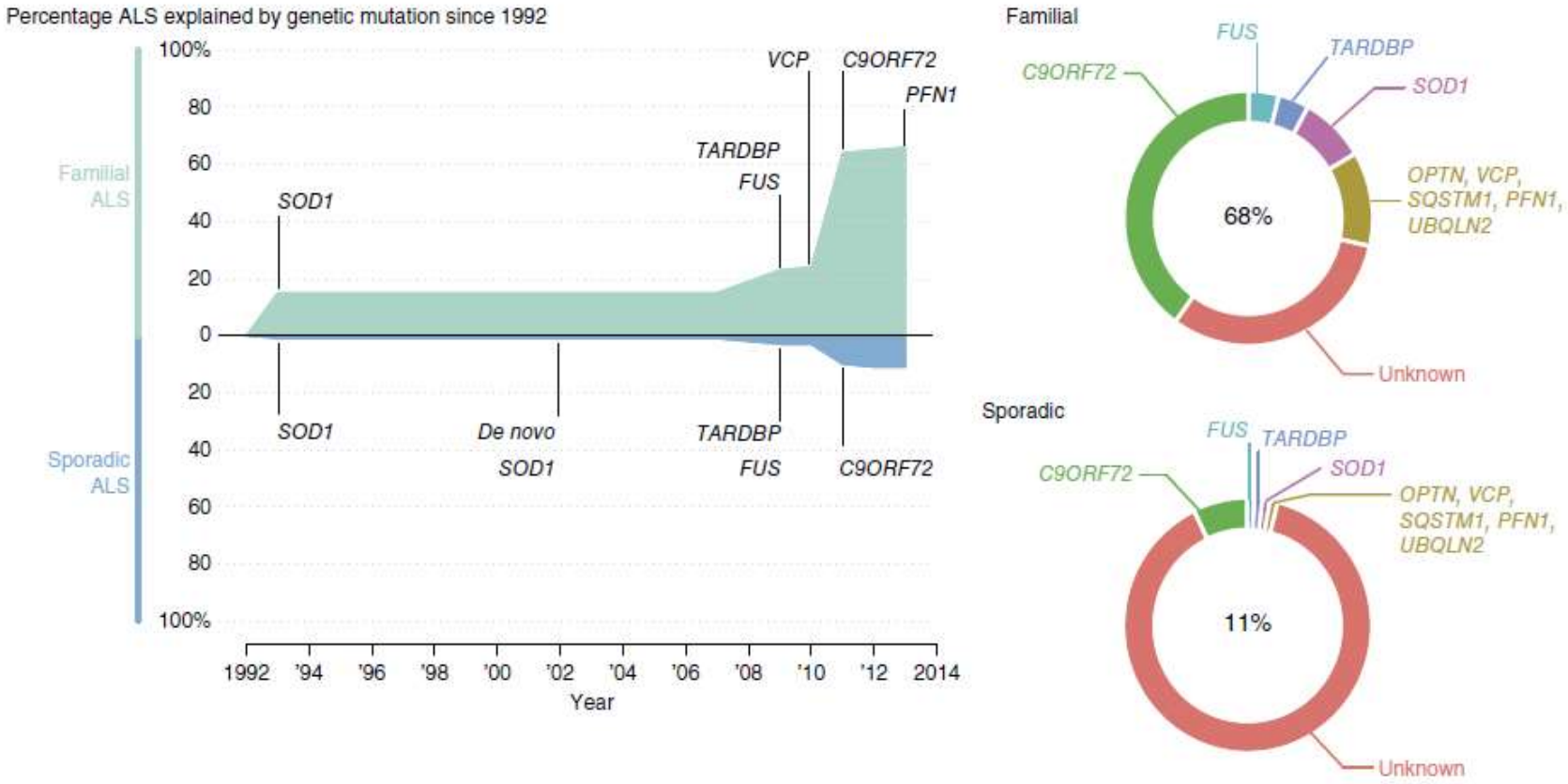
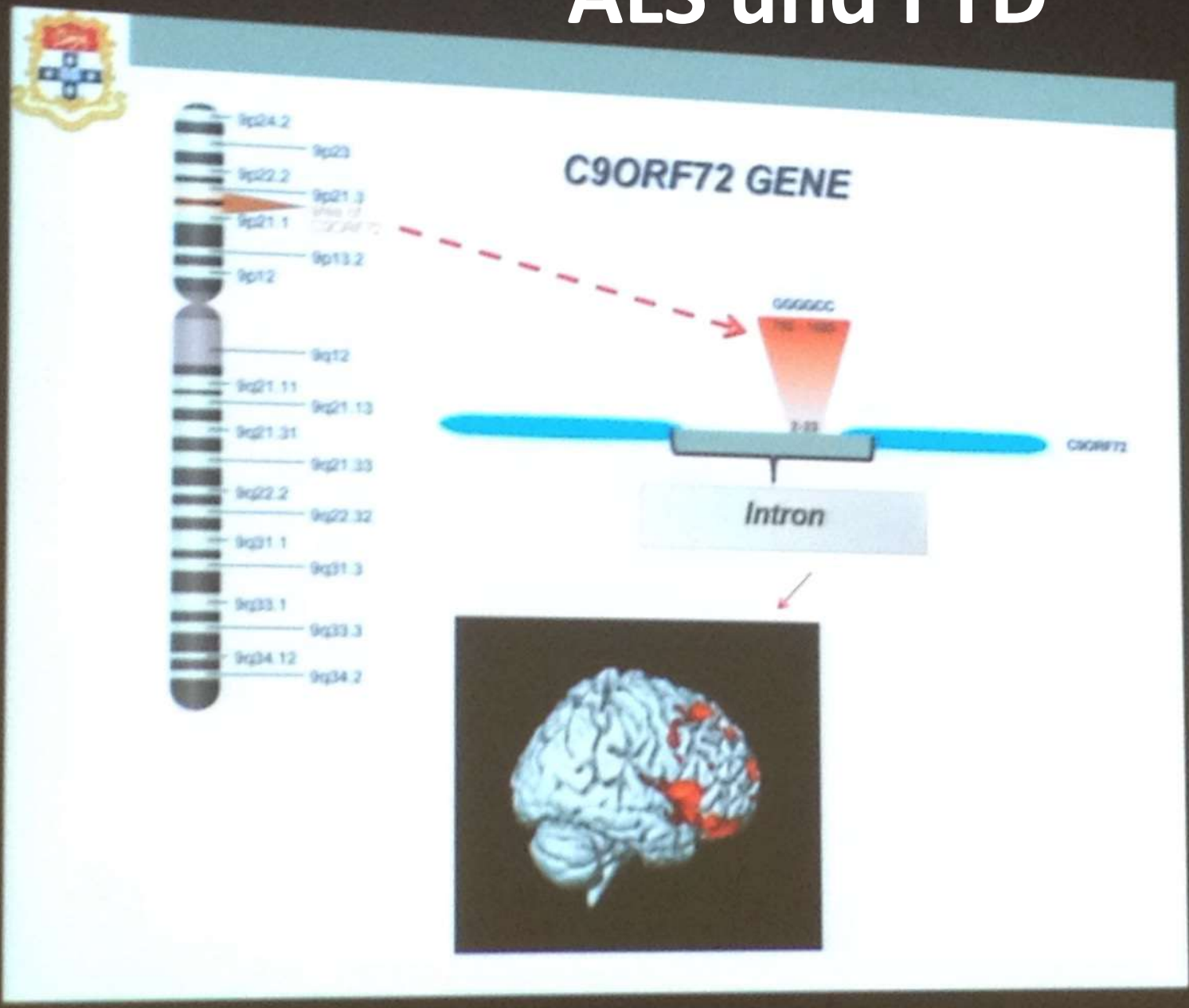


Figure 1 Timeline of gene discoveries in familial and sporadic ALS. Values represent the proportion of ALS explained by each gene in populations of European ancestry. References are provided in the main text.

Renton et al. Nature Neuroscience, 2014

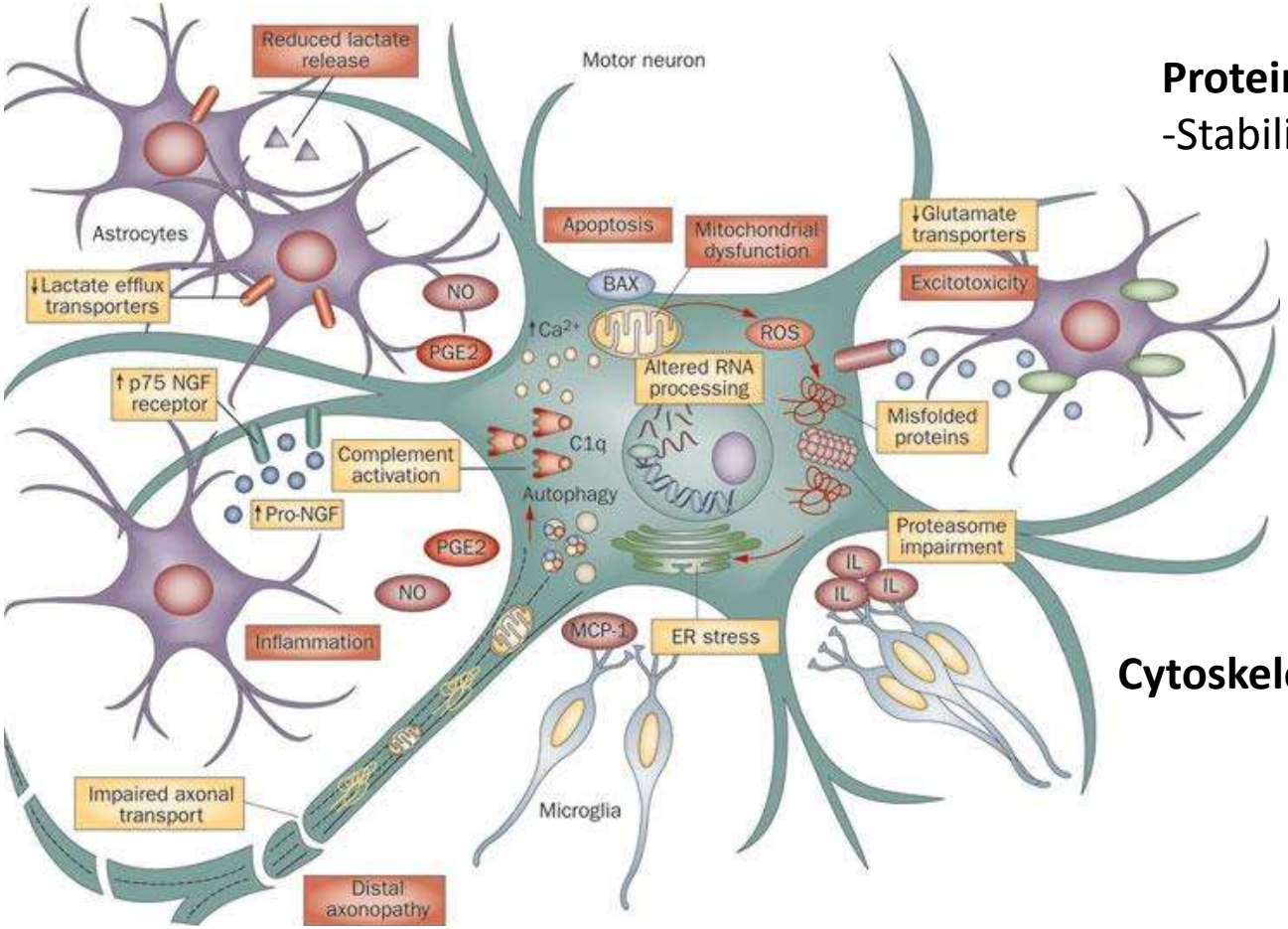
Neu entdeckt: TBK1-Mutationen
Serine/threonine-proteinkinase bei 202 FALS

ALS und FTD



Project MiNE: 15.000 Blutproben

Pathophysiologie



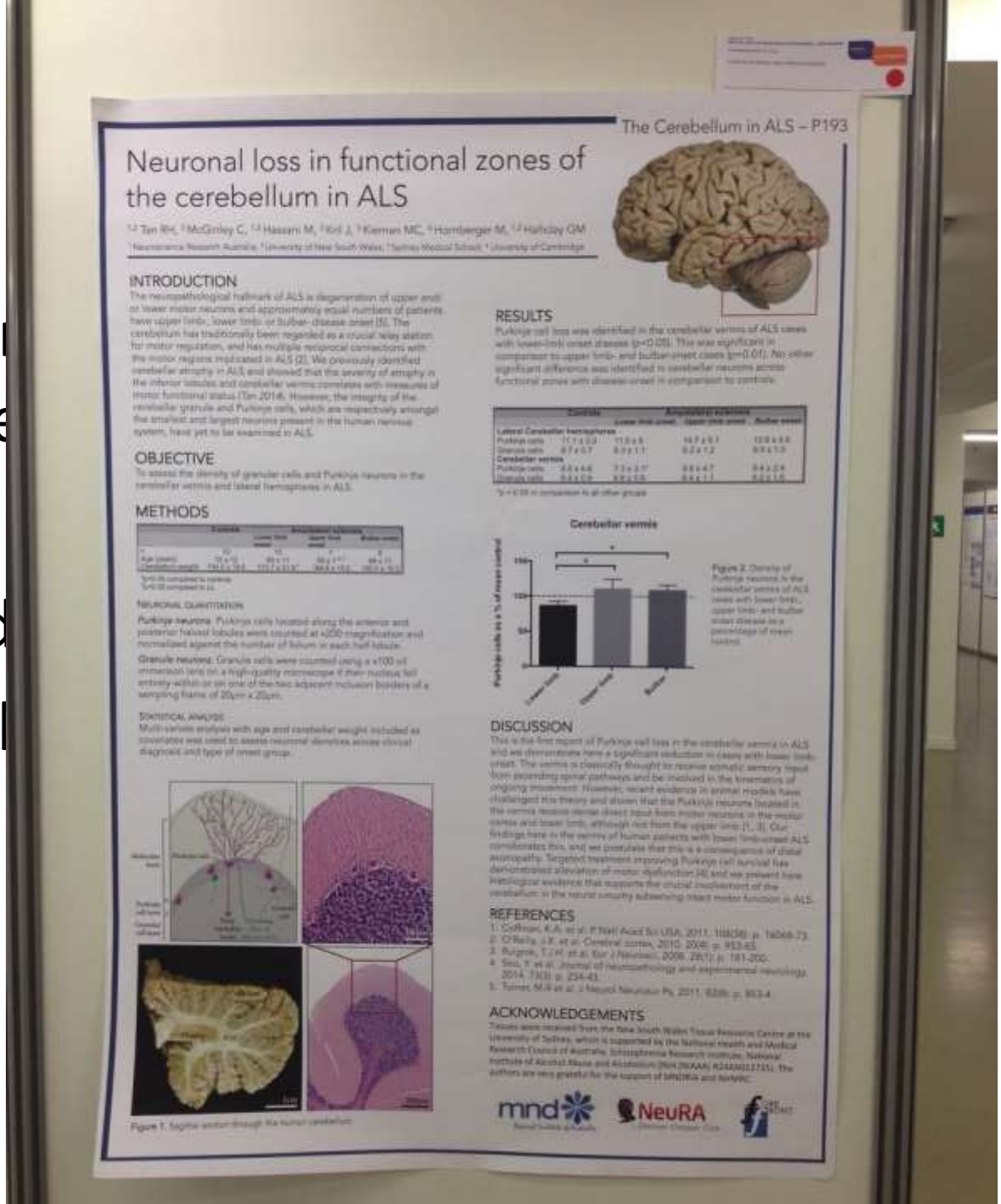
Protein:
-Stabilisierung/Faltung/Degeneration

RNA-Metabolismus:
Axonaler Transport

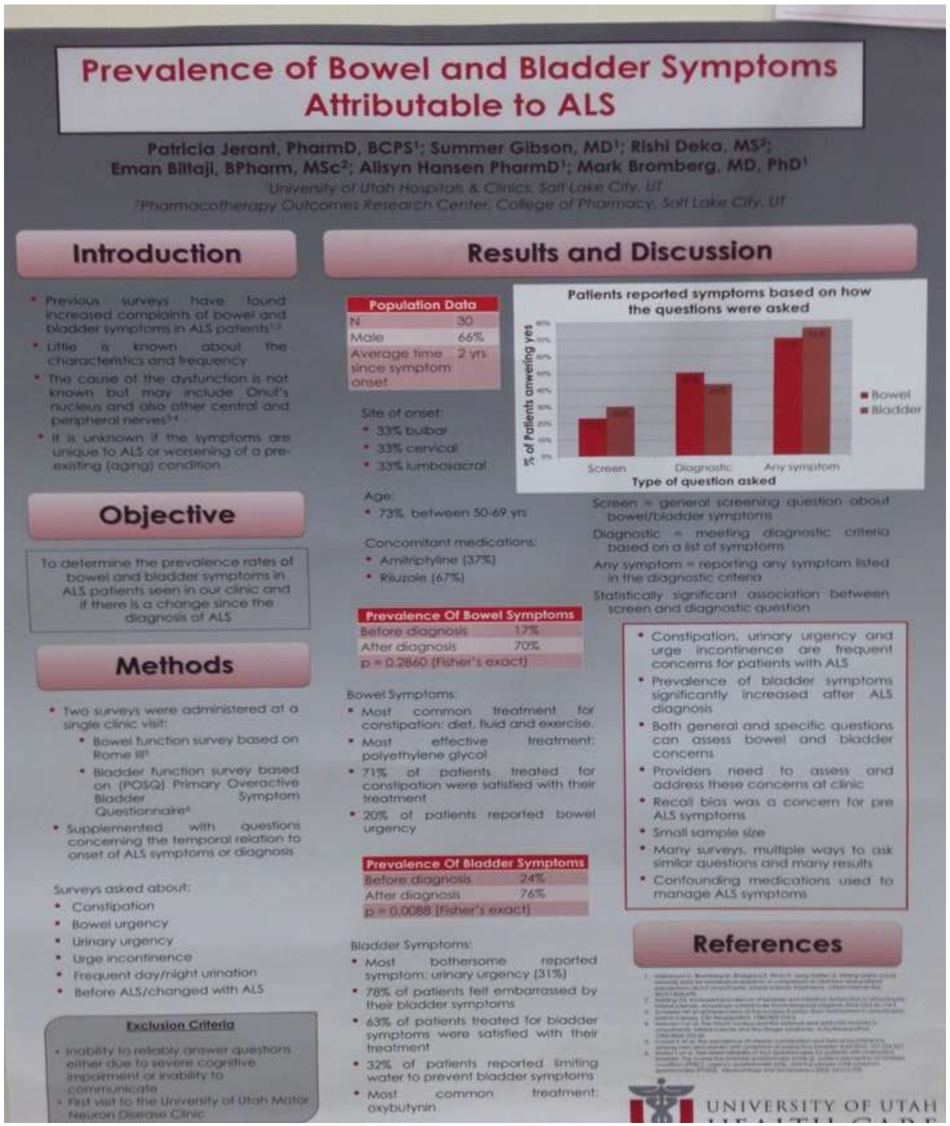
Cytoskeletale Biologie

Andere Zellen (non-neuronal cells):
Astrozyten, Mikroglia, Oligodendrozyten

- Kognitive/Ver
  temporale De
- Schmerzen
- Extrapyramid
- Kleinhirnzeich



Symptome



Prevalence of Bowel and Bladder Symptoms Attributable to ALS
Patricia Jerant, PharmD, BCPS[1]; Summer Gibson, MD[1]; Rishi Deka, MS[2]; Eman Biltaji, BPharm, MSc[2]; Alisyn Hansen PharmD[1]; Mark Bromberg, MD, PhD[1]
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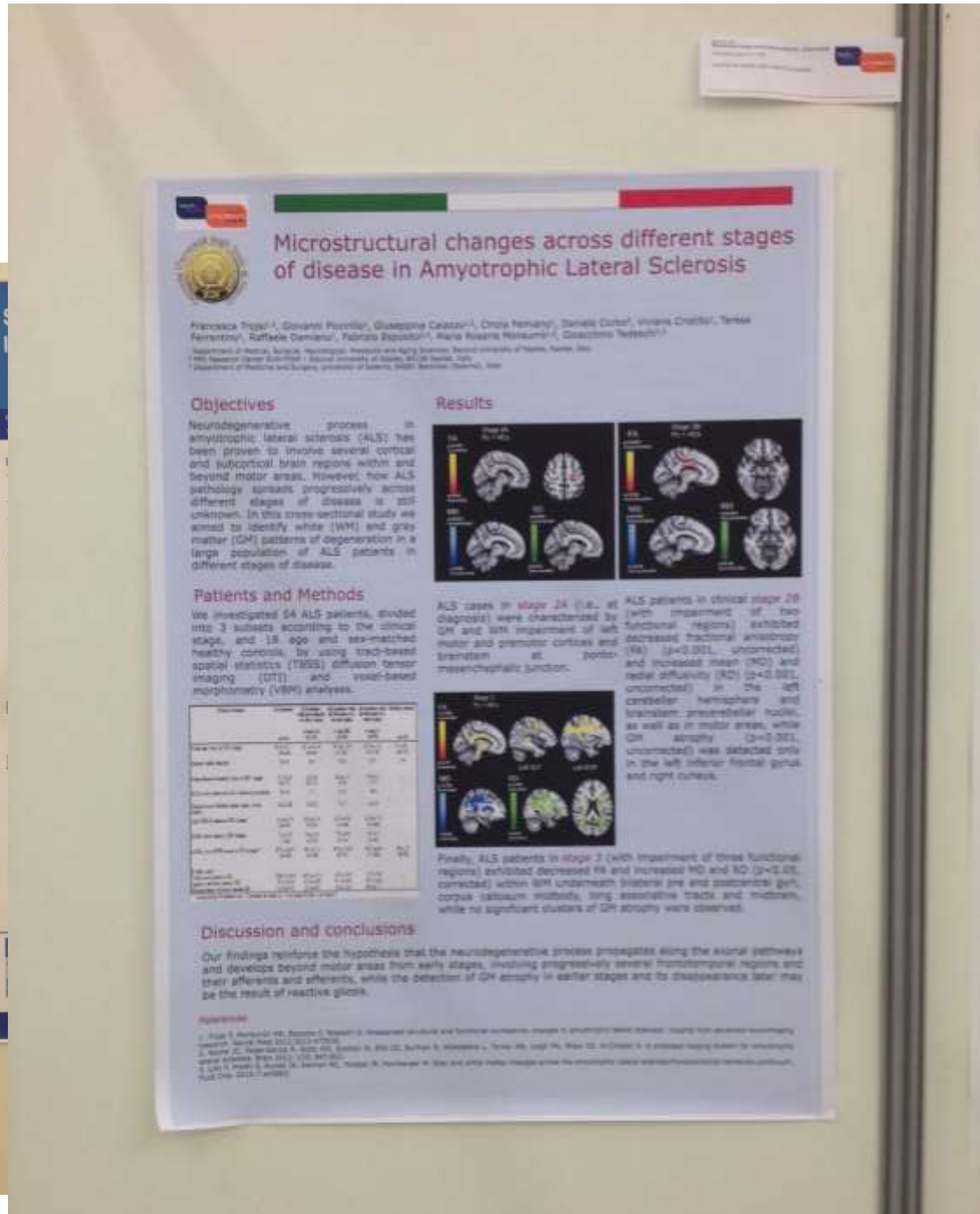
Introduction
Previous surveys have found increased complaints of bowel and bladder symptoms in ALS patients
Little is known about the characteristics and frequency
The cause of the dysfunction is not known but may include Onuf's nucleus and also other central and peripheral nerves
It is unknown if the symptoms are unique to ALS or worsening of a pre-existing (aging) condition
Objective
To determine the prevalence rates of bowel and bladder symptoms in ALS patients seen in our clinic and if there is a change since the diagnosis of ALS
Methods
Two surveys were administered at a single clinic visit:
Bowel function survey based on Rome III
Bladder function survey based on (POSQ) Primary Overactive Bladder Symptom Questionnaire
Supplemented with questions concerning the temporal relation to onset of ALS symptoms or diagnosis
Surveys asked about:
Constipation
Bowel urgency
Urinary urgency
Urge incontinence
Frequent day/night urination
Before ALS/changed with ALS
Exclusion Criteria
Inability to reliably answer questions either due to severe cognitive impairment or inability to communicate
First visit to the University of Utah Motor Neuron Disease Clinic
Results and Discussion
Population Data
N 30
Male 66%
Average time since symptom onset 2 yrs
Site of onset:
33% bulbar
33% cervical
33% lumbosacral
Age:
73% between 50-69 yrs
Concomitant medications:
Amitriptyline (37%)
Riluzole (67%)
Patients reported symptoms based on how the questions were asked
% of Patients anwering yes
Screen
Diagnostic
Any symptom
Type of question asked
Bowel
Bladder
Screen = general screening question about bowel/bladder symptoms
Diagnostic = meeting diagnostic criteria based on a list of symptoms
Any symptom = reporting any symptom listed in the diagnostic criteria
Statistically significant association between screen and diagnostic question
Prevalence Of Bowel Symptoms
Before diagnosis 17%
After diagnosis 70%
p = 0.2860 (Fisher's exact)
Bowel Symptoms:
Most common treatment for constipation: diet, fluid and exercise.
Most effective treatment: polyethylene glycol
71% of patients treated for constipation were satisfied with their treatment
20% of patients reported bowel urgency
Prevalence Of Bladder Symptoms
Before diagnosis 24%
After diagnosis 76%
p = 0.0088 (Fisher's exact)
Bladder Symptoms:
Most bothersome reported symptom: urinary urgency (31%)
78% of patients felt embarrassed by their bladder symptoms
63% of patients treated for bladder symptoms were satisfied with their treatment
32% of patients reported limiting water to prevent bladder symptoms
Most common treatment: oxybutynin
Constipation, urinary urgency and urge incontinence are frequent concerns for patients with ALS
Prevalence of bladder symptoms significantly increased after ALS diagnosis
Both general and specific questions can assess bowel and bladder concerns
Providers need to assess and address these concerns at clinic
Recall bias was a concern for pre ALS symptoms
Small sample size
Many surveys, multiple ways to ask similar questions and many results
Confounding medications used to manage ALS symptoms
References
UNIVERSITY OF UTAH

MRI


The spectrum of basal ganglia pathology across the ALS/ALS-FTD continuum
P27


Microstructural changes across different stages of disease in Amyotrophic Lateral Sclerosis
Objectives
Patients and Methods
Results
Discussion and conclusions

P19 WHAT DO ALS PATIENTS DIE OF? – AN AUTOPSY STUDY OF 70 ALS PATIENTS

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Keywords: causes of death, autopsy, survival

Background: Death is the definitive hallmark of amyotrophic lateral sclerosis and primary endpoint in most treatment studies. Despite its importance limited data are available about the definitive causes of death in ALS nowadays. Previous autopsy studies (1) pointed out that defining the cause of death based solely on a clinical examination is not a reliable method to reveal the true cause of death. Treatment of our patients was according to the EFNS guidelines for patient care from 2005 (2). It is unclear if treatments such as non-invasive ventilation (NIV) or percutaneous gastrostomy (PEG) have an impact on the cause of death.

Objectives: The aim of this study was to gain a better understanding of causes of death in ALS patients and to investigate how these supportive treatments have an impact on the survival and the causes of death in ALS patients.

Methods: Seventy ALS patients were followed in our outpatient clinic and autopsied including a complete macroscopic and microscopic post mortem analysis between 2003 and 2014. Viscera for the pathological causes of death and relevant concomitant diseases were also studied. Neural tissue and CSF was stored for upcoming projects. Median time from point of death to autopsy was 4 h.

Results: In this study, the main cause of death was respiratory failure (69/70 patients). In 39/70, aspiration pneumonia and broncho-pneumonia led to death. 22//70 died of hypoxia and 5 patients requested assisted suicide inducing respiratory failure. Pulmonary embolism alone or in combination with pneumonia was detected in six. Both bulbar ($n = 3$) and spinal onset patients ($N = 3$) had embolism without any clear correlation to mobility status. A single patient died from a complication after PEG insertion. Average survival in patients using NIV was 7 month longer than without NIV and even more distinct in the NIV group comparing only limb onset patients. Bronchopneumonia was more frequent in patients using NIV versus non-NIV patients (19/38 versus 5/26, $p < 0.003$). The proportion of aspiration pneumonia was significantly lower in patients with PEG (7/43 versus 7/26, $p < 0.003$). PEG had no effect on survival or BMI at death. Genetic testing could be performed in 32 patients prior to death. Disease-causing mutations (*SOD1* or *C9orf72*) were found in about 1/4 of this cohort.

Discussion and conclusion: In this first autopsy study after establishing of the EFNS guidelines, NIV has a positive effect on survival but may be a risk factor for bronchopneumonia. PEG insertion lowers the risk of aspiration pneumonia but has no effect on survival. No correlation was observed between pulmonary embolism and ambulatory disability or site of onset.

References:

1. Corcia *et al.* Amyotroph Lateral Scler. 2008; 9(1): 59–62.
2. Andersen *et al.* Eur J Neurol. 2005; 12(12): 921–38.

Todesursachen

69/70: respiratorisch

39/70: Aspirationspneumonie

Seltener bei PEG (7/43 vs. 7/26)

Broncho-Pneumonie:

Häufiger bei NIV (19/38 vs. 5/26)

22/70 Hypoxie

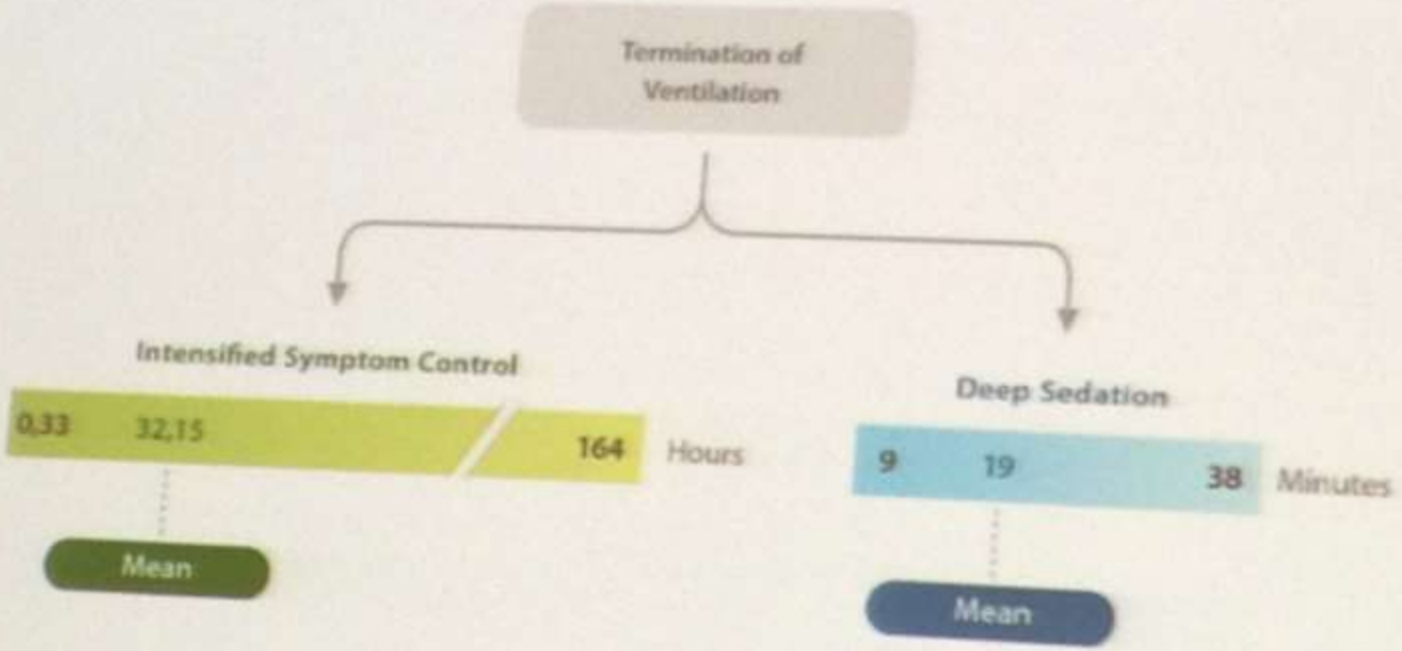
1/70 PEG-Komplikation

5/70: assist. Suizid

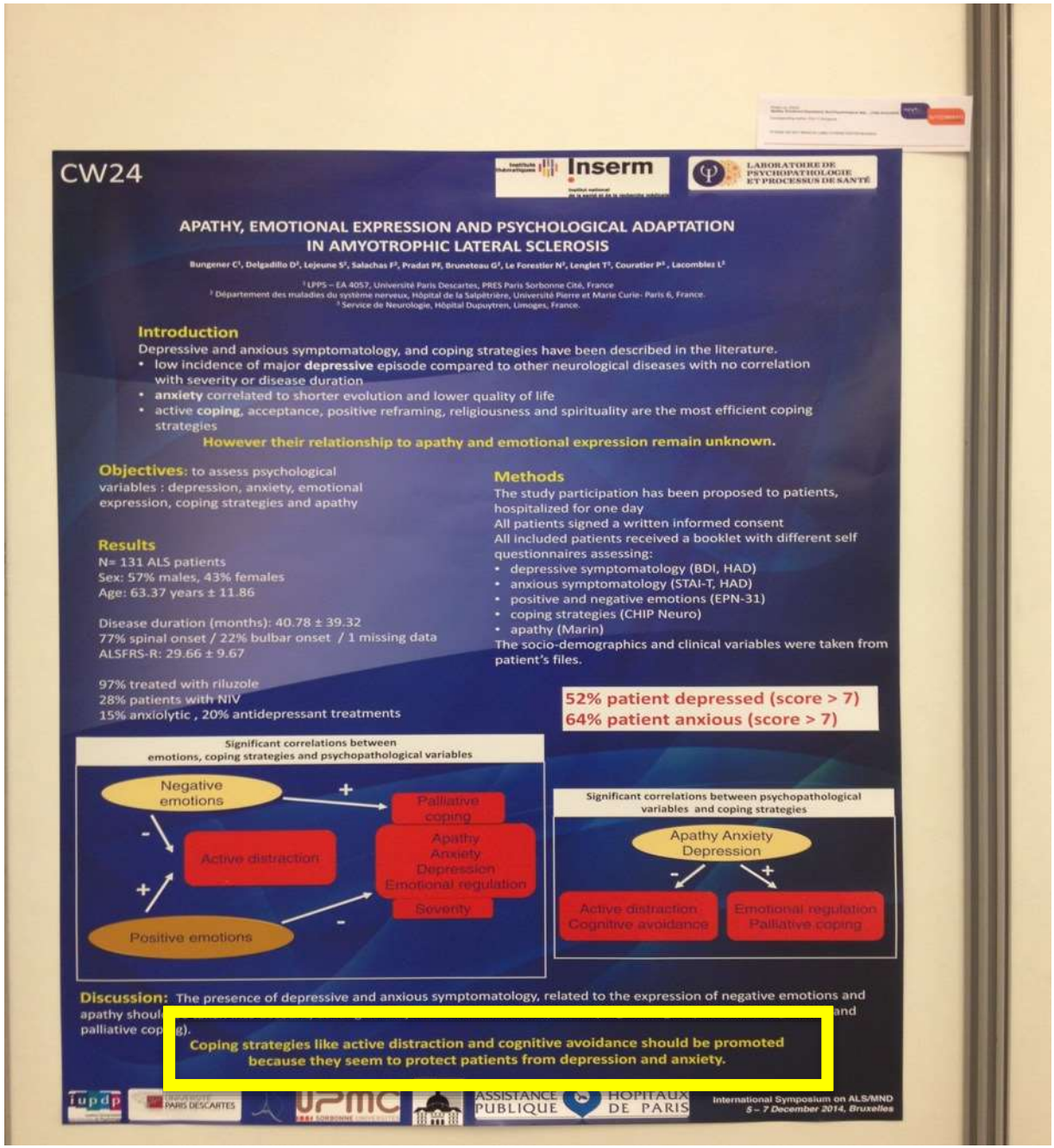
Advance care planning – daily practice in the ALS

- 2 tertiary ALS centres, located in Amsterdam and Utrecht:
  - where all patients with (suspected) MND are seen for (confirmation of) diagnosis;
- > 40 local ALS teams:
  - give local daily support,
  - are associated with the 2 main centres,
  - follow one nationwide treatment policy
  - with **early** initiation of discussions and **timely** decisions about symptomatic treatment options as two of the main treatment aims;

Termination of Ventilation: Latency to Death



Krankheits-verarbeitung



ITB bei schwerer Spastik

REHAB Basel
Zentrum für Querschnittgelähmte und Hirnverletzte
Im Burgfelderhof 40, Postfach, CH-4025 Basel

25th International Symposium on ALS/MND
5 -7 December 2014
Brussels, Belgium

University Hospital Basel
Neuromuskuläres Zentrum
Petersgraben 4, CH-4031 Basel

P 278

Intrathecal Baclofen For Spasticity In Motor Neuron Disease (MND): Long-term Experiences

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Background/Objectives/Methods

Magangement of severe spasticity in motor neuron disease (MND) is often unsatisfactory due to intolerance or inefficacy of oral medications. In patients with primary lateral sclerosis (PLS) and upper motor neuron predominant ALS, intrathecal baclofen (ITB) therapy can be an option. However, little is known about long-term outcome in these patients.

Objectives

To report on long-term experiences with ITB for severe spasticity in MND patients in Switzerland.

Methods

A total of 16 patients, referred by ALS clinics for evaluation of ITB therapy, were examined by a neurologist, an occupational-, a speech-, and a physiotherapist at baseline. In all patients, ITB was administered by a probatory external pump, connected with a subcutaneous intrathecal catheter about 40 – 60 cm above L3/L4 puncture level, dosage increased according to clinical signs, oral antispastic medication tapered off and stopped.

ALS Functional Rating Scale (ALSFRS-R), Functional Independence Measure scores, spasticity (modified Ashworth scale) speech, swallowing, transfers, and gait were evaluated before and under ITB therapy. Only in case of clear benefit, a permanent ITB pump was implanted. All patients were followed in ALS clinics.

Results

From 2/2007 to 5/2014, sixteen patients (12 men, 4 women), mean age 48.5 years, were treated with ITB via probatory external pump. Four patients were diagnosed with PLS, 12 with ALS. At baseline, mean disease duration was 59 months, ALSFRS-R 29.2. In all patients spasticity was reduced, no side effects occurred. Four patients did not go on a permanent ITB pump because symptoms did not improve or deteriorated.

A permanent pump (Synchromed II, Medtronic) was implanted in 12 patients, mean ITB starting dosage 50 µg/d. All patients, followed in ALS clinics (one lost to follow-up because he moved to Italy), continued ITB therapy. Seven of these patients (and one who did not get an ITB pump implanted) died of respiratory failure due to progression of MND. In this group, mean duration of ITB treatment was 23 months, compared to 28 months in the four patients who are still alive. At last evaluation, mean ALSFRS-R was 15.6, and 27.5, ITB dosage 55.6 µg/d, and 135.6 µg/d respectively.

Probatory external ITB pump: setting of dose

Definite ITB pump: setting of dose

Synchromed II, Medtronic

Discussion and Conclusions

In MND patients, the pattern of muscle tone and strength varies substantially and individually. Severe spasticity might require ITB therapy, but progression of atrophic paresis has to be considered. In our patients, escalation of ITB dosage in the course of the disease was often needed.

Conclusions

ITB can safely and effectively reduce spasticity and is well tolerated in long-term course of selected patients with MND. It might also facilitate transfers and gait, as long as flaccid paresis do not progress, and relieve pain in some cases. Therefore, ITB should be considered for palliation of severe spasticity in MND. Because symptoms and signs vary significantly in individual MND patients, and ITB therapy is an invasive and expensive method, it should be indicated and evaluated by an experienced multi-professional team in an inpatient setting.

PT	AGE (y)	DIA-GNOSIS	DIS DUR (mth)	ALS-FRS-R BASE-LINE	FINAL ITB DOSAGE (µg/d) PROBAOTRY OR DEFINITE ITB PUMP	EFFECT UNDER PROBATORY ITB THERAPY							ALS-FRS-R LAST FOLLOW UP	ITB DOSAGE (µg/d) LAST FOLLOW UP	ITB DUR (mth) LAST FOLLOW UP
						PAIN RELIEF	MAS	TRANS FERS	GAIT	DYS-ARTHRIA	DYS-PHAGIA	ITB PUMP IMPLANTED			
IR ♂	65	ALS	29	34	43.5	na	+	+	+	+	+	yes	ltfu	ltfu	ltfu
FM ♀	58	PLS	96	26	48	na	+	-	-	no	-	no	28	na	na
RE ♀	31	PLS	72	24	66	+	+	no	no	no	no	no	14*	na*	na*
SR ♂	53	ALS	65	33	48	na	+	+	+	+	+	yes	22.5	342.3	61
KM ♂	28	ALS	11	25	45	+	+	-	-	-	-	yes	26*	45*	2*
SP ♂	56	ALS	57	33	60	na	+	+	+	+	+	yes	18*	88.6*	56*
BE ♂	66	ALS	72	24	54	na	+	-	-	no	no	no	19	na	na
SS ♀	43	ALS	30	27	42	no	+	+	+	+	no	yes	13*	47.2*	27*
PR ♂	56	ALS	72	31	36	no	+	-	-	no	no	no	30	na	na
FH ♂	55	ALS	12	30	42	+	+	+	+	no	no	yes	15*	60*	6*
KR ♂	46	ALS	30	30	45	na	+	+	+	no	no	yes	13*	54*	13*
LR ♂	75	ALS	44	32	49	na	+	+	+	+	na	yes	10*	54*	22*
BU ♂	40	ALS	43	14	40.5	na	+	+	na	+	no	yes	7*	40*	13*
HF ♀	60	PLS	156	38	42	+	+	+	+	+	no	yes	38	48	23
FJ ♂	64	ALS	81	34	66.1	78	+	+	+	+	no	yes	27	75	18
KH ♂	56	ALS	71	20.5	70	na	+	+	+	+	no	yes	22	77	11
Mean	53.3		58.8	28.5	49.4								15.6*/27.3	55.5*/135.6	23*/28

DIS-Disease, DUR-Duration, ITB-Intrathecal Baclofen, ltfu-lost to follow-up, MAS-modified Ashworth Scale, mth-months, na-not applicable, no-no effect, PT-Patient, y-years,+ improvement, - worsening, *died

Localisation of definite ITB pump and catheter

References

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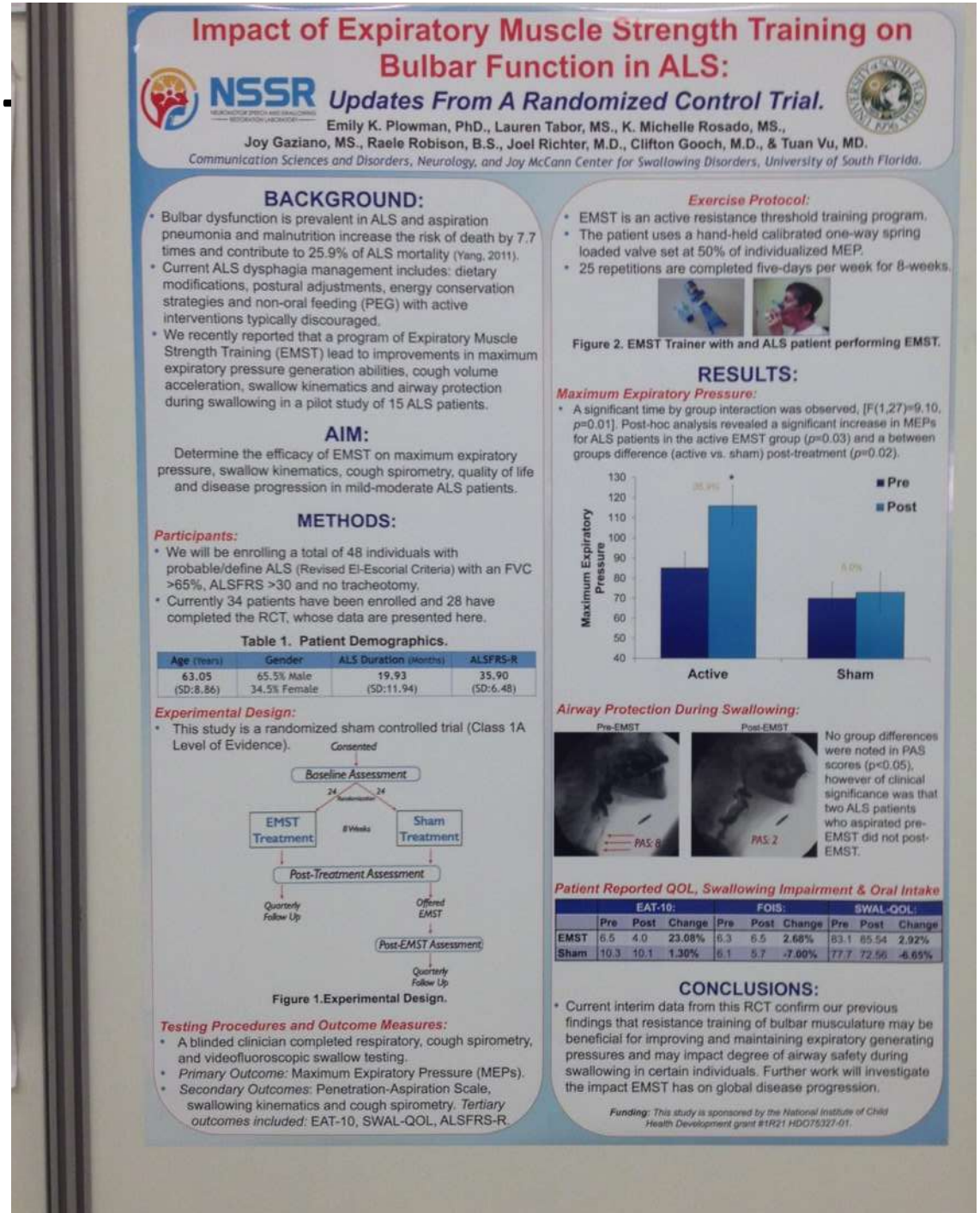
Expirations-training bei Dysphagie



Impact of Expiratory Muscle Strength Training on Bulbar Function in ALS:

Updates From A Randomized Control Trial.

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Joy Gaziano, MS., Raele Robison, B.S., Joel Richter, M.D., Clifton Gooch, M.D., & Tuan Vu, MD.
Communication Sciences and Disorders, Neurology, and Joy McCann Center for Swallowing Disorders, University of South Florida.

BACKGROUND:

- Bulbar dysfunction is prevalent in ALS and aspiration pneumonia and malnutrition increase the risk of death by 7.7 times and contribute to 25.9% of ALS mortality (Yang, 2011).
- Current ALS dysphagia management includes: dietary modifications, postural adjustments, energy conservation strategies and non-oral feeding (PEG) with active interventions typically discouraged.
- We recently reported that a program of Expiratory Muscle Strength Training (EMST) lead to improvements in maximum expiratory pressure generation abilities, cough volume acceleration, swallow kinematics and airway protection during swallowing in a pilot study of 15 ALS patients.

AIM:

Determine the efficacy of EMST on maximum expiratory pressure, swallow kinematics, cough spirometry, quality of life and disease progression in mild-moderate ALS patients.

METHODS:

Participants:

- We will be enrolling a total of 48 individuals with probable/define ALS (Revised El-Escorial Criteria) with an FVC >65%, ALSFRS >30 and no tracheotomy.
- Currently 34 patients have been enrolled and 28 have completed the RCT, whose data are presented here.

Table 1. Patient Demographics.

Age (Years)	Gender	ALS Duration (Months)	ALSFRS-R
63.05 (SD:8.86)	65.5% Male 34.5% Female	19.93 (SD:11.94)	35.90 (SD:6.48)

Experimental Design:

- This study is a randomized sham controlled trial (Class 1A Level of Evidence).

Figure 1.Experimental Design.

Testing Procedures and Outcome Measures:

- A blinded clinician completed respiratory, cough spirometry, and videofluoroscopic swallow testing.
- *Primary Outcome:* Maximum Expiratory Pressure (MEPs).
- *Secondary Outcomes:* Penetration-Aspiration Scale, swallowing kinematics and cough spirometry. *Tertiary outcomes included:* EAT-10, SWAL-QOL, ALSFRS-R.

Exercise Protocol:

- EMST is an active resistance threshold training program.
- The patient uses a hand-held calibrated one-way spring loaded valve set at 50% of individualized MEP.
- 25 repetitions are completed five-days per week for 8-weeks.

Figure 2. EMST Trainer with and ALS patient performing EMST.

RESULTS:

Maximum Expiratory Pressure:

- A significant time by group interaction was observed, [F(1,27)=9.10, p=0.01]. Post-hoc analysis revealed a significant increase in MEPs for ALS patients in the active EMST group (p=0.03) and a between groups difference (active vs. sham) post-treatment (p=0.02).

Airway Protection During Swallowing:

No group differences were noted in PAS scores (p<0.05), however of clinical significance was that two ALS patients who aspirated pre-EMST did not post-EMST.

Patient Reported QOL, Swallowing Impairment & Oral Intake

	EAT-10:			FOIS:			SWAL-QOL:		
	Pre	Post	Change	Pre	Post	Change	Pre	Post	Change
EMST	6.5	4.0	23.08%	6.3	6.5	2.68%	83.1	85.54	2.92%
Sham	10.3	10.1	1.30%	6.1	5.7	-7.00%	77.7	72.56	-6.65%

CONCLUSIONS:

- Current interim data from this RCT confirm our previous findings that resistance training of bulbar musculature may be beneficial for improving and maintaining expiratory generating pressures and may impact degree of airway safety during swallowing in certain individuals. Further work will investigate the impact EMST has on global disease progression.

Funding: *This study is sponsored by the National Institute of Child Health Development grant #1R21 HD075327-01.*

Hilfsmittel