# Comparison of Communication Ability Stage with Adverse Clinical Signs in Patients with Amyotrophic Lateral Sclerosis (ALS) on Tracheostomy Invasive Ventilation (TIV)

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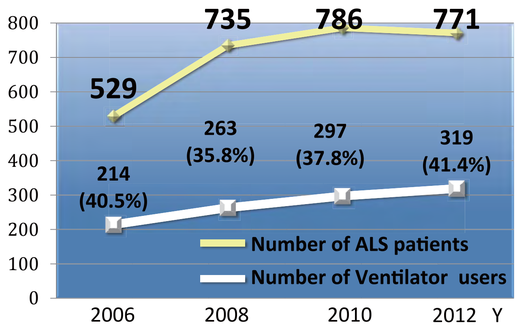
## 1 . Background

Patients with amyotrophic lateral sclerosis (ALS) on tracheostomy invasive ventilation (TIV) :

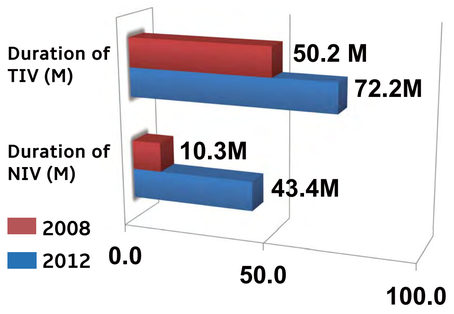
- Lives long time [1)]
- Have adverse clinical signs
- Develop communication impairment with disease progression [2)]

The appropriate care and to maintain communication ability become important a classification of advanced ALS focusing on the patient's communication ability. [3)]

### Number of ALS patients and ventilator users in Tokyo




### Duration of Ventilation becomes long




### Stage of communication ability

| Stage | Level | Definition |
|---|---|---|
| I | Normal | communicates in sentences |
| II | Difficult | communicates with one word responses |
| III | | communicates with nonverbal yes/no responses |
| IV | | cannot communicate, except for unreliable yes/no |
| V | Impossible | cannot communicate by any means |

Hayashi et al.2013

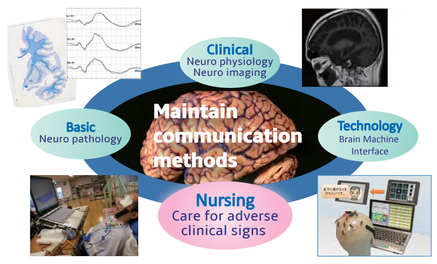
References

1) Tokyo Metropolitan specific resarch for Intractible disease ,2013 2) Nakayama Y, Ogura A, Matsuda C. J. J. Intrac. Ill. Nurs 2010;14:179-93. 3) Hayashi K, et al. Rinsho Shinkeigaku 2013; 53:98-103.

## 2 . Objective

To clarify the relationship between the stages of communication ability and adverse clinical signs in ALS patients on TIV.

### Our multi-disciplinary research team




## 3 . Methods

**Subject :** 46 patients with ALS on TIV at home from 2005 to 2013.

**Collected Data :** sex, age of onset, duration of disease, duration of TIV, and time from onset to start of TIV. Incidence of adverse clinical signs

**Data analysis :** Classified subjects into three groups by stage of communication ability at the last observation point.

Comparison of three groups by the the Kruskal-Wallis test performed using SPSS, version 21.

p-values ≦0.05 were considered significant.

### 16 adverse clinical signs

**Voluntary movement**
- fatigability of eye movement
- dry eye
- drooling or dry mouth
- megaloglossia

**Infections**
- otitis media
- Pneumonia
- urinary tract infections

**Autonomic dysfunction**
- unstable blood pressure
- disturbance of thermoregulation
- dysuria

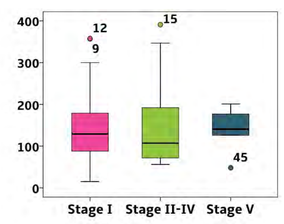
**Others**
- tracheal granuloma
- Cholelithiasis
- urinary stones
- Decubitus
- Nausea
- unstable blood glucose

## 4 . Results

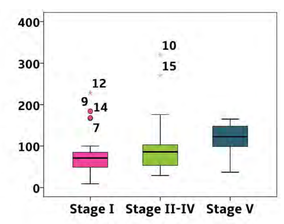
### 1. Patients Characteristics

| | Stage I 21 ( 45.6% ) | Stage II ~ IV 19 ( 41.4% ) | Stage V 6 ( 13.0 % ) |
|---|---|---|---|
| Sex (men) | 14 ( 66.7% ) | 13 ( 68.4% ) | 3 ( 50.0% ) |
| Age at onset (median year-old) | 52.0 | 60.0 | 56.0 |
| Bulbar onset patients | 5 ( 23.8% ) | 4 ( 21.1% ) | 1 ( 16.7 % ) |
| duration of disease (median months) | 129.0 | 107.0 | 140.5 |
| duration of TIV (median months) | 71.0 | 86.0 | 122.5 |
| time from onset to start of TIV. (median months) | 59.0 | 27.0 | 24.0 |
| Number of adverse clinical signs | 4.0 | 7.0 | 9.5 |

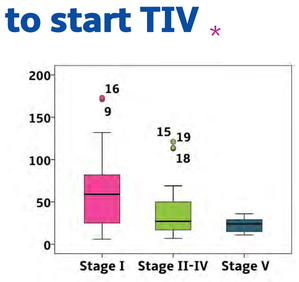
### Duration of disease



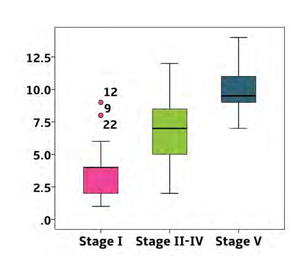

### Duration of TIV




### Time from onset to start TIV *

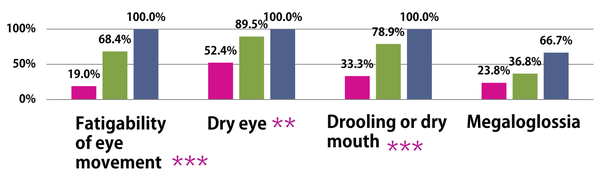



### Number of signs ***

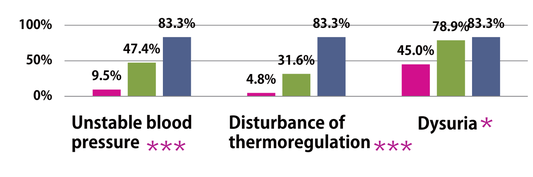



### 2. 16 adverse clinical signs

#### Voluntary movement



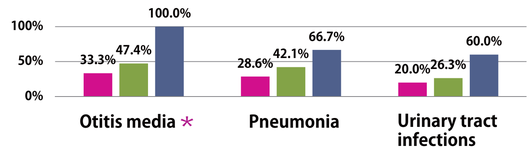

#### Autonomic dysfunction



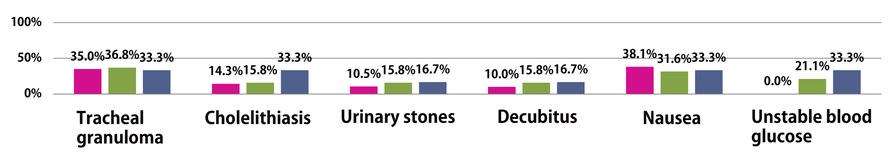

stage I
stage II-IV
stage V

P: * < 0.05
** < 0.01
*** < 0.001

#### Infections




#### Others

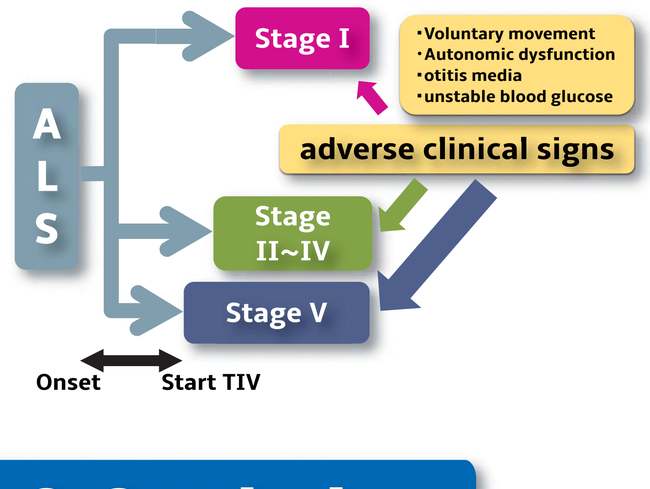



## 5. Discussion

### Several type of ALS patients

Who maintain stage I
- Ventilator needs slowly
- Had not many adverse clinical signs

Who progress stage II~IV or V
- Rapid disease progression
- Ventilator needs early phase
- Had various adverse clinical signs




## 6. Conclusion

We found that the patients with ALS in advanced stages showed
- an early requirement for TIV
- had more adverse signs.

Clinicians should give careful attention to the adverse signs of ALS patients on TIV to prevent communication impairment.

This work supported by JSPS KAKENHI Grant Number 25293449.

# Relationship between Adverse Clinical Signs and progression of Communication Impairment in Patients with Amyotrophic Lateral Sclerosis (ALS) on Tracheostomy Invasive Ventilation (TIV)


**Y Nakayama[1], T Shimizu[2], C Matsuda[1], M Haraguchi[1], Y Mochizuki[3,4], K Hayashi[2], T Hirai[2], M Nagao[2], A Kawata[2], K Oyanagi[5]**

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5. Department of Brain Disease Research, Shinshu University School of Medicine


## Summary of this study

We found that the patients with ALS in advanced stages showed
an early appearance of opthalmoplegia
and multisystem neurodegeneration.
Clinicians should give careful attention to the adverse signs of ALS patients on TIV to prevent communication impairment.

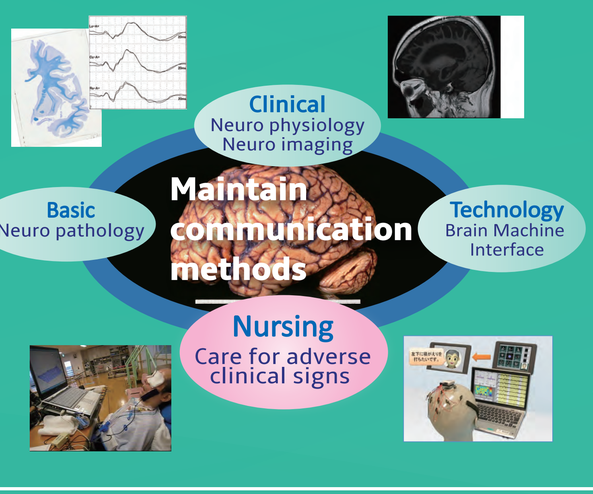
## 1 . Background

Patients with ALS on TIV :
- Live long time
- Have adverse clinical signs
- Develop communication impairment with disease progression

The adverse clinical signs affect to maintain communication ability.

We proposed a classification of advanced ALS focusing on the patient's communication ability.

### Our multi-disciplinary research team




### Stage of communication ability

| Stage | Level | Yes or No | Definition |
|---|---|---|---|
| I | Normal | ○ | communicates in sentences |
| II | Difficult | ○ | communicates with one word responses |
| III | Difficult | ○ | communicates with nonverbal yes/no responses |
| IV | Difficult | × | cannot communicate, except for unreliable yes/no |
| V | Impossible | × | cannot communicate by any means |

Hayashi K, Mochizuki Y, Nakayama Y, et al. Communication disorder in amyotrophic lateral sclerosis after ventilation — a proposal of staging and a study of predictive factor. Rinsho Shinkeigaku 2013

## 2 . Objective

Purpose of this study, to clarify which adverse clinical signs are affected communication stage progression in ALS patients on TIV.

## 3 . Methods

Subject : 60 patients with ALS on TIV at home from 2005 to 2014.

ALS/TIV 60
- Remain Stage I ~ III
- Progress Stage IV~V

Collected Data : sex, age of onset, duration of disease, duration of TIV, and time from onset to start of TIV. Incidence of adverse clinical signs.

Data analysis : Classified subjects into two groups(Stages I-III and IV-V) by stage of communication ability at the end point.
Cox proportional hazard model was used to compare between two groups.
Data analysis was performed using SPSS, version21.
p-values ≦0.05 were considered significant.

### 16 adverse clinical signs

**Voluntary movement**
- fatigability of eye movement
- dry eye
- drooling or dry mouth
- megaloglossia

**Autonomic dysfunction**
- unstable blood pressure
- disturbance of thermoregulation
- dysuria

**Infections**
- otitis media
- pneumonia
- urinary tract infections

**Others**
- tracheal granuloma
- cholelithiasis
- urinary stones
- decubitus
- nausea
- unstable blood glucose

## 4 . Results

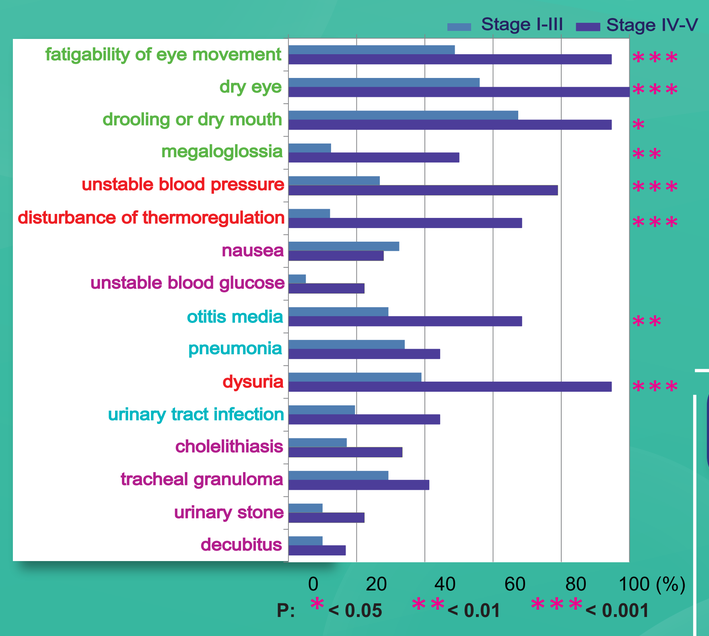
19(31.7%) of the patients progressed stages IV-V. Their duration from onset to opthalmoplegia was early and had more adverse clinical signs.

### Patients Characteristics

| Stage | Stage I - III | Stage IV - V | p-value |
|---|---|---|---|
| Patients, n (%) | 41(68.3) | 19(31.7) | |
| Males,n (%) | 30 (73.9) | 10(52.6) | .146 |
| Mean age at onset ±SD, years | 55.76±12.23 | 55.26±11.72 | .882 |
| Bulbar onset patients, n (%) | 7 (17.1) | 4(21.1) | .730 |
| Clinical event, n (%) | | | |
| Overt oculomotor limitation | 17 (41.5) | 19 (100.0) | <.0001 *** |
| Total quadriplegia | 20(48.8) | 17 (89.5) | .004 ** |
| Mean disease duration ±SD,m | 130.5±85.14 | 161.58±100.26 | .252 |
| Mean TIV duration ±SD,m | 73.0±54.17 | 126.9±78.86 | .0012 * |
| Mean time from onset to clinical event ±SD,m | | | |
| Need for TIV | 56.76±46.52 | 34.79±35.13 | .049 * |
| Need for feeding tube | 57.76±47.83 | 39.84±43.43 | .169 |
| Development of overt oculomotor limitation | 118.0±86.17 | 78.86±71.9 | .072 |
| Progression to total quadriplegia | 115.63±85.44 | 74.43±52.17 | .088 |

P: * < 0.05 ** < 0.01 *** < 0.001

### Incidence of Adverse Clinical Signs



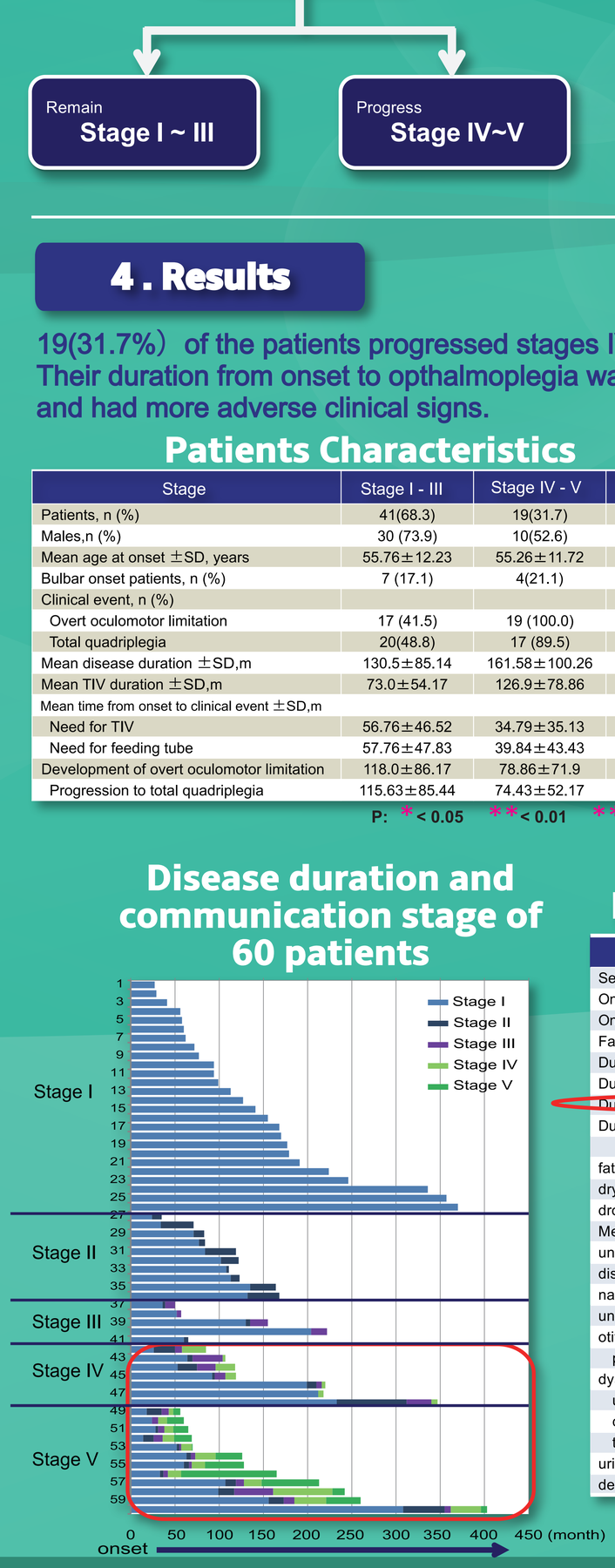

P: * < 0.05 ** < 0.01 *** < 0.001

### Multivariate analyses for StageIV by Cox proportional hazarad model

| | | HR | 95%CI | p-value |
|---|---|---|---|---|
| Onset age | years | .936 | 0.838-1.046 | .243 |
| Duration from onset | months | .974 | 0.945-1.003 | .078 |
| Duration from the onset to TPPV | months | .994 | 0.945-1.073 | .880 |
| Duration from the onset to opthalmoplegia | months | .907 | 0.854-0.963 | .001 *** |
| Duration from the onset to quadriplegia | months | .972 | 0.930-1.017 | .216 |
| fatigability of eye movement | | 11.36 | 0.003-46805 | .567 |
| unstable blood pressure | | 19.366 | 2.158-173.81 | .008 ** |
| disturbance of thermoregulation | | 5.969 | 1.156-30.836 | .033 * |
| dysuria | | 65.09 | 2.19-1934.7 | .016 * |

P: * < 0.05 ** < 0.01 *** < 0.001

### Disease duration and communication stage of 60 patients




### Univariate analyses for StageIV by Cox proportional hazarad model

| | HR | 95%CI | p-value |
|---|---|---|---|
| Sex (man vs woman) | .2.049 | 0.827-5.007 | .121 |
| Onset age (years) | 1.060 | 1.010-1.113 | .018 * |
| Onset symptom (non-bullbar vs bulbar) | 1.509 | 0.484-4.705 | .478 |
| Familial or mutation (non-familial nor mutation vs familial) | | | |
| Duration from onset (months) | .981 | .969-0.994 | .003 * |
| Duration from the onset to TPPV (months) | .958 | 0.931-0.985 | .002 * |
| Duration from the onset to opthalmoplegia (months) | .960 | 0.942-0.977 | .000 *** |
| Duration from the onset to quadriplegia (months) | .974 | 0.959-0.989 | .001 ** |
| | | | |
| fatigability of eye movement | 10.746 | 1.429-80.807 | 0.021 * |
| dry eye | 33.868 | 0.406-2824 | 0.119 |
| drooling or dry mouth, | 4.115 | 0.544-31.106 | 0.17 |
| Megaloglossia | 2.019 | 0.779-5.235 | 0.148 |
| unstable blood pressure | 4.021 | 1.33-12.154 | 0.014 * |
| disturbance of thermoregulation | 4.01 | 1.489-10.800 | 0.006 * |
| nausea | 0.724 | 0.257-2.045 | 0.543 |
| unstable blood glucose | 1.839 | 0.594-5.694 | 0.29 |
| otitis media | 2.257 | 0.85-5.995 | 0.102 |
| pneumonia | 1.17 | 0.450-3.043 | 0.748 |
| dysuria | 13.546 | 1.805-101.64 | 0.011 |
| urinary tract infection | 1.39 | 0.517-3.734 | 0.514 |
| cholelithiasis | 1.673 | 0.617-4.538 | 0.312 |
| tracheal granuloma | 1.45 | 0.522-4.026 | 0.476 |
| urinary stone | 1.186 | 0.38-3.70 | 0.768 |
| decubitus | 0.88 | 0.242-3.199 | 0.846 |

P: * < 0.05 ** < 0.01 *** < 0.001

## 5. Discussion

### Vicious circle of Adverse Clinical signs and Communication ability




Need for nursing care to maintain genaral conditions

### Several types of ALS patients

Who progress stages IV –V had more adverse clinical signs
- unstable blood pressure
- disturbance of thermoregulation
- dysuria

This suggested that stages IV or V shows multisystem neurodegeneration involving the oculomotor nuclei and limbic system.
Future study is required to related ALS-plus.


Study Supported by: JSPS KAKENHI (Grant-in-Aid for Scientific Research (B)) Grant Number 25293449
No potential Conflict of Interest (COI) to disclose

# Respirator-aided long-term survival cases of amyotrophic lateral sclerosis (ALS) with communication abilities, motoneuron system-confined degeneration, and scanty TDP-43 aggregation

# ---a subgroup of ALS?

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## Not all the patients with ALS on long-term mechanical ventilation (LTMV) develop into a totally locked-in state

**Totally-locked in state (Communicaion stage V)**

About 13% of cases on LTMV

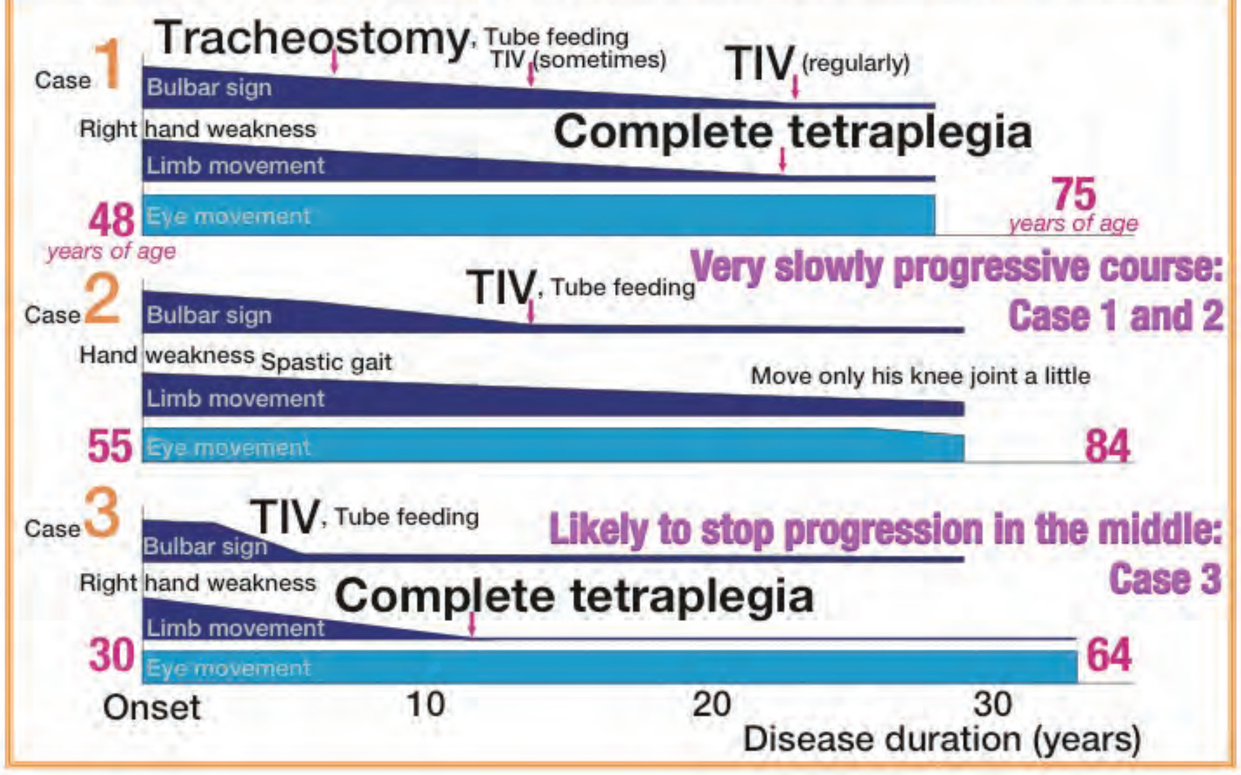
- Very rapid progression
- Lost of all voluntary movements
- Can not communicate by any means
- Severe degeneration of motor neuron system
- Multiple system degeneration beyond motor neuron system

**Maintain communication abilities**

What type of ALS?

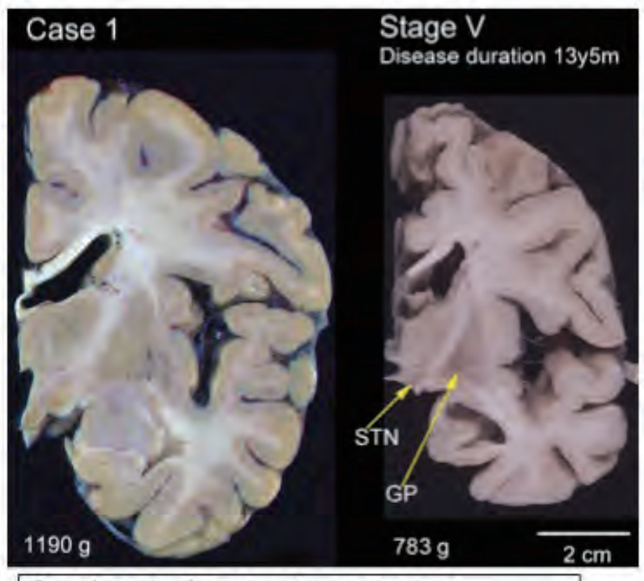
**Methods: Three autopsied ALS cases with an approximately 30-year survival and good communication abilities were clinicopathologically investigated.**

## All three cases could communicate in sentences via eye movements until death

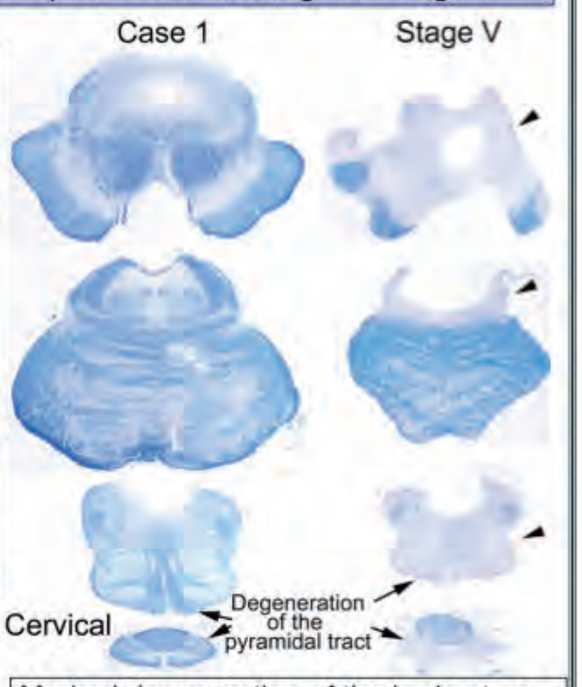



## Motor neuron system-confined degeneration

Comparison with cerebral, brain stem and spinal cord findings of stage V

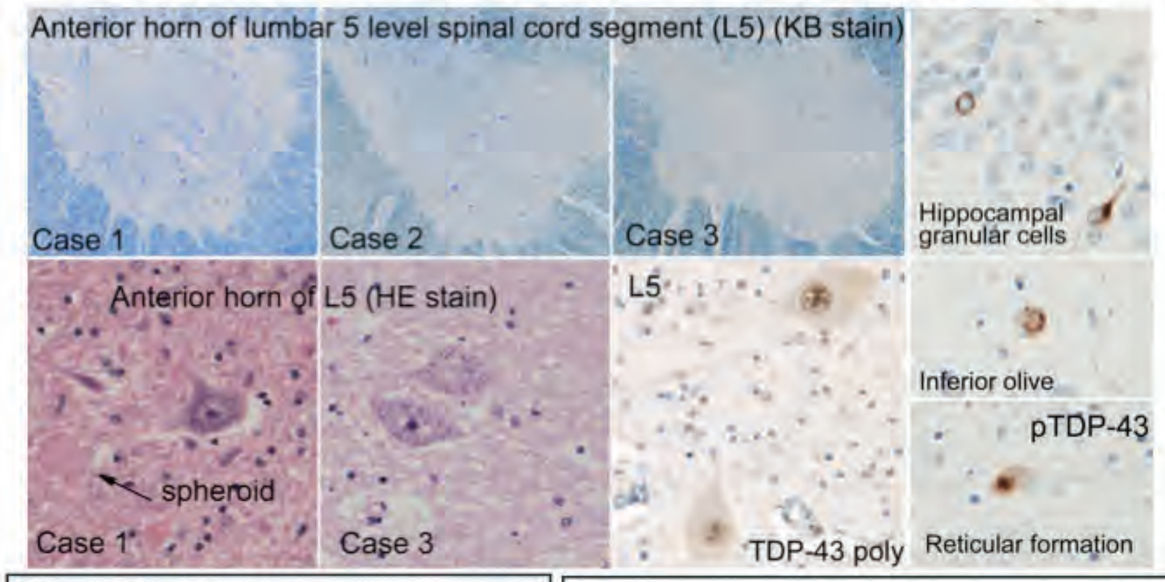



Cerebrum of present cases were preserved (Case 1). Marked cerebral atrophy with degeneration of subthalamic nucleus (STN) and globus pallidus (GP) were seen in the case with stage V.




Marked degeneration of the brain stem tegmentum (arrowheds) and spinal cord were seen in stage V.

## Lower motor neuron and TDP-43 aggregation




Normal–looking motor neurons remained. Neither hypertrophic astrocytes nor macrophages were observed.
These findings correspond to very slowly progressve clinical course.

There were no TDP-43-immunoreactive inclusions in the lower motor neurons and occasional ones in non-motor neurons in case 3. There wore no Bunina bodies. These findings are different from the findings of classical ALS.

## Several types of long-duration ALS

### *On TIV*

- ✓ Very long-survival with good communication ability: present cases

  Mean disease duration of ALS on TIV (61 cases) was 8 year 5 months in our 134 autopsied ALS
- ✓ Rapid progress into a totally locked-in state/ stage V [Hayashi H, Kato S. J Neurol Sci 93:19, 1989]

### *No TIV*

- ✓ Lower motor-predominant and illness ranged from10 to 20 without TIV [Kato et al. Brain Nerve 45:267-272, 1993, Nishihara et al Acta Neuropathol 117:45-53, 2009]

## Conclusions

### A distinct subgroup of ALS?

**Clinically**

- ✧ Much slower disease progression
- ✧ Maintained good communication via eye movements in spite of survival on LTMV

**Neuropathologocally**

- ✧ Motor neuron system-confined degeneration
- ✧ Remaining good-shaped motor neurons
- ✧ A few TDP-43 immunoreactive inclusions



This work supported by JSPS KAKENHI Grant Number 25293449