



international
symposium
on ALS/MND

25th International Symposium on ALS/MND

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Brussels, Belgium

**ALS: Einblicke
Neuigkeiten
Dr. Kathi Schweikert
11.12.2014**



Neuigkeiten 2014

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

Genetik

Percentage ALS explained by genetic mutation since 1992

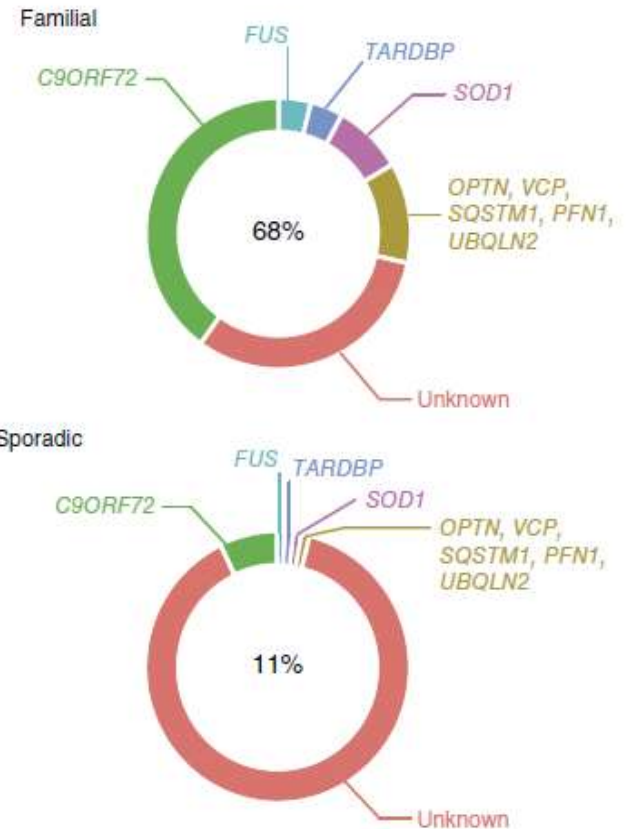
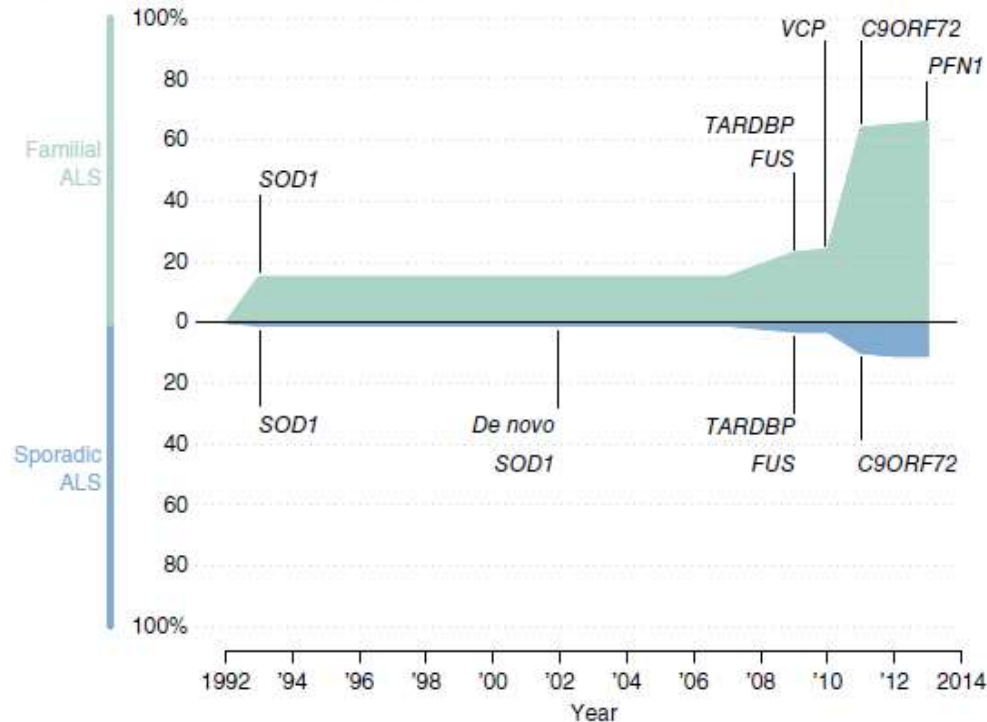
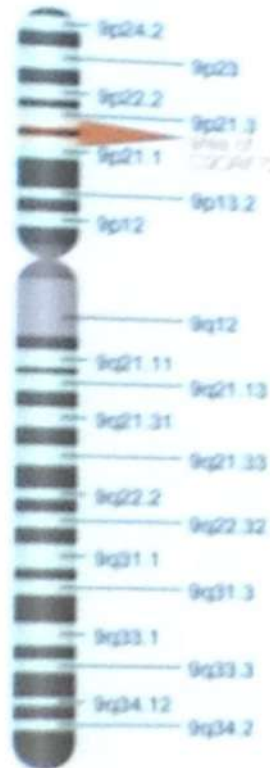


Figure 1 Timeline of gene discoveries in familial and sporadic ALS. Values represent the proportion of ALS explained by each gene in populations of European ancestry. References are provided in the main text.

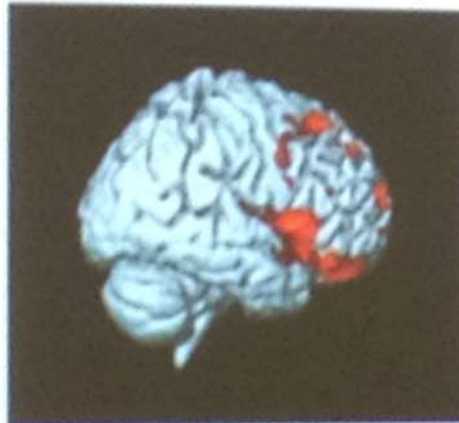
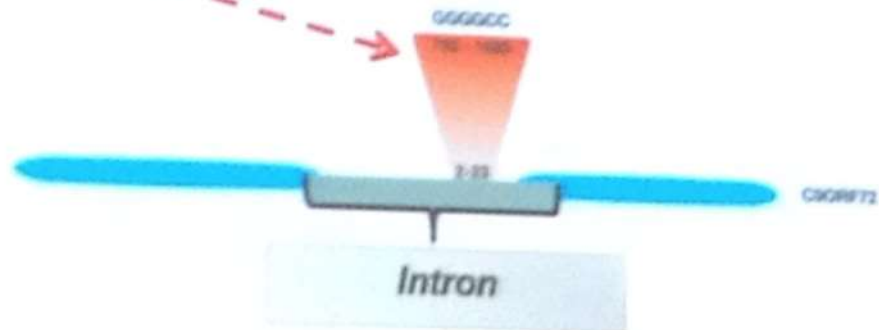
Renton et al. Nature Neuroscience, 2014

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

ALS und FTD



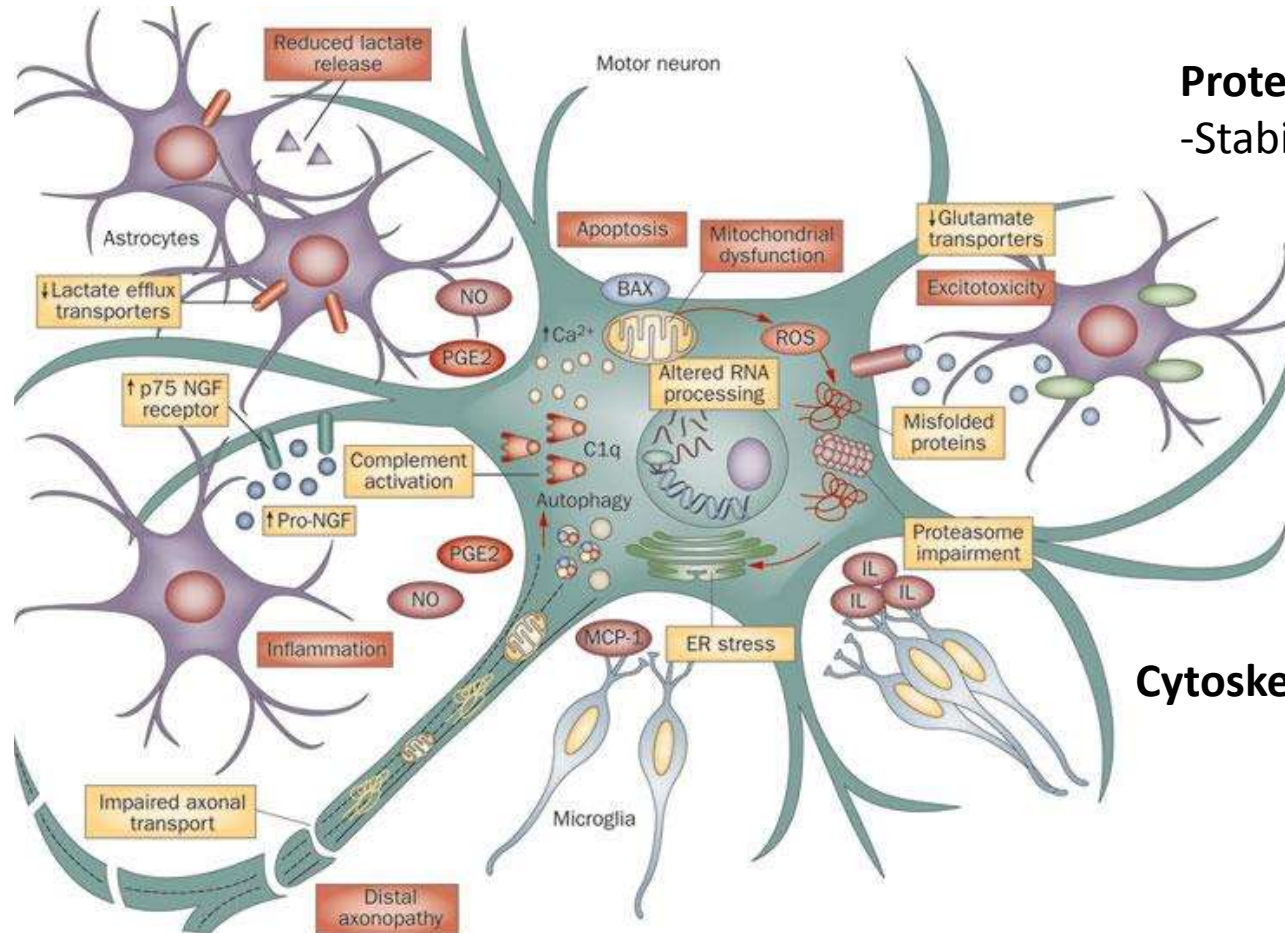
C9ORF72 GENE



Project MiNE: 15.000 Blutproben



Pathophysiologie



Protein:

-Stabilisierung/Faltung/Degeneration

RNA-Metabolismus:

Axonaler Transport

Cytoskeletale Biologie

Andere Zellen (non-neuronal cells):

Astrozyten, Mikroglia, Oligodendrozyten

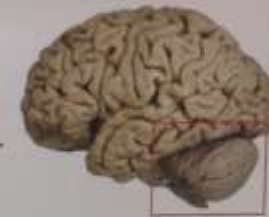
- Kognitive/Verhaltens- und temporale Dysfunktionen
- Schmerzen
- Extrapyramidenzeichen
- Kleinhirnzeichen

Neuronal loss in functional zones of the cerebellum in ALS

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The Cerebellum in ALS – P193



INTRODUCTION

The neuropathological hallmark of ALS is degeneration of upper and/or lower motor neurons and approximately equal numbers of patients have upper limb, lower limb or bulbar-onset disease (SC). The cerebellum has traditionally been regarded as a crucial relay station for motor regulation, and has multiple reciprocal connections with the motor regions implicated in ALS [2]. We previously identified cerebellar atrophy in ALS and showed that the severity of atrophy in the inferior olivary and cerebellar vermis correlates with measures of motor functional status [Tan 2014]. However, the integrity of the cerebellar granule and Purkinje cells, which are respectively amongst the smallest and largest neurons present in the human nervous system, have yet to be examined in ALS.

OBJECTIVE

To assess the density of granule cells and Purkinje neurons in the cerebellar vermis and lateral hemispheres in ALS.

METHODS

	Controls	Lower limb onset	Bulbar-onset	Upper limb onset
n	12	12	12	12
Age (years)	59.4 ± 10.5	59.4 ± 11.1	59.4 ± 11.1	59.4 ± 11.1
Disease length (years)	10.0 ± 3.0	10.0 ± 3.0	10.0 ± 3.0	10.0 ± 3.0

Values are mean ± SD.

NEURONAL QUANTIFICATION

Purkinje neurons. Purkinje cells located along the anterior and posterior foliate lobules were counted at x200 magnification and normalized against the number of folium in each half lobule.

Granule neurons. Granule cells were counted using a x100 oil immersion lens on a high-quality microscope if their nucleus fell entirely within or on one of the two adjacent inclusion borders of a sampling frame of 20µm x 20µm.

STATISTICAL ANALYSIS

Multi-variate analysis with age and cerebellar weight included as covariates was used to assess neuronal densities across clinical diagnosis and type of onset group.

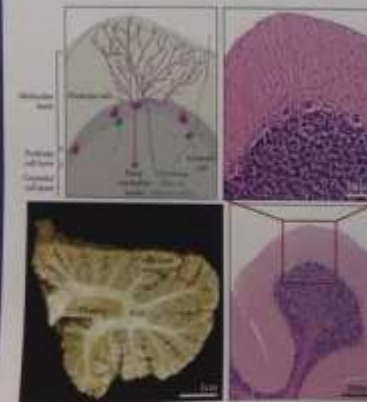


Figure 1. Sagittal section through the human cerebellum.

RESULTS

Purkinje cell loss was identified in the cerebellar vermis of ALS cases with lower-limb onset disease ($p < 0.05$). This was significant in comparison to upper limb- and bulbar-onset cases ($p = 0.01$). No other significant difference was identified in cerebellar neurons across functional zones with disease-onset in comparison to controls.

	Controls	Upper limb onset	Bulbar onset	Lower limb onset
Granule cells	117.1 ± 2.2	112.6 ± 1.1	112.6 ± 1.1	112.6 ± 1.1
Purkinje cells	87.4 ± 5.7	87.4 ± 5.7	87.4 ± 5.7	87.4 ± 5.7
Cerebellar vermis	8.8 ± 4.6	8.8 ± 4.6	8.8 ± 4.6	8.8 ± 4.6
Granule cells	8.8 ± 4.6	8.8 ± 4.6	8.8 ± 4.6	8.8 ± 4.6

* $p < 0.05$ in comparison to all other groups

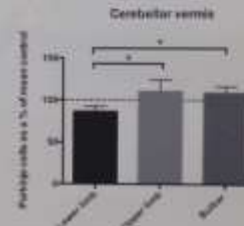


Figure 2. Density of Purkinje neurons in the cerebellar vermis of ALS cases with lower limb, upper limb- and bulbar-onset disease as a percentage of mean control.

DISCUSSION

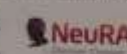
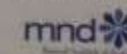
This is the first report of Purkinje cell loss in the cerebellar vermis in ALS and we demonstrate here a significant reduction in cases with lower limb-onset. The vermis is classically thought to receive somatic sensory input from ascending spinal pathways and be involved in the formation of ongoing movement. However, recent evidence in animal models have challenged this theory and shown that the Purkinje neurons located in the vermis receive direct input from motor neurons in the motor cortex and lower limb, although not from the upper limb [1, 3]. Our findings here in the vermis of human patients with lower limb-onset ALS corroborates this, and we postulate that this is a consequence of distal atrophy. Targeted treatment improving Purkinje cell survival has demonstrated alleviation of motor dysfunction [4] and we present here histological evidence that supports the crucial involvement of the cerebellum in the neural circuitry subserving intact motor function in ALS.

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2. O'Reilly, J.K. et al. *Cerebral cortex*, 2010; 20(6): 953-65.
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5. Turner, M.R. et al. *J Neurol Neurosurg*, 2011; 133(5): 853-4.

ACKNOWLEDGEMENTS

These were obtained from the New South Wales Tissue Resource Centre at the University of Sydney, which is supported by the National Health and Medical Research Council of Australia, Schizophrenia Research Institute, National Institute of Alcohol Abuse and Alcoholism (NIAA) (K24AA012751). The authors are very grateful for the support of MNDRA and NeuRA.



Symptome

Prevalence of Bowel and Bladder Symptoms Attributable to ALS

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Introduction

- Previous surveys have found increased complaints of bowel and bladder symptoms in ALS patients^{1,2}
- 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^{3,4}
- 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 III⁵
 - Bladder function survey based on (POSQ) Primary Overactive Bladder Questionnaire⁶
- 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/diagnosed 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%)

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

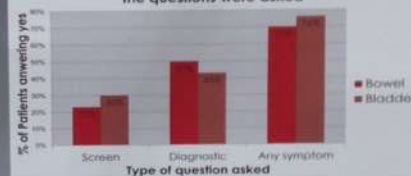
Prevalence Of Bladder Symptoms

Before diagnosis	24%
After diagnosis	76%
p = 0.0088 [Fisher's exact]	

Bladder Symptoms:

- Most bothersome reported symptom: urinary urgency (31%)
- 76% 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

Patients reported symptoms based on how the questions were asked



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

- 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

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6. Johnson M, Bromberg M, Deka R, et al. Bowel and bladder symptoms in amyotrophic lateral sclerosis: a cross-sectional study. *Aliment Pharmacol Ther*. 2010;32(12):1711-1718.



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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

Todesursachen

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.

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

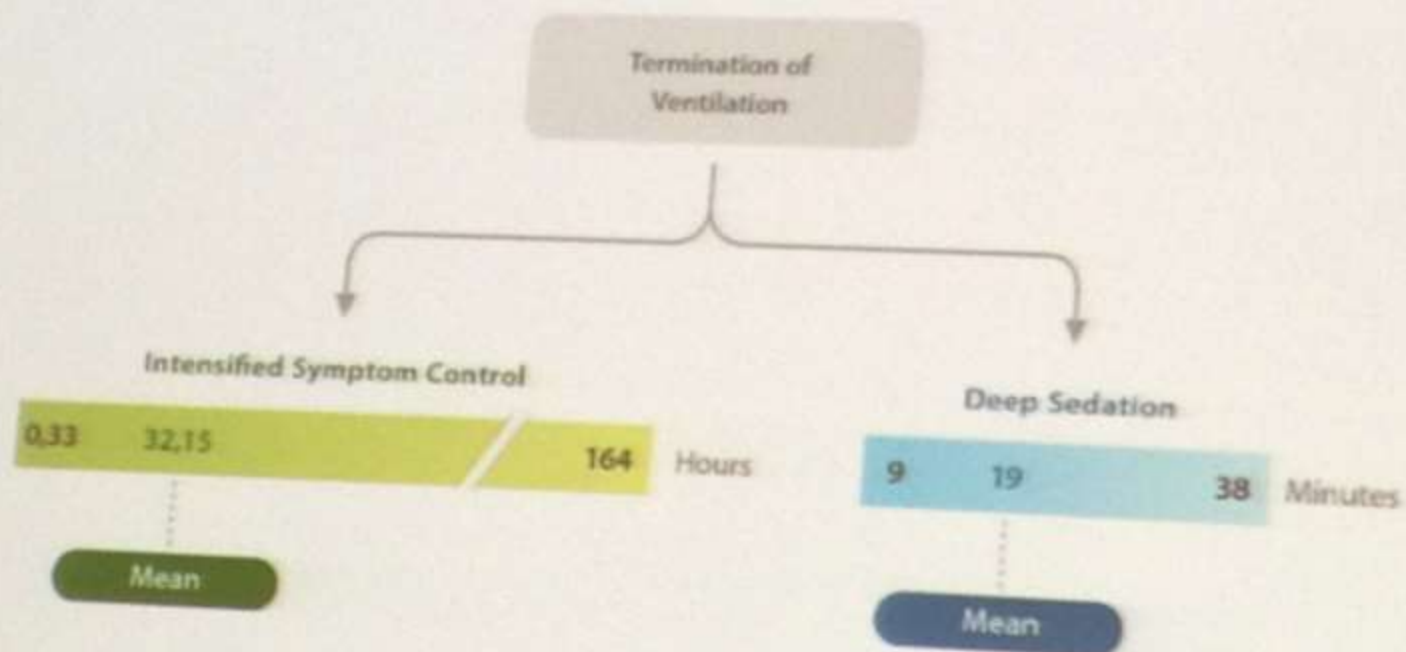
5/70: assist. Suizid

Advance care planning – daily practice in the



- 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

CW24



APATHY, EMOTIONAL EXPRESSION AND PSYCHOLOGICAL ADAPTATION IN AMYOTROPHIC LATERAL SCLEROSIS

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Introduction

Depressive and anxious symptomatology, and coping strategies have been described in the literature.

- low incidence of major **depressive** episode compared to other neurological diseases with no correlation with severity or disease duration
- **anxiety** correlated to shorter evolution and lower quality of life
- active **copng**, acceptance, positive reframing, religiousness and spirituality are the most efficient coping strategies

However their relationship to apathy and emotional expression remain unknown.

Objectives: to assess psychological variables : depression, anxiety, emotional expression, coping strategies and apathy

Results

N= 131 ALS patients

Sex: 57% males, 43% females

Age: 63.37 years \pm 11.86

Disease duration (months): 40.78 \pm 39.32

77% spinal onset / 22% bulbar onset / 1 missing data

ALSFRS-R: 29.66 \pm 9.67

97% treated with riluzole

28% patients with NIV

15% anxiolytic , 20% antidepressant treatments

Methods

The study participation has been proposed to patients, hospitalized for one day

All patients signed a written informed consent

All included patients received a booklet with different self questionnaires assessing:

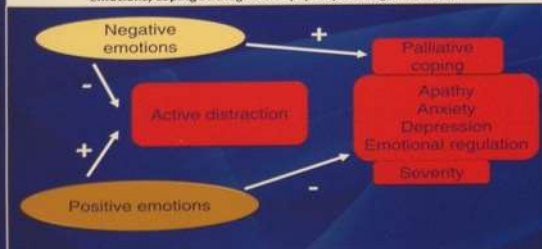
- depressive symptomatology (BDI, HAD)
- anxious symptomatology (STAI-T, HAD)
- positive and negative emotions (EPN-31)
- coping strategies (CHIP Neuro)
- apathy (Marin)

The socio-demographics and clinical variables were taken from patient's files.

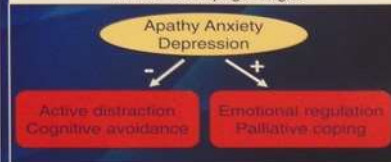
52% patient depressed (score > 7)

64% patient anxious (score > 7)

Significant correlations between emotions, coping strategies and psychopathological variables



Significant correlations between psychopathological variables and coping strategies



Discussion: The presence of depressive and anxious symptomatology, related to the expression of negative emotions and apathy should be taken into account in the management of ALS patients (palliative coping).

Coping strategies like active distraction and cognitive avoidance should be promoted because they seem to protect patients from depression and anxiety.

P 278 Intrathecal Baclofen For Spasticity In Motor Neuron Disease (MND): Long-term Experiences

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ITB bei schwerer Spastik

Background/Objectives/Methods

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

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

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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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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	65.5% Male	19.93	35.90
(SD:8.86)	34.5% Female	(SD:11.94)	(SD:6.48)

Experimental Design:

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

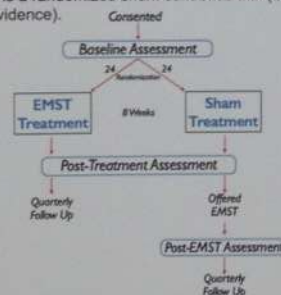


Figure 1. Experimental Design.

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.

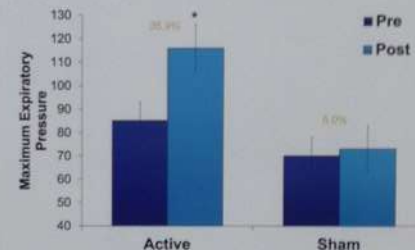


Figure 2. EMST Trainer with and ALS patient performing EMST.

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	-7.66%	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.

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