Motor neurone diseases

P1468
UNC13A influences survival in an Italian population-based series

A. Calvo1, G. Restagno2, M. Brunetti2, I. Ossola2, E. Majounie1, A.E. Renton4, A. Canosa1, U. Manera1, E. Bersano1, C. Moglia1, G. Mora5, B.J. Traynor4, A. Chiò1

1ALS Center, University of Torino, S. Giovanni Battista Hospital, 2Molecular Genetic Unit, A.S.O. O.I.R.M.-S. Anna, Torino, Italy, 3Neuromuscular Diseases Research Unit, 4Molecular Genetics Unit, Laboratory of Neurogenetics, NIA, Bethesda, MD, USA, 5ALS Center, Salvatore Maugeri Foundation-IRCCS, Milano, Italy

Background: It has been recently shown that the common variant rs12608932 in gene UNC13A is associated with amyotrophic lateral sclerosis (ALS) susceptibility and may be an independent modifier of ALS survival in populations of North-European ancestry (Van Es, 2009; Diekstra, 2012).

Aim: To evaluate the effect of UNC13A on survival in a population-based series of ALS cases of Italian ancestry.

Methods: 261 samples and 247 ethnically matched controls were genotyped on Infinium HumanHap550 (Illumina), and 236 on Infinium HumanHap610-Quad (Illumina); 535,468 SNPs were common across both platforms, including the rs12608932 single nucleotide polymorphism (SNP). Survival was assessed with Kaplan-Meir curves and compared with the logrank test.

Results: The study included 497 apparently sporadic ALS patients (mean age 61.6 years [SD 11]) resident in Piemonte, Italy. The minor allele frequency was similar in cases and controls (33% vs. 32%, p=0.91). However, we found a significant association with survival for both additive and recessive genetic models. Patients carrying the CC (minor allele) genotype had a 12-months shorter survival than those carrying AA or AC genotypes (median survival time, CC 2.5 years [95% CI, 1.5-3.4] vs. AA or AC 3.5 years [3.1-3.8]; p=0.017). This effect was independent from patients' age at onset, gender, site of symptom onset, phenotype and use of NIV and PEG in a stepwise forward Cox multivariable model (p=0.02; HR=1.42).

Comment: In the Italian population, UNC13A has a strong independent modifier effect on ALS survival. This finding has implications relevant to both, understanding ALS pathogenesis and in defining therapeutic interventions.

P1469
Preliminary results of the French MSA-fluoxetine study

O. Rascol, French MSA-Fluoxetine Study Group

Clinical Pharmacology, Toulouse University Hospital, Toulouse, France

Introduction: Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder characterized clinically by any combination of parkinsonian, autonomic, cerebellar or pyramidal symptoms. To date, no drug has proved sufficient efficacy to halt the neurodegenerative process in MSA. The therapeutic strategy relies on the control of clinical symptoms of parkinsonism and autonomic dysfunction. Not only a dopaminergic deficit, but also a serotonergic one, could be implicated in the physiopathology of MSA, as suggested by a recent study showing an improvement of behavioural and neuropathological deficits with fluoxetine in a model of MSA (Ubhi, et al. Exp Neurol 2012;234:405-16).

Objective: To test the clinical effect of fluoxetine 40mg/day on subjects with MSA, measured by change from baseline to month 3 in the total UMSARS (part I + part II) score.

Methods: Multi-centred, randomized, double-blind, placebo controlled study on 81 MSA subjects. Only baseline data and preliminary result of main outcome are presented here.

Results: The two groups were similar at baseline concerning age (63.5 vs. 63.1), gender (men: 58.5% vs. 65%), UMSARS (I + II) (40.2 vs. 40.3), Beck Depression Inventory Scale (11.8 vs. 12.3), SCOPA-AUT score (20 vs. 22.9), Epworth sleepiness scale (8.3 vs. 7.7), apathy, and orthostatic hypotension (40% vs. 60%). No significant difference according treatment group was found for change from baseline in the total UMSARS score after 3 months of fluoxetine (3.1 vs. 1.4).

Conclusion: Further analyses with adjustment and imput for missing values are needed to confirm these preliminary results.
P1470
TDP-43 and FUS pathology in amyotrophic lateral sclerosis
Y. Fujita1, M. Kitani1, M. Takatama2, M. Ikeda1, K. Okamoto1
1Neurology, Gunma University Graduate School of Medicine, 2Internal Medicine, Geriatric Research Institute and Hospital, Maebashi, Japan

Introduction: TAR DNA-binding protein of 43-kDa (TDP-43) and fused in sarcoma (FUS), which are the key proteins of ALS, have structural and functional similarities. However, the relationship of these proteins have not been established. Therefore, we examined the relationship of TDP-43 and FUS proteins in ALS using immunohistochemical methods.

Methods: We studied the spinal cord sections from 12 common sporadic ALS (SALS) patients and 4 ALS patients with FUS-positive cytoplasmic inclusions (including 3 familial cases and 2 patients with mutations in the FUS gene). The sections were stained with haematoxylin and eosin (HE), and immunostained with anti-FUS, anti- phosphorized-TDP-43 (pTDP-43), and anti-non-phosphorylated TDP-43 antibodies.

Results: All pTDP-43-positive inclusions except one were negative for anti-FUS antibody in SALS. Although most of the 42 neurons without abnormal pTDP-43 immunoreactivity showed nuclear staining of FUS, 6 of 40 neurons with fine granular pTDP-43 immunoreactivity and 13 of 22 neurons with skein-like or round inclusion did not show nuclear staining of FUS. On the other hand, all basophilic inclusions (BIs) and FUS-positive inclusions were not stained with anti-pTDP-43 and anti-TDP-43 antibodies. Furthermore, the nuclear staining of TDP-43 was well preserved in all neurons with BIs and FUS-positive inclusions.

Conclusion: These results suggest that the pathogenesis of FUS proteinopathy is independent from that of TDP-43 proteinopathy; however, abnormal TDP-43 may interact with the FUS protein in SALS pathogenesis.

P1471
Survival in amyotrophic lateral sclerosis - prognostic factors
S. Pinto, A. Pinto, M. de Carvalho
Institute of Molecular Medicine and Faculty of Medicine, University of Lisbon, Portugal

Introduction: Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease with short survival due to respiratory failure. We aimed to test the survival predictive value of the classical prognostic factors in addition to the phrenic nerve motor responses in a large ALS population.

Methods: We included 254 ALS patients followed in our tertiary center from 1997 and 2006 in whom phrenic nerve stimulation was performed and who fulfilled the inclusion criteria. ALS was spinal-onset in 175 (group1- G1) and bulbar-onset in 79 (group2- G2). Features recorded at first visit were: gender, age at symptom onset, onset region, diagnostic delay, forced vital capacity (FVC), ALS functional rating scale (ALS-FRS) including the respiratory sub-score of the reviewed ALS-FRS and mean amplitude of motor responses by phrenic nerve stimulation (PhrenAmpl). All patients were on riluzole.

Results: Survival analysis was evaluated by Kaplan-Meier log-rank and multivariate Cox proportional hazards. Independent factors negatively affecting survival were bulbar-onset, elderly age, short diagnostic delay, FVC and small PhrenAmpl for the complete population. Small PhrenAmpl and short diagnostic delay were also independent factors for G1 and G2, but age at onset and FVC were also independent predictors for G2.

Discussion: Prognostic factors in our population are in accordance with those described by others. PhrenAmpl showed to be an independent prognostic factor. It is non-volitional and easily standardized and quickly performed. FVC depends on patient co-operation and is not reliable in patients with facial weakness. Phrenic nerve stimulation should be included in the routine assessment of ALS patients.

P1472
Rasch analysis of the Epworth Sleepiness Scale in patients with post-polio syndrome
C.J. Gibbons1,2, I.M. Pomeroy1, A. Tennant1, C.A. Young1
1Walton Centre Foundation NHS Trust, Liverpool, 2Collaboration for Leadership in Applied Health Research and Care (GM CLAHRC), University of Manchester, 3Academic Department of Rehabilitation Medicine, University of Leeds, UK

Introduction: The Epworth Sleepiness Scale (ESS) has been widely used to assess sleepiness in clinical trials for neurology patients. The scale has not previously been validated for use in patients with post-polio syndrome (PPS). Data collected in a PPS population were applied to the Rasch model to ensure the scale was reliable, unidimensional and free from differential item functioning (DIF) or local dependency.

Methods: A questionnaire pack containing the ESS was sent to 282 (88% response) consecutive patients with a confirmed diagnosis of PPS.

Results: The ESS displayed reasonable fit to the Rasch model [χ2(24) =37.80, p=0.04]. Differential item functioning was not present for either age or gender. Scale reliability was acceptable (PSI=0.86). Mild local dependency (r=0.20) was apparent between items 3 'Sitting inactive' and 6 'Sitting and talking'. Collapsing items 3 and 6 into a testlet improved fit and revealed local dependency between items 1 'Sitting and reading' and 2 'Watching TV'. Collapsing these items into a testlet led to a solution with excellent model fit [χ2(18) =22.55, p=0.21]. The final scale was unidimensional (0.71% T-tests significant) and free from DIF or local dependency. Category thresholds were well ordered and item 'difficulties' were widely distributed (-3.2 to 3 logits).

Conclusion: The Epworth Sleepiness Scale demonstrates good psychometric and scaling properties in this population. The scale may be used with confidence in clinics and research with PPS patients.
P1473

Work in progress: quality of life (QoL) and neurological disease - trajectories of outcome in neurological conditions (TONiC): a study protocol

C.J. Gibbons1,2, R. Cousins3, I.M. Pomeroy4, H. Ando1-3, A. Al-Chalabi4, J. Chataway3, C. Constancinescu6, J. Ealing7, C. Hawkins8, K. Morrison9, J. Palace10, N. Robertson11, D. Rog7, N. Scolding11, B. Sharrack11, P. Shaw14, K. Talbot15, T. Williams8, A. Tennant17, C.A. Young1, on behalf of the TONiC Group

1Walton Centre Foundation NHS Trust, Liverpool, 2Collaboration for Leadership in Applied Health Research and Care (GM CLAHRC), University of Manchester, 3Health Sciences, Liverpool Hope University, Liverpool, 4King's College Hospital, 5National Hospital for Neurology and Neurosurgery, London, 6University of Nottingham, 7Salford Royal Hospital, Manchester, 8University Hospital of North Staffordshire, Stoke-on-Trent, 9University Hospital Birmingham NHS Foundation Trust, Birmingham, 10University of Oxford, Oxford, 11University of Cardiff, 12University of Bristol, 13Sheffield Teaching Hospitals, 14Sheffield Institute of Translational Neuroscience (SITRaN), University of Sheffield, 15John Radcliffe Hospital, Oxford, 16The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, 17Academic Department of Rehabilitation Medicine, University of Leeds, UK

Background: Maintaining quality of life (QoL) in neurological illness is a key treatment priority for clinical care teams. Understanding the complex variables and relationships that influence QoL and the manner these relationships develop over time are important in improving care and designing better services.

Aims: We aim to examine the factors influential for QoL of individuals with multiple sclerosis (MS), and motor neurone disease (MND). This process includes longitudinal assessment over four time points, development of new disease-specific scales and validation of existing scales that measure different factors related to QoL.

Methods: The study will be run in five phases across fourteen hospital sites

Phase One: In depth interviews and focus groups conducted with patients, to explore QoL issues and identify potential items for disease-specific questionnaire scales.

Phase Two: Face to face interviews and focus groups conducted with patients to identify gross questionnaire problems. Professionals invited to participate in Delphi discussion to discuss factors and model design to be tested.

Phase Three: Baseline questionnaire administration.

Phase Four: Test-retest assessment (four to six weeks).

Phase Five: 6-, 12- and 24-month questionnaire administration.

Quantitative analyses will be conducted using Rasch analysis and Structural Equation Modelling.

Discussion: The TONiC study is a large longitudinal study designed to explore quality of life for people living with neurological illness. It uses quantitative models based on qualitative investigation with the patients that experience these conditions first-hand. By creating and validating longitudinal models of QoL, key intervention points can be identified to enhance care delivery.

P1474

Familial adult spinal muscular atrophy associated with VAPB gene

M.R.G. de Freitas, V. Kosac, O.J.M. Nascimento

Neurology, Federal Fluminense University, Niterói, Brazil

Introduction: Familial spinal muscular atrophy (FSMA) associated with VAPB gene is a rare autosomic dominant disease of late onset and slow progression. Most cases were evaluated in Brazil and they were linked to the mutation P56S. The phenotype may vary among families. The objective is to report four generations of four families in Rio de Janeiro.

Methods: We studied 41 patients of 4 families with clinical history, physical exam, electrophysiological study and genetic test.

Results: All patients presented a late onset and slow progressing disease with fasciculations, proximal weakness and amyotrophy, hypoactive deep tendon reflex, except one patient with brisk reflex. One patient showed tongue fasciculations and respiratory insufficiency. Electrophysiological studies showed patterns of lower motor neuron disease and genetic test showed P56S mutation of VAPB gene.

Conclusion: Although it is a rare motor neuron disease, FSMA with this mutation could be much more prevalent in Brazil than expected. Moreover many cases may be underdiagnosed. Genetic test should be performed whenever it is suspected, mainly in our country.
P1475

Effects of hypertension in ALS. Results of a population-based study

C. Moglia1, A. Calvo1, A. Ilardi1, A. Canosa1, U. Manera1, L. Mazzini2, G. Mora3, A. Chio4, PARALS
1Neuroscience, University of Torino, Torino, 2Università del Piemonte Orientale, Novara, 3Fondazione Salvatore Maugeri, Milano, Italy

Background: Factors related to cardiovascular risk have been assessed in ALS with uneven findings. A recent paper showed that a beneficial vascular risk profile is associated with an increased risk of ALS (Sutjeda et al, 2011).

Aim: To assess the effect of arterial hypertension in a population-based series of ALS patients.

Methods: The study population consisted of the 1260 ALS cases incident in Piemonte and Valle d’Aosta in the period 1995-2004. Patients were affected by definite, probable or probable laboratory-supported ALS. Arterial hypertension was indicated as systolic pressure ≥160 and diastolic pressure ≥100.

Results: A total of 272 patients (21.6%) were affected by hypertension at the time of onset of ALS. Patients with hypertension had a significantly lower age at onset of ALS than patients without hypertension in both genders (women, 68.1 [SD 8.3] years vs. 64.2 [11.9] years, p=0.0001; men, 67.8 [8.9] years vs. 63.7 [11.5] years, p=0.0001). No relationship between hypertension and site of onset (bulbar vs. spinal) was found. Patients with hypertension were more likely to have also diabetes mellitus (HR 2.9, 95% c.i. 1.8-4.6, p=0.0001) and frontemporal dementia (FTD) (HR, 1.8, 95% c.i. 1.1-2.9, p=0.01). Hypertension did not influence ALS outcome.

Conclusions: We have found that a preceding arterial hypertension is associated to a delayed onset of ALS in population-based series. This finding is in line with the previous observation that a beneficial vascular risk profile is associated to an increased risk of ALS.

P1476

Ataxin-1 and ataxin-2 intermediate-length PolyQ expansions in ALS patients

R. Spataro1, W. Sproviero2, R. Mazzzei2, F. Cavalcanti2, F. Condino2, T. Colletti1, V. La Bella1, F.L. Conforti2
1Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo, 2Institute of Neurological Sciences, National Research Council, Cosenza, Italy

Introduction: A number of studies have shown that ataxin-2 (ATXN-2) intermediate poly-CAG expansions with CAA interruptions are a risk factor for amyotrophic lateral sclerosis (ALS). The present work was undertaken with the aim to investigate the frequency of Ataxin-1 (ATXN-1) and ATXN-2 PolyQ expansions in a cohort of sporadic and familial ALS patients from South Italy.

Methods: The PolyQ lengths of ATXN-1 and ATXN-2 in 405 sALS, 13 fALS and 296 unrelated controls without history of neurodegenerative disorders (NC) were assessed. Genotyping of the ataxin-1 and ataxin-2 CAG repeat number was performed using fluorescent-labelled primer PCR with capillary electrophoresis on an ABI3130xl sequencer and analyzed with GeneMapper software version 4.0.

Results: We found that 57 out of the 806 ATXN-1 alleles in the sALS cohort harboured a ≥32 PolyQ repeat length, as compared to 13 out of the 544 NC alleles (p=0.0001, c2 test). For ATXN-2, a ≥28 PolyQ repeat length was found in 22 of the 808 sALS alleles and in only 3 of the 586 NC alleles (p=0.0041, c2 test). Further, the analysis of ATXN-1 and ATXN-2 PolyQ repeat length expansions in fALS revealed that ATXN-1 might be a potential risk factor also in these patients. ATXN-1 CAT and ATXN-2 CAA interruptions were detected in ALS patients only. Age at onset, site of onset, and sex were not significantly related to the ATXN-1 and/or ATXN-2 PolyQ repeat length expansions.

Conclusion: Both ATXN-1 and ATXN-2 PolyQ intermediate expansions are independently associated to an increased risk for ALS.
P1477

**High vascular risk profile is associated with prolonged survival in ALS**

M.A. Rubio Perez, J. Pascual Calvet, J. Jiménez Conde, A.J. Santiago Ois, E. Munteis Oliva, J. Roquer Gonzalez

*Neurology Department, Parc de Salut Mar, Barcelona, Spain*

**Introduction:** Recent studies show that a beneficial vascular risk profile increases amyotrophic lateral sclerosis (ALS) susceptibility. Also, low levels of vascular endothelial growth factor (VEGF) represent a risk factor for ALS, and correlate with shorter survival. Chronic vascular hypoxic situations as coronary, cerebral and peripheral arterial diseases stimulate VEGF production.

The aim of the study is to analyze the impact of the vascular risk profile in the survival of our population of ALS patients.

**Methods:** Retrospective analysis of our ALS registry of patients diagnosed between 1991 and 2011. Demographic and clinical data like age of onset and clinical form at onset were collected.

Patients were classified in two groups according to their vascular risk profile. 'High Vascular Risk' profile was defined as having suffered a clinical event (stroke, coronary or peripheral arterial disease) or the presence of at least 3 vascular risk factors.

**Results:** 161 patients were analyzed (49.7% men, 50.3% female), with median age of 64 years (IQR 55-73). 128 patients were dead (79.5%), with median survival time of 32 months (IQR 20-53). Factors associated with survival in univariate analysis were sex, age of onset, clinical form at onset and high vascular risk profile. Multivariate analysis showed an independent association with survival with the following variables: age (HR 1.028; p<0.001), clinical form at onset (HR 1.705; p=0.009), and high vascular risk profile (HR 0.592; p=0.014).

**Conclusion:** We found an association between a high vascular risk profile and increased survival in our population. Other prognostic markers were age of onset and clinical form at onset.

---

P1478

**Inhibition of APP beta-cleavage site affects survival and motor functions of ALS transgenic mice**

P. Rabinovich Toidman, M. Becker, B. Solomon

*Department of Molecular Microbiology and Biotechnology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel*

**Background:** Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease defined by motor neuron loss. Recent studies have reported an increase in amyloid precursor protein (APP) levels and in its cleavage products in ALS patients indicating their possible involvement in this disease. APP is a transmembrane protein processed either by ß-secretase or ß-secretase followed by ß-secretase. The APP cleavage products mediate a reduction in synaptic transmission, synaptic loss, neurite retraction and programmed cell death.

**Objective:** Elucidation of the role of APP cleavage products in pathology of ALS.

**Methods:** ALS mice models that express mutant superoxide dismutase 1 (SOD1) were treated intraventricularly with monoclonal antibody that blocks the ß-secretase cleavage site on APP. Levels of APP cleavage product called soluble APP-ß, number of motor neurons, motor functions and survival were assessed.

**Results:** Inhibition of APP cleavage resulted in a decrease in the levels of soluble APP-ß, an increase in number of motor neurons, delayed disease onset, improved motor capacities of ALS affected mice and better survival.

**Conclusions:** APP cleavage products might contribute to the degeneration in ALS, and early inhibition of APP process may ameliorate disease progression.
P1479

No heart involvement in SBMA patients

G. Querin1, P. Melacini1, L. Morandi2, L. Mazzini1, V. Silani3, A. Gaiani1, C. D'Ascenzo4, E. Pegoraro1, G. Soraru1
1University of Padova, 2Istituto Neurologico ‘C.Besta’, Milan, 3University of Novara, 4University of Milan, Italy

Background: Spinal and bulbar muscular atrophy (SBMA) is an adult-onset, X-linked, lower motor neuron disease, characterized by slowly progressive muscle weakness and atrophy. The disease is caused by an expansion of a CAG repeat encoding a polyglutamine tract within the androgen receptor (AR) gene. Nuclear accumulation of pathological AR, which is toxic to motor neurons, has been observed in tissues other than the nervous system including the heart.

Materials and methods: To test the hypothesis of the presence of heart disease in SBMA we carried out a full cardiologic evaluation (12-lead ECG, Echocardiography and 24-hour ECG Holter) in 26 genetically defined SBMA patients.

Results: Patients' age range was 32 - 75 yrs (mean age 54.4 yrs). 10 patients had high blood pressure and were under antihypertensive medications. No patients displayed clinical signs of heart disorders at the cardiologic examination. The 12-lead ECG findings were normal or consistent with left ventricle (LV) hypertrophy in the oldest patients suffering from high blood pressure. Similarly, echocardiography showed no abnormalities other than mild concentric LV hypertrophy in patients with hypertension. No patients showed significant rhythm abnormalities at the 24-hour ECG Holter.

Conclusions: Our findings do not support the hypothesis of a primary heart involvement in SBMA.

P1480

Rigorous control of a supervised exercise protocol improves function and survival in amyotrophic lateral sclerosis patients

J.P. Lopes Almeida1, A. Cardoso Pinto1, M. de Carvalho2
1Department of Physical Medicine and Rehabilitation, University of Lisbon Medical School, Santa Maria Hospital, 2Neuromuscular Unit, Institute of Molecular Medicine, University of Lisbon Medical School, Lisbon, Portugal

Introduction: The uncertainty about exercise in Amyotrophic Lateral Sclerosis (ALS) is mostly derived from paucity of randomized trials and lack of rigorous control of exercise intensity. We hypothesized that exercising till fatigue (as evaluated by Borg scale and cardiopulmonary exercise test, CPET), is suitable for ambulatory ALS patients.

Methods: Prospective, quasi-randomized, single-blinded controlled trial. 40 consecutive ALS patients, were assigned to the control group (G1, n=20) and the intervention group (G2, n=20). Patients in G1 followed standard care and exercised to fatigue with no supervision at home. G2 underwent a supervised moderate progressively resisted exercise program 3 times/week (treadmill ramp protocol levelled 20% lower than determined by CPET), while compensating lower limb weakness and respiratory failure with body-weight-supporting-systems and non-invasive-ventilation, correspondingly. All patients performed CPET and respiratory function tests (RFT) at 3-month interval. Primary outcomes were ALSFRS-R scores and slopes and RFT/CPET parameters. Secondary outcomes included survival analysis.

Results: No clinical or laboratorial differences were observed between groups for any variable at admission. All ALSFRS scores improved in G2 throughout follow-up course (p<0.05); survival from the intervention was statistically increased in G2 (p=0.021) and when adjusted to exercise variables. A linear decline in respiratory function was seen in both groups, but not significant. Peak oxygen uptake, ventilation/minute and VO2/work rate at one-year were significantly lower in G2 (p<0.01).

Conclusion: A well-controlled exercise protocol is feasible and should be prescribed to ALS patients since it improves survival and respiratory efficiency, with less deconditioning. Determinants of exercise are significant predictors of survival.
P1481

Reduced expression of BTBD10 in anterior horn cells in amyotrophic lateral sclerosis

N. Furuta1, Y. Fujita1, M. Takatama1, M. Matsuoka3, K. Okamoto1
1Department of Neurology, Gunma University Graduate School of Medicine, 2Geriatrics Research Institute and Hospital, Maebashi, 3Department of Pharmacology, Tokyo Medical University, Shinjuku, Japan

Background: BTBD10 was shown to activate Akt by inhibiting protein phosphatase 2A (PP2A)-mediated dephosphorylation. The overexpression of BTBD10 suppressed motor neuron death. However, it remains unclear whether expression of BTBD10 is related to motor neuron degeneration in human amyotrophic lateral sclerosis (ALS).

Materials and methods: We examined the spinal cords of 22 patients with sporadic ALS and 5 control cases. Mirror paraffin sections were prepared for immunohistochemistry, which was carried out using rabbit polyclonal anti-BTBD10 antibody, anti-phosphorylation-dependent TDP-43 (pTDP-43) antibody, and anti-TGN46 antibody, which recognizes an intrinsic membrane protein of trans-Golgi network (TGN). We compared the neuronal immunoreactivity between BTBD10 and TGN46 / pTDP-43.

Results: BTBD10 was expressed in neurons in the spinal anterior horns and only minimally expressed in astrocytes. In control cases, BTBD10-positive small granular cytoplasmic immunostaining was observed diffusely in the anterior horn cells. In ALS cases, BTBD10-positive neurons were significantly decreased in the remaining neurons, and the reduction of BTBD10 immunoreactivity occurred more frequently in large neurons than in small neurons. Mirror sections disclosed that neurons with reduction of BTBD10 immunoreactivity showed more frequently fragmentation of Golgi apparatus and pTDP-43 positive inclusions. Bunina bodies and round inclusions showed no BTBD10 immunostaining.

Conclusion: Reduction of BTBD10 immunoreactivity was observed in the large anterior horn neurons, and the majority of these neurons had fragmented Golgi apparatus and pTDP-43 positive inclusions. These results suggest that reduced BTBD10 expression may be related to the neuronal degeneration in ALS.

P1482

Novel candidate proteins for early diagnosis in animal models and patients of amyotrophic lateral sclerosis

Molecular Pharmacology, Department of Biofunctional Evaluation, Gifu Pharmaceutical University, Gifu, Japan

Introduction: The diagnosis of amyotrophic lateral sclerosis (ALS) is difficult at an early stage due to lack of definitive biomarkers. Our aim was to identify characteristic serum protein patterns that could provide candidate biomarkers for ALS.

Methods: We divided mutant superoxide dismutase 1 (SOD1)H46R rats into 3 groups based on disease progression: pre-symptom (90 days), onset, and end-stage. After separation of serum proteins using two-dimensional electrophoresis, we selected clear protein spots and identified 2 candidate proteins - inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) and glutathione peroxidase 3 (GPX3).

Results: The 120-kDa ITIH4 increased at the onset of the disease and the cleaved 85-kDa ITIH4 at the end-stage in the sera of the SOD1H46R rats. In clinical samples, expression of the 85-kDa ITIH4 was substantial in the sera and in vascular endothelial cells in sporadic ALS patients, and was not detected in controls or patients with Alzheimer’s or Parkinson’s disease. 100-kDa ITIH4 was specifically increased in myelitis patients, but not in ALS. GPX3 protein levels in the sera of SOD1H46R rats were upregulated pre-symptom and gradually decreased as the disease progressed. In clinical samples, GPX3 protein levels were lower in the sera of the patients with ALS than in those of controls, patients with Alzheimer’s disease, Parkinson’s disease, or myelitis.

Conclusion: These results indicate that ITIH4 and GPX3 are potential biomarkers for diagnosis of ALS and that observing changes in these expression levels may be useful in obtaining important clinical information on the progression of disease in ALS patients.
P1483

Pattern of spread and survival in sporadic ALS “How does ALS progress?”

F. Kimura¹, C. Fujimura-Kiyono¹, H. Tani², S. Ishida¹, H. Nakajima¹, T. Hirose¹
¹Division of Neurology, The First Department of Internal Medicine, Takatsuki-City, ²Osaka Medical College, Osaka, Japan

Objective: To define patterns of spread through the order of lower motor neuron involvement (first, second or third order), relationships between interval or sites of affected areas from onset to involvement of a second region, and prognosis, including 5-year survival, normal preservation of motor function at onset of respiratory symptoms and cumulative occurrence of each region and direction of spread.

Method: 150 patients with sporadic amyotrophic lateral sclerosis (ALS) underwent follow-up at 3 month intervals until the appearance of respiratory symptoms. Symptom appearances were determined using the revised version of the ALS Functional Rating Scale.

Result: Median survival with combined type onset (two regions simultaneously) was shorter (18 months) than with bulbar onset (26 months, p<0.01). The interval from onset to involvement of the second region correlated significantly with survival, independent of particular combinations. 5 year survival rate was 21% for lower limb onset, 18% for upper limb onset and 16% for bulbar onset. Early manifestations of bulbar symptoms within 1 year were associated with worse survival (p<0.001) although no significant difference in survival was seen between groups with and without bulbar symptoms (p=0.51). In terms of cumulative occurrence, symptoms spread longitudinally to adjacent regions. Bulbar function remained preserved in 27%, lower limb function in 10% and upper limb function in 2.7%.

Conclusion: The interval between onset and involvement of the second region is an important predictor of survival. The data support the contiguous anatomical propagation of lower motor neuron involvement in sporadic ALS.

P1484

ALS incidence and prevalence in the U.S.: estimates from large administrative databases

D. Perlroth¹,², R. Conrad²,³, H. Cheung², D. Lakdawalla²,³, L.A. White⁴
¹Center for Primary Care and Outcomes Research, Stanford University, Stanford, ²Precision Health Economics, ³Shaef er Center for Health Policy and Economics, University of Southern California, Los Angeles, CA, ⁴Biogen Idec, Weston, MA, USA

Introduction: Most ALS epidemiologic estimates are based on samples of <1 million persons. We estimated U.S. ALS incidence and prevalence using two large healthcare claims databases.

Methods: We used 2005-2007 claims data from a Medicare 20% sample for patients aged 65 years and over, and Ingenix Touchstone for patients aged 18 to 64 years. There were 18 million person-years of data in Medicare, and 7 million person-years in Ingenix. ALS cases were included if they had ≥2 medical claims with ICD-9 diagnostic code 335.20 separated by at least 90 days. We extrapolated these findings to estimate the epidemiology of ALS in the overall U.S. population.

Results: Annually on average, there were 477 (range 454 to 516) new ALS cases in Medicare sample and 42 (range 36 to 53) in Ingenix. Mean prevalent ALS cases were 1,670 in Medicare and 138 in Ingenix. This resulted in an estimated annual ALS incidence of 7.7 cases per 100,000 persons over age 65, and 2.5 per 100,000 persons aged 18-64. The estimated annual ALS prevalence was 26.9 cases per 100,000 over age 65 and 8.2 per 100,000 aged 18-64. The overall U.S. adult population ALS incidence was 7,530 new cases annually, or 3.4 per 100,000 with an annual prevalence of 25,400 cases, or 11.3 per 100,000.

Conclusion: ALS incidence and prevalence estimates from these data are slightly higher (7-10%) than previous estimates based on smaller samples sizes. The number of persons diagnosed and living with ALS may be larger than previously thought.
P1485
Potential biomarkers in the blood of ALS patients: mitochondrial SOD and aconitase enzymatic activities

C. González Mingot1, P. Íñarrea2, C. Iñíguez1, J.L. Capablo1, J. Costán1, F.J. Miana4, J. García4, R. Osta6, P. Larrodé1
1Neurology Department, University Clinical Hospital of Zaragoza, 2Biochemical Department of Biology Faculty, Zaragoza University, 3Neurology Service, Miguel Servet Hospital of Zaragoza, 4Neurology Department, University Clinical Hospital of Zaragoza, 5Physiology Department of University Faculty, Zaragoza University, Zaragoza, Spain

Background: Oxidative stress-mediated mitochondrial degeneration plays a role in motor neuron death caused by mutant SOD1 effects in Amyotrophic Lateral Sclerosis (ALS). It has not yet been established whether oxidative stress is a cause or a consequence of this neurodegeneration. There is altered antioxidant defence enzyme (ADE) activity in the peripheral tissues of familial and sporadic ALS patients. This study attempts to confirm the alteration in mitochondrial ADE activity and to try to determine whether the altered enzyme activity in ALS is independent of a patient’s condition.

Methods: We measured mitochondrial SOD1, SOD2 and aconitase enzymatic activities in 22 controls and 26 SALS patients at different stages of the disease. We correlated mitochondrial antioxidant activity with clinical and prognostic variables.

Results: Mitochondrial antioxidant enzymatic activity was significantly lower in the 26 ALS patients than in the 22 controls (SOD 1 \(p<0.001\), aconitase \(p<0.005\)). Cases with lower SOD1 (\(p<0.05\) and aconitase (\(p<0.005\)) activity levels died before those with higher levels. Patients with higher levels of SOD1 (\(p<0.05\) and aconitase (\(p<0.05\)) activity survived longer. Aconitase activity was also higher in patients with earlier onset ages (\(p<0.01\)) and in those with predominantly upper motor neuron (MN) signs. SOD2 activity was significantly correlated with ALSFRS scores and nutritional parameters.

Conclusions: Mitochondrial SOD1 and aconitase activities are independent prognostic factors for ALS, whereas SOD2 activity is influenced by the functional and nutritional status of ALS patients.

P1486
A functional variant in the PON1 gene is associated with shorter survival in patients with amyotrophic lateral sclerosis

N. Ticozzi1, F. Verde1, C. Morelli1, C. Tiloca1, D. Sangalli1, I. Fogh1,2, A. Ratti1,3, S. Messina1, V. Silani1,3
1Department of Neurology, IRCCS Istituto Auxologico Italiano, Milano, Italy, 2MRC Centre for Neurodegeneration Research, Institute of Psychiatry, King's College London, UK, 3Department of Neuroscience, University of Milan Medical School, Milano, Italy

Introduction: The paraoxonases (PON) are a family of enzymes involved in preventing lipid membrane peroxidation, and in detoxification of exogenous compounds. Several studies have suggested an association between single nucleotide polymorphisms (SNP) in the PON genes and increased risk of developing amyotrophic lateral sclerosis (ALS). Our study aims to assess whether the functional SNP rs661 in PON1, which alters the substrate specificity of the enzyme, has an effect on disease phenotype.

Methods: 341 Italian patients with sporadic ALS were genotyped using the Human 660W-Quad BeadChip (Illumina), and rs661 genotypes obtained with the GenomeStudio software. Phenotypic traits analyzed included: age at onset, site of onset, distribution and severity of muscular involvement, global functional impairment, disease duration and the time from onset to the start of non-invasive ventilation (NIV).

Results: In comparison with patients homozygous for the major allele (A) of rs661, individuals with at least one copy of the G-allele presented more frequently with a bulbar (28.8% vs. 19.3%; \(p=0.01\)) or respiratory onset (10.7% vs. 1.6%; \(p<0.01\)). Also, GG patients often showed a symmetrical (48.1% vs. 19.8%; \(p<0.01\)) and proximal (50.0% vs. 27.6%; \(p=0.04\)) distribution of the motor deficit. Lastly, individuals homozygous for the G-allele had a shorter time-to-NIV (14.3 vs. 31.2 months; \(p=0.01\)), and reduced survival (26.8 vs. 41.4 months; \(p<0.01\)).

Conclusion: The G-allele of rs661 may increase the susceptibility of motor neurons innervating bulbar and axial muscles to neurodegeneration in ALS, ultimately resulting in a faster respiratory decline and shorter survival.
P1487

The copy number of 5q13 locus genes and the severity of spinal muscular atrophy in Russian patients

V. Zabnenkova, E.L. Dadali, A.V. Polyakov
Research Centre for Medical Genetics, Moscow, Russia

Introduction: Proximal spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by the loss of α-motor neurons in the spinal cord. With an incidence of 1 in 10,000 live births and a carrier frequency of 1 in 50, SMA is the most frequent genetic cause of infantile death. SMA patients are subdivided into types I-III according to age of onset and achieved motor abilities. These forms of proximal SMA are caused by mutations in SMN1 gene. About 95% of SMA cases are caused by homozygous deletion of the SMN1 gene or conversion events. The phenotype variability of the disease with such molecular homogeneity may be explained by presence of phenotype modifiers.

Methods: It has been developed a quantitative assay based on Multiplex Ligation-dependent Probe Amplification (MLPA) for this study.

Results: The SMNc and NAIP gene-copy number has been analyzed for establishing the phenotype-genotype correlation in 200 SMA patients (SMAI n=77, SMAII n=58, SMAMIII n=65). 77.9% of SMAI patients showed two copies of SMNc, 60.4% of SMAII patients had three or four copies of SMNc and 54.1% of SMAMIII had four to five copies. The NAIP gene is deleted in 36.4%, 6.9% and 4.6% affected individuals with SMA I, II and III types, respectively.

Conclusions: The copy number of SMNc gene is a modifying factor of severity of SMA. The absence of the gene NAIP, indicating a considerable deletion in the locus 5q13, may be an additional criterion, modifying the severity of the disease.

P1488

Prevalence of medical comorbidity among ALS patients in a U.S. health insurance claims database

J.R. Williams, D.A. Kerr, W. Farwell
Biogen Idec, Cambridge, MA, USA

Introduction: Motor and respiratory decline in amyotrophic lateral sclerosis (ALS) is well documented, but information on medical comorbidities is limited. This study estimated the prevalence of comorbidities among ALS patients within a large U.S. health insurance claims database.

Methods: Subjects (n=1845) with ≥2 ALS medical claims (ICD-9 code 335.20) between 2004 and 2011 were identified, then age- and gender-matched to controls without a claim for any motor neuron diseases (n=3690). Comorbidity categories were defined using the Agency for Healthcare Research and Quality’s Clinical Classification System. Prevalent comorbidity was defined as ≥1 medical claim with an ICD-9 code within a particular category, unrelated to ALS sequelae. 12-month prevalence and odds ratios (OR) were calculated.

Results: The five most prevalent comorbidity categories were “hypertension” (41.4%, OR=1.4), “disease of the heart” (36.0%, OR=1.7), “disorders of lipid metabolism” (28.2%, OR=0.8), “diseases of arteries; arterioles; and capillaries” (19.0%, OR=2.1), and “mood disorders” (17.2%, OR=3.1). The five comorbidity categories with the greatest increased odds relative to controls were “immunity disorders” (3.9%, OR=16.4), “systemic lupus erythematosus and connective tissue disorders” (2.6%, OR=6.1), “other infection; including parasitic” (5.1%, OR=5.8), “delirium, dementia, amnestic, and other cognitive disorders” (7.4%, OR=5.5), and “epilepsy; convulsions” (3.4%, OR=4.4). All ORs were statistically significant, p<0.05. Additional comorbidity categories with the highest prevalence and greatest increased odds will be presented.

Conclusions: Cardiac diseases were the most prevalent comorbidities, while immune-related disorders, cognitive impairment, and seizures were more increased compared to controls. Understanding the full comorbidity profile in ALS will aid in therapeutic decision making for patients with ALS.
P1489

Ocular motor apraxia: an uncommon early sign in amyotrophic lateral sclerosis

C. Morelli1, N. Ticcozzi1, A. Doretti1,², A. Lafronza1, F. Verde1, D. Sangalli1, B. Poletti1, A. Ciammola1, S. Messina1, V. Silani1,²
1Department of Neurology, IRCCS Istituto Auxologico Italiano, 2Department of Neurosciences, University of Milan Medical School, Milano, Italy

Introduction: Acquired ocular motor apraxia (AOMA) is characterized by loss of voluntary control of saccades and smooth pursuit. To our knowledge, this is the first report of two patients with amyotrophic lateral sclerosis (ALS), also developing AOMA.

Methods: Patient 1 developed an atypical parkinsonism at age 62, followed three years later by slowly progressive ALS and fronto-temporal dementia (FTD). Progressive fixation of gaze, ocular and eyelid apraxia appeared at age 67. Patient 2 started complaining of cramps and fasciculations in the lower limbs at age 77, and was diagnosed with classic ALS. Six months later he developed ocular and eyelid apraxia, and, subsequently, FTD. The patient developed akinetic mutism and died nine months after onset. In both cases, neuropsychological assessment suggested a frontal and parietal dysfunction. Neuroradiological tests showed bilateral cortical atrophy of the frontal and parietal lobes. Genetic screening was negative.

Results: The patients were diagnosed as having ALS-plus syndromes (corticobasal degeneration in case 1, and FTD in case 2). Both patients showed a prominent involvement of fronto-parietal areas, compatible with AOMA.

Conclusion: An unrecognized bilateral involvement of frontal and parietal lobes may underlie the impairment of ocular movements observed in some ALS patients. Early detection of AOMA may predict an incoming dementia, thus assuming a negative prognostic significance.

P1490

Over-representation of the L144F SOD1 mutation in Serbian ALS patients due to founder effect

D. Keckarevic1, Z. Stevic2, M. Keckarevic-Markovic1, M. Kecmanovic1, S. Romac1
1Faculty of Biology, University of Belgrade, 2Clinic of Neurology, School of Medicine, University of Belgrade, Serbia

Objectives: Approximately 5-10% of ALS cases are familial (FALS), and the remaining ones are sporadic or apparently sporadic (SALS). So far, more than 300 different mutations have been identified in at least six major genes of which mutations in the gene encoding Cu/Zn superoxide dismutase (SOD1) are most numerous. Founder effect was reported for A4V, G41S, I113T, and R115G SOD1 mutations. Here we present results of the haplotype analysis in a group of Serbian ALS cases harbouring L144F mutation confirming the existence of a founder effect.

Methods: Genomic DNA was isolated from blood samples taken from 191 unrelated ALS patients. Coding sequence of SOD1 gene was analyzed by direct sequencing, followed by haplotype analysis of 8 surrounding STR loci.

Results: Sequencing analysis revealed presence of mutations in 37 ALS cases (26/37 FALS and 11/154 SALS). Mutation L144F was detected in 22 FALS and 4 SALS cases. Haplotype analysis showed that all L144F chromosomes could have common origin.

Conclusion: Results of the sequencing analysis confirmed that SOD1 mutations are the most frequent cause in Serbian ALS patients. Haplotype analysis suggests that over-representation of L144F mutation could be explained by actual Balkanian origin of L144F mutation and founder effect.
P1491

VEGF evaluation in amyotrophic lateral sclerosis: interplay with respiratory function and exercise

S. Pinto1, R. Carrilho2, A. Pinto1, J. Costa2, M. de Carvalho1
1Institute of Molecular Medicine and Faculty of Medicine, University of Lisbon, 2Instituto de Tecnologia Química e Biológica, Lisbon, Portugal

Objectives: The role of vascular endothelial growth factor (VEGF) in the pathogenesis of ALS is a critical point. We have addressed this issue by evaluating VEGF expression in a large population of patients.

Methods: We measured VEGF plasma level in 83 ALS patients, 20 controls and 10 patients with other neuromuscular diseases matched for age. ALS patients were divided into 4 groups: patients with severe respiratory insufficiency undergoing non-invasive ventilation (NIV) (G1); patients chronically on NIV (G2); patients submitted to exercise (G3); and ALS patients with absent respiratory impairment.

Results: 30 ALS patients were included in G1, 14 in G2, 12 in G3 and 27 in G4. VEGF levels were similar in controls and in all ALS groups analysed. There was no correlation between VEGF level and gender, onset type, age, disease duration, ALS-FRS-R and respiratory function measurements, except for G2 in which VEGF was negatively correlated to forced vital capacity (p=0.025). VEGF level increased significantly in G2 after NIV (p=0.01) and in G3 after exercise (p=0.02) but remained stable in the rest of patients.

Discussion: VEGF is modulated in ALS by 2 relevant interventions, NIV in patients with severe respiratory impairment and following exercise. This observation suggests that both NIV and exercise can drive neuroprotective mechanisms in ALS.

P1492

Amyotrophic lateral sclerosis (ALS) in Iran: focusing on functional disability and quality of life trends

S. Nafissi1, H. Shamshiri1, E. Mir2, B. Pourmirza2, M. Etemadifar3, R. Abolfazli1, K. Basiri1, K. Gharagozli4, B. Zamani1, H. Ayromlou5, M.H. Harirchian1, on behalf of Iran ALS Study Group
1Tehran University of Medical Sciences, 2Sanofi-Medical Department, Tehran, 3Isfahan University of Medical Sciences, Isfahan, 4Shahid Beheshti University of Medical Sciences, Tehran, 5Tabriz University of Medical Sciences, Tabriz, Iran

Introduction: Many studies from different parts of the world have reported disease course, disability and quality of life of ALS patients. Very few studies on this devastating disease have been conducted in the Middle East. The main goal of this study was to evaluate ALS progression, disability and quality of life in a multicenter, prospective study in Iran.

Methods: 358 ALS cases were registered from 24 neurology centres all around the country. Demographic data, Manual Muscle Test scoring (0-130), ALS Functional Rating Scale, ALSAQ-40, ALS health scoring system, Rilutek consumption, disease onset, presence of positive family history and consanguinity were recorded. Follow-up visits were performed after 6 and 12 months.

Results: Patients were 17 - 89 years old (mean=54.96), 62% were male. 22.9% of patients had bulbar onset ALS (19.4% of males and 28.7% of females). 65.6% of patients used Rilutek continuously. During 12 months follow-up, 14.8% of patients died because of ALS complication (4.2% in mild, 8.6% in moderate, 23.2 in severe and 41.7 in terminal stages). This rate was 14.1% in limb onset and 17.1% in bulbar onset groups. Death rate in the Rilutek group was 13.6 vs. 17.1 in other patients. Overall, for 0-6 and 6-12 months periods, mean score decrements for MMT score was 13.94 and 10.93, ALSFRS-R 4.77 and 3.66, ALSAQ score 13.85 and 14.61, respectively. Also the scores were analyzed and compared in all aforementioned groups and subgroups.
Novel crystalloid oligodendro-gliopathy in complex hereditary spastic paraplegia

A. Wöhrer¹, L. Laszlo¹, J. Finsterer², C. Stöllberger¹, J. Furtner¹, W. Rinner¹, K. Molnar¹, H. Budka¹, G. Kovacs⁴

¹Medical University of Vienna, ²Danube University Krems, ³KAR, ⁴Clinical Institute of Neurology, Vienna, Austria

Objectives: Hereditary spastic paraplegia (HSP), comprises a group of so far 48 clinically and genetically heterogeneous disorders associated with either isolated spastic paraparesis (pure HSP) or with additional neurological or non-neurological manifestations (complicated HSP).

Methods and results: Here we present a case of an adult-onset, apparently autosomal dominant complicated form of HSP. Onset of clinical symptoms was at the age of 40 years and characterised by slowly progressive corticospinal tract dysfunction, dysarthria, disorientation, extrapyramidal symptoms, and bilateral ptosis. Cranial MRI revealed hyperintensities on T2-weighted sequences mostly in the posterior limb of the internal capsule. The proband deceased at the age of 64 years. As morphological substrate for the slowly progressive clinical symptoms, comprehensive neuropathological and ultrastructural evaluation revealed a novel oligodendrogliopathy with distinctive, partly ubiquitinated and p62 positive fibrillar inclusions evolving into crystalloid deposits, containing elements of the oligodendroglial cytoskeleton (α- and β-tubulin, TPPP/p25). In the central nervous system accumulation of crystalloid structures has been related to histiocytes but not to glial cells.

Conclusions: This study has implications for the understanding on how the human central nervous system reacts to protracted dysfunction and disruption of the oligodendroglial cytoskeleton, including development of crystalloid structures, which have not yet been reported in neurodegenerative disease such as HSP.

Methyl esterification of erythrocyte membrane proteins in response to oxidative stress in amyotrophic lateral sclerosis: a case-control study

L. Daniele
Department of Neurological Sciences, Second University of Naples, Italy

Objectives: Amyotrophic lateral sclerosis is a degenerative disorder of upper and lower motor neurons. Aim of study was to evaluate levels of methylation in erythrocyte membrane proteins of ALS patients as possible marker of oxidative stress

Materials and methods: Blood samples of 17 ALS patients (10 men, 7 women, 57±23 years) and 13 healthy age sex matched controls were processed to assess methylation of intact erythrocytes membrane proteins as index of abnormal levels of L-isoaspartyl residues and intracellular concentrations of methyl donor S-adenosylmethionine and AdoMet demethylated product S-adenosylhomocysteine via high performance liquid chromatography.

Results: Methyl accepting capability in erythrocyte membrane proteins of ALS patients was lower than in controls and abnormal L-isoaspartyl residues were significantly higher in ALS patients (p<0.05). AdoMet concentration was about 50% lower in ALS patients while AdoHcy levels were equivalent measuring a lower AdoMet/AdoHcy ratio in ALS patients (p<0.05).

Discussion and conclusions: Methyl transfer reactions mediated by AdoMet are involved in oxidative damage repair. Increased formation of L-isoaspartyl residues is one of the major structural alterations occurring in erythrocyte membrane proteins. Abnormal residues are converted into normal L-aspartyl residues by methyltransferase (PIMT). PIMT is ubiquitous and its repair function is crucial in erythrocytes. Our results suggest the presence of injured action of PIMT in ALS patients' erythrocytes with accumulation of L-isoaspartyl residues responsible for abnormal protein conformation. We hypothesize injured mechanisms of DNA methylation dependent on AdoMet/AdoHcy ratio with deregulated gene expression. DNA hypomethylation damage epigenetic control of long-term silencing genes expression with involvement in ALS.
**P1495**

**Intravenous immunoglobulin for post-polio syndrome: a randomized, double-blind, placebo-controlled study**

M. Turri¹, L. Bertolasi¹, E. Frasson², M. Acler¹, M. Ferlisi¹, F. Pimazzoni¹, A. Gajofatto¹, G. Didonè², M. Bordignon³, S. Vicentini³, E. Dall’Ora¹, F. Brigo¹, A. Fiaschi¹, M. Martini⁴, B. Danzi², S. Monaco¹

¹Clinical Neurology, University of Verona, ²Neurology, ³Management Control, Cittadella Hospital, Padova, ⁴Rehabilitation Medicine, Malcesine, Italy

**Objective:** Post-polio syndrome refers to an increase of disabilities experienced by many polio survivors decades after acute infection expressed by a clinical worsening or appearance of new symptoms. Pro-inflammatory cytokines production within the CNS indicates an underlying inflammatory process. The aim of this paper is to describe the effects of intravenous immunoglobulin in post-polio syndrome.

**Design:** Single-center randomized, double-blind, placebo-controlled study of efficacy of intravenous immunoglobulin in post-polio syndrome.

**Subjects:** 50 patients were randomly assigned to receive infusion of either intravenous immunoglobulin or placebo.

**Methods:** Primary endpoint was to demonstrate the efficacy of immunoglobulin in improving quality of life measured with short-form-36 (SF-36) questionnaire increasing physical component score (PCS). Secondary endpoints were improvement of physical performance, pain, fatigue and muscle strength. Patients were tested before the first infusion and two and four months thereafter.

**Results:** SF-36 physical component score did not significantly improve in patients who received immunoglobulin, but we obtained a statistically significant improvement in SF-36 mental component score (MCS) (p=0.015) and the subscale scores for physical and emotional roles (p=0.05, p=0.023) two months after treatment. No difference was found in physical performance, pain, fatigue and muscle strength between the two groups. None of the outcome variables tested four months after treatment differed significantly between the groups.

**Conclusions:** Single treatment of intravenous immunoglobulin improves MCS and physical and emotional role subscales, but does not improve SF-36 PCS. Further studies are needed to identify responding subgroups and to test the effects of immunoglobulin after repeated treatments.

**P1496**

**Increased neurotrophin-3 of the skin of patients with amyotrophic lateral sclerosis**


Neurology, Teikyo University Chiba Medical Center, Ichihara, Japan

**Objectives:** Recently, it was found that immunoreactivities of ciliary neurotrophic factor (CNTF), leukaemia inhibitory factor (LIF) and insulin-like growth factor-I (IGF-I) were markedly increased in the skin of patients with amyotrophic lateral sclerosis (ALS) compared with controls. These observations serve to emphasize the potential importance of neurotrophic factors in ALS. Neurotrophin-3 (NT-3) also belongs to the neurotrophic factors and is known to promote motoneuron survival. However, little is known concerning NT-3 of skin in ALS patients.

**Methods:** We examined NT-3 immunoreactivity of biopsy specimens of skin overlying the left biceps from 13 ALS patients and 13 control subjects with other neurologic disorders. A densitometric analysis was performed using an image analysis program.

**Results:** The optical density for NT-3 immunoreactivity of the epidermis in ALS patients (mean±SD, 1.07±0.38) was significantly higher (p<0.01) than in control subjects (0.52±0.22). The optical density of the reticular dermis in ALS patients (mean±SD, 0.71±0.36) was also significantly higher (p<0.001) than in controls (0.23±0.31). The above densities of NT-3 immunoreactivity in ALS patients showed a progressive increase in relation to duration of illness. This positive correlation was highly significant (r=0.89, p<0.001 and r=0.73, p<0.001, respectively) in the epidermis and in the reticular dermis.

**Conclusion:** These data suggest that NT-3 may have a trophic role in skin of ALS patients and may help to explain why decubitus formation is rare in ALS.
P1497
Impaired cytoplasmic-nuclear transport (intranuclear changes and nuclear envelope alterations) occurs at the early pre-symptomatic stage of amyotrophic lateral sclerosis

Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

The present study aimed to examine the temporal relationship of immunohistochemical changes in the anterior horn cells (AHCs) from mutant superoxide dismutase 1 (mSOD1) transgenic mice related to impaired cytoplasmic-nuclear transport as a potential pathomechanism of amyotrophic lateral sclerosis (ALS) and to examine whether these changes occur in animal and human specimens. We performed immunohistochemical analyses for six autopsied patients with ALS, 6 non-neurologic disease controls, 18 mSOD1 transgenic mice, and 18 non-transgenic mice. Compared to non-transgenic mice aged 8 weeks, consequently, mSOD1 transgenic mice aged 12, 16, and 18 weeks exhibited the following: 1) chronological significant decreases in the immunostaining intensity of a nucleoporin Nup62 in the AHC nuclear envelope; 2) chronological significant increases in morphological irregularities of the AHC nuclear envelope immunostained with Nup62; and 3) chronological significant decreases in the immunostaining intensity of karyopherin b1 in the AHC nucleus. mSOD1 transgenic mice showed significant decreases in the immunostaining intensity of vascular endothelial growth factor (VEGF) and increases in hypoxia-inducible factor 1a (HIF-a) in the AHC nucleus. Our study indicated that impaired cytoplasmic-nuclear transport (intranuclear changes and nuclear envelope alterations) occurred at the early presymptomatic stage (8 weeks after birth) in the mSOD1 mice, with nuclear envelope alterations (decreased immunostaining intensity and increased morphological irregularities) presumably preceding intracytoplasmic changes. These data indicate the correlation of immunohistochemical changes in the AHCs from ALS model animals and ALS patients. Further study will be required to specify the cell compartment where the changes occur first.

P1498
Evaluation of autonomic dysfunction in patients with amyotrophic lateral sclerosis using the heart rate variability (HRV)

Neurology, Hanyang University, Seoul, Republic of Korea

Background and aims: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive loss of motor neurons, however it is increasingly recognized that non-motor manifestations may occur, including autonomic nervous system dysfunction. Therefore, our first objective in these studies was to evaluate autonomic dysfunction in patients with ALS. Second objective was to define associated clinical characteristics and heart rate variability (HRV)

Methods: 86 patients with sporadic ALS were compared to 213 healthy controls. HRV and clinical characteristics (duration of the disease, site of onset, ALS functional rating scale-revised (ALSFRS-R) was collected. 40 of 86 patients were examined twice within a month to evaluate reliability of HRV.

Results: A decrease in HRV was found in the ALS patients, indicating dysfunction of autonomic cardiac control (p<0.0001). ALSFRS-R was positively associated with HRV (p<0.05). There were no differences of HRV parameters between first and second exam of HRV.

Conclusions: These results suggest that cardiac autonomic dysfunction in patients with ALS has sympathetic-activated balanced with decreasing both sympathetic and parasympathetic components. HRV is related to disability of the disease.
**P1499**

Targeting GPNMB-mediated neuronal protection as a novel therapeutic strategy for amyotrophic lateral sclerosis


Molecular Pharmacology, Department of Biofunctional Evaluation, Gifu Pharmaceutical University, Gifu, Japan

**Introduction:** Amyotrophic lateral sclerosis (ALS) is an incurable and fatal neurodegenerative disease characterized by the loss of motor neurons. Despite substantial research, the causes of ALS remain unclear. Understanding these causes may be critical for the development of effective therapies. The purpose of this study was to identify a novel target factor involved in ALS.

**Methods:** Glycoprotein non-metastatic melanoma protein B (GPNMB) was identified as an ALS-related factor using DNA microarray analysis with mutant superoxide dismutase (SOD1G93A) mice. The crucial roles of GPNMB were demonstrated through in vitro and in vivo biochemical and morphological methods, including clinical tissue sample studies.

**Results:** GPNMB was greatly induced in the spinal cords of ALS patients and a mouse model as the disease progressed. It was especially expressed in motor neurons and astrocytes. In an NSC34 motor neuron cell line, glycosylation of GPNMB was inhibited by interaction with SOD1G93A, increasing motor neuron vulnerability, whereas extracellular fragments of GPNMB secreted from activated astrocytes attenuated the neurotoxicity of SOD1G93A in neural cells. Furthermore, GPNMB expression was substantial in the sera of sporadic ALS patients compared to that of other diseased patients.

**Conclusion:** This study suggests that GPNMB can be a novel target for therapeutic intervention for suppressing motor neuron degeneration in ALS.

**P1500**

Review of the compliance with the Awaji-Shima criteria for the diagnosis of MND in a clinical setting

R. Sans¹, E. Villamil²

¹Clinical Neurophysiology, Betsi Cadwaladr University Health Board, Rhyl, UK, ²Clinical Neurophysiology, Somnia, Malaga, Spain

**Introduction:** After the change in diagnostic criteria for MND there has been an enhanced role of EMG in the diagnosis of the condition.

**Objective:** This is an audit study to assess the compliance with recommended guidelines in a General DGH.

**Patients and methods:** All patients referred to our department to specifically exclude MND were included, in a period of 12 months (July 2010 to July 2011). The EMG studies were revised in order to determine the amount of muscle studies by EMG, its locations and the findings in each muscle. NCS were also reviewed to exclude other causes of symptoms.

**Results:** 37.5% of patients referred had definitive or probable MND according to Iwaji-Shima criteria; 37.5% had polyneuropathies and 18.75% had normal results. Other findings were present in 6.25% of cases. Mean number of muscles sampled was 5, in 2 or 3 territories.

**Conclusions:** Most patients had no need for extensive EMG sampling as the changes were diagnostic enough. However, some patients might have benefited of more extensive bulbar and thoracic regions EMG sampling.
P1501

Perception of ALS patients, carers and doctors regarding clinical management


1Neurology, University Hospital La Paz, Madrid, 2Neurology, Hospital Carlos III, 3Neurology, Hospital Gregorio Marañón, 4Neurology, Hospital 12 de Octubre, 5Neurology, University Hospital San Carlos, 6Advance Directives Register, Regional Health Service, Madrid, Spain

Non-invasive positive pressure ventilation (NIPPV) increases survival and improves patient’s quality of life. Invasive mechanical ventilation (IMV) can prolong survival in ALS. Percutaneous endoscopic gastrostomy (PEG) improves nutrition but also no improvement in QOL is known. The use of these procedures has often been controversial.

Objective: To evaluate the point of view of ALS patients, carers and physicians about the use of NIPPV, IMV, PEG.

Methods: 30 ALS patients, 30 caregivers and 30 physicians from four different hospitals were examined with a cross-sectional survey. The survey consists of three groups of questions related to accepting or refusing the procedures in different levels.

Results: Patients: mean age: 56.5; 76% males; mean ALSFRS 31.6; duration of disease 568.6 days (sd 354.4); FVC 72.6. 90% of ALS patients have a carer. All doctors agree to use NIPPV in all patients and situations and 96% of them to use the PEG for nutrition. With respect to NIPPV 50% of patients agree with the opinion of physicians and caregivers and 26.6% regarding PEG. IMV was the most controversial procedure; only 20% of patients accepted IMV, like the caregivers and doctors. Physicians showed very different opinions: from acceptance to rejection of IMV.

Conclusion: Our findings demonstrate that the perception of the patients, caregivers and doctors in relation to PEG, IMV and NIPPV is very different. This study identified some issues to take into account in order to better meet their needs. Decisions should be taken by all together.

P1502

The association between VEGF-2578C/A polymorphism and amyotrophic lateral sclerosis in a Russian population

E.V. Lysogorskaia, N.Y. Abramycheva, M.N. Zakharova, S.N. Illarioshkin

Research Center of Neurology Russia Academy of Medical Science, Moscow, Russia

Introduction: Amyotrophic lateral sclerosis is a devastating neurodegenerative disorder with an important genetic contribution. Studies of association of ALS with the 2578C/A, 1154G/A and 634G/C polymorphisms in the vascular endothelial growth factor (VEGF) gene yielded contradictory results. We investigated the VEGF 2578C/A polymorphism in a Russian cohort of patients with ALS.

Methods: An ALS group comprised 192 patients (103/192 males and 89/192 females) aged from 20 to 83 years (52 ±13.4); and a control group comprised 128 age- and sex-matched persons. All studied individuals were Slavs. TaqMan PCR was used for the VEGF 2578C/A detection.

Results: The significant difference of the allele distribution was observed between ALS cases and controls (χ2=11.1; p=0.004). The 2578A/A genotype increased the disease risk to an adjusted odd of 1.66 (95% CI 1.03-2.29). Males carrying 2578A/A had more increased risk of ALS (OR=2.18; 95% CI 1.90-2.47). We found significant association of the 2578A/A genotype with earlier disease onset (OR=1.3; 95% CI 1.21-1.40) and rapid progression (OR=1.7; 95% CI 1.27-2.13).

Conclusions: Our data show that VEGF 2578C/A genotype can modulate the risk of ALS in a Russian population.
P1503

**X-linked bulbar and spinal muscular atrophy; experiences from a single center**

J.K. Kim¹, D.H. Kim¹, S.H. Choi²

¹Dong-A University Hospital, ²Wallace Memorial Baptist Hospital, Busan, Republic of Korea

**Background and objectives:** Bulbar and spinal muscular atrophy (BSMA, Kennedy disease) is an X-linked degenerative disease of the motor neuron caused by an expansion of CAG repeat within the androgen receptor gene. We tried to characterize the presenting manifestation for early and easy clinical diagnosis of BSMA.

**Methods:** 9 clinically compatible BSMA patients were included. All patients were from a single center during the period 2010 to 2011. Initial clinical manifestations, neurological examinations and laboratory findings including genetic study were investigated.

**Results:** Mean age was 47.9 years and mean duration from symptom onset to diagnosis was 45.9 months. From the neurological manifestations, the most frequent and consistent finding was perioral tremor (100%) typically provoked by movements such as talking and postural hands tremor (100%). Gynecomastia was observed in 5 patients (62.5%) and only half of cases had bulbar symptom and sign. Fasciculations and hypo/a-reflexia were found only in 4 patients (50%). All patients showed the pattern of chronic motor dominant polyneuropathy with axonal involvement in NCSs and needle electromyography. Decremental responses in Jolly test were found in all cases from 6 patients studied. This means abnormal neuromuscular transmission is not a rare manifestation of BSMA during a certain stage of this disease.

**Conclusion and discussion:** Perioral tremor is the most frequent and consistent finding in BSMA and it showed a typical action induced pattern. This supports us making clinical diagnosis of BSMA easier. The pattern and distribution of motor weakness in tongue and limb muscle are variable.

P1504

**IVIg treatment in post-polio patients; quality of life before and after 6 months - results from an open clinical study**

G. Östlund, L. Broman, L. Werhagen, K. Borg

Division of Rehabilitation Medicine Department of Clinical Sciences Karolinska Institutet Danderyd Hospital, Stockholm, Sweden

**Introduction:** Vitality (Gonzalez et al 2006) and pain (Farbu et al 2007) were significantly improved in post-polio (PPS) patients after IVIg treatment. Characteristics of responders and non-responders have not been pinpointed.

**Aims:** To evaluate quality of life after IVIg treatment in PPS patients before and after 6 months and to identify parameters influencing the outcome.

**Methods:** Open trial, prospective follow-up study. 113 PPS patients from a Swedish PPS outpatient-clinic who had received one IVIg treatment were included. Quality of life, pain and physical activity were measured by Short form 36 (SF-36), Visual Analogue Scale (VAS) and Physical Activity Scale for the Elderly (PASE) and were answered before treatment and after 6-month. Clinical examination of medical records was performed before IVIg treatment. Descriptive statistics were done for all variables before treatment. To compare SF-36, VAS-pain and PASE before treatment and at 6-month follow-up, Wilcoxon non-parametric tests were performed.

**Results:** SF-36: Bodily pain (BP) (p=0.002), and Vitality (VT) (p=0.008) were significantly increased after 6 month. Increased BP and VT scores were seen in those under 65 years of age and in those with paresis only in lower extremities. Increasing BP, was seen in those who were working, increasing VT was seen in patients with pain.

**Conclusions:** SF-36: Bodily pain and vitality were improved 6 months after IVIG treatment. Age below 65 years and pain before treatment may be indicators for future identification of responders.
P1505
The involvement of GPNMB in neuronal cell death by endoplasmic reticulum stress

Molecular Pharmacology, Department of Biofunctional Evaluation, Gifu Pharmaceutical University, Gifu, Japan

Introduction: Glycoprotein transmembrane non-metastatic melanoma B (GPNMB) is a single transmembrane protein. GPNMB is involved in the pathogenesis of several cancers and glaucoma. However, the involvement of GPNMB in the central nervous system is unclear. Recently, it has been reported that GPNMB is localized in the rough endoplasmic reticulum (ER), suggesting that GPNMB has several roles in ER. The purpose of this study was to investigate the effects of GPNMB against ER stress-induced neuronal cell death.

Methods: We used mouse motor neuron (NSC34) cells and evaluated the roles of GPNMB against ER stress by GPNMB knockdown using siRNA and treating with recombinant extracellular fragments of GPNMB. Furthermore, we investigated the protein and mRNA expressions of glucose-regulated protein 78 (GRP78/BiP) and C/EBP homologous protein (CHOP), ER stress-related factors.

Results: The protein expression of GPNMB was increased by thapsigargin-induced ER stress as well as the protein and mRNA expressions of BiP and CHOP. GPNMB knockdown significantly increased the ER stress-induced neuronal cell death, and suppressed the induction of BiP protein and mRNA, but not CHOP. Moreover, the recombinant GPNMB had protective effects against ER stress-induced neuronal cell death with no effects on BiP expression.

Conclusion: These results suggest that intracellular GPNMB may regulate the transcription of BiP and have protective effects against thapsigargin-induced ER stress.

P1506
Compound heterozygosity with two mutations in the HEXB gene produces adult Sandhoff disease presenting as a motor neuron disease

S.-Y. Kang
Neurology, School of Medicine, Jeju National University, Jeju, Republic of Korea

Introduction: Sandhoff disease is a rare autosomal recessive metabolic disorder of GM2 gangliosides. It is caused by a lack of functional N-acetyl-β-D-glucosaminidase A and B due to mutations in the HEXB gene. Little information is available on molecular defects involved in adult Sandhoff disease presenting as motor neuron disease phenotype.

Case report: We describe a 55-year-old woman with adult Sandhoff disease presenting as motor neuron disease. The assay of total hexosaminidase involving A and B showed decreased level of these activities. Analysis of HEXB gene demonstrated two point mutations. The two mutations were located at the exon 5 (c.619A>G) and exon 11 (c.1250C>T).

Conclusion: Compound heterozygosity of these two mutations may trigger the development of adult Sandhoff disease with a motor neuron disease phenotype. In patients with motor neuron disease in the setting of a possibly recessive disorder, Sandhoff disease should be suspected, even when the onset age is over 50 years.
P1507

Functional gait and pulmonary function in patients with amyotrophic lateral sclerosis: a direct relationship

B. Heredia Camacho¹, M. Castillo¹, A. Hochsprung¹, G. Izquierdo Ayuso²
¹Biofunctional Neuropyisotherapy, ²Neurology, University Hospital Virgen Macarena, Sevilla, Spain

Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease marked by progressive loss of motor neurons, muscle wasting and respiratory dysfunction. Hypothesis: one of the factors influencing the progressive loss of functional gait is respiratory dysfunction.

Methods: Participants: 11 patients with suspected or definitive diagnosis of ALS, with a functional gait, included in a Physical Therapy programme of once-a-week assistance. Informed consent was obtained from each subject. Five consecutive measures of VC and FEV1 were obtained from spirometry. Walking was documented using an 8-meters GaitRite electronic walkway, and a Functional Ambulance Profile (FAP) was obtained. Each measure was observed and a graphic was made in order to compare each parameter (FEV1, VC and FAP). A 2-way ANOVA and a Bonferroni post-test were made.

Results: 6 patients obtained a negative progression in FAP. Of them, 5 registered a lower FEV1 and 3 subjects, a lower VC. 2 of them, obtained the same measure in VC. At the same time, from 3 patients with a better FAP score, 2 obtained a better VC and also a higher FEV1. Both measures have a significant interaction (p<0.0001).

Conclusions: FAP score is positively correlated with CV and FEV1 measures. Furthermore, these functional respiratory measures demonstrate a good correlation with the functional evolution in patients with ALS. In addition, a specific respiratory program must be included in a Biofunctional Neurophysiotherapy program. Because of the small number of patients included, more studies are necessaries.

P1508

A case report of a patient with ALS and an obsessive-compulsive disorder carrying expansion of C9ORF72

C. Moglia, A. Calvo, A. Canosa, E. Bersano, A. Ilardi, G. Restagno, A. Chio
Neuroscience, University of Torino, Italy

It has been recently reported that a large proportion of patients with familial ALS and frontotemporal dementia are associated with a hexanucleotide repeat expansion in the first intron of c9orf72. We describe a patient with a diagnosis of ALS-FTD with psychiatric onset. At the age of 50 hour patient developed a depressive disorder. Some months later, muscle weakness at the right hand occurred, followed by worsening of the mood disorder. The collection of familial history revealed that the patient's father died after a 5-year history of ALS. Neither cognitive nor behavioural impairment were reported. Genetic analysis revealed a hexanucleotide expansion in the first intron of the c9orf72 gene. MRI documented a marked hyperintensity along the corticospinal tract; MRI fibre-tracking revealed bilateral reduction of fractional anisotropy along the corticospinal tract. Brain PET-CT presented reduced uptake of the radioactive tracer in the motor cortex bilaterally, in the fronto-mesial cortex bilaterally, between the anterior and the middle cingulate gyrus and in the postero-lateral occipital cortex bilaterally. The clinical and neuropsychological assessment was consistent with a diagnosis of FTD, associated to OCD, hallucinations and depressive mood disorder. Later the patient developed dysarthria, dysphagia, lower limbs weakness and hypotrophy and worsening of spasticity at upper and lower limbs. 14 months after the onset of the motor neuron disease, he is still alive, wheelchair-bound.

The association of ALS, FTD, depression, psychotic manifestations and OCD could set up a distinctive phenotype related to c9orf72 gene expansion. Nevertheless, this hypothesis needs to be confirmed by further observations.
P1509
Effects of neurotrophic factors on oxidative and nitrosative stress in amyotrophic lateral sclerosis G93A murine model
I. Kochergin1,2, L. Brylev1,2, M. Onufriev2, I. Barskov1, M. Zakharova1, I. Zavalishin1, N. Gulyaeva2
1Research Center of Neurology RAMS, 2Institute of Higher Nervous Activity and Neurophysiology, RAS, Moscow, Russia

P1510
Amyotrophic lateral sclerosis as a paraneoplastic syndrome
A. Riahi, M. Messelmani, H. Khaled, M. Mansour, J. Zaaouali, R. Mrissa
Neurology, Military Hospital, Tunis, Tunisia

P1511
Neurodegenerative overlap syndrome: a case report
M. Minar, P. Valkovic
Second Department of Neurology, Comenius University, Bratislava, Slovak Republic

P1512
Vestibular evoked myogenic potentials in amyotrophic lateral sclerosis
N. Tarasevich, S. Likhachev, U. Lukashevich, Y. Rushkevich
Republican Research and Practical Centre of Neurology and Neurosurgery, Minsk, Belarus

P1513
Hirayama disease: a report of two cases
A. Jaoua, S. Benamor, S. Benammou
CHU Sahloul, Sousse, Tunisia

P1514
Cramp-fasciculation syndrome in the differential diagnosis of amyotrophic lateral sclerosis
J. Domínguez Bértalo1, A. Hernández González1, B. Miguel Martin1, C. Valencia Guadalajara1, A. Lopez Garcia1, G. Martin Palomeque2, A. Castro Ortiz2
1Neurology, 2Neurophysiology, Hospital General Ciudad Real, Spain

P1515
Metabolomics as a tool for studying neurodegenerative diseases
A. Wuolikainen1,2, the Erling-Persson Metabolomics Project at Umeå University
1Department of Chemistry, 2Computational Life Science Cluster (CLiC), Umeå University, Umeå, Sweden

P1516
Neurolathyrism in Ethiopia
H.D. Belay, H. Demissie
Department of Neurology, Addis Ababa University, Addis Ababa, Ethiopia

P1517
Cervical flexion myelopathy caused by a spinal intradural cyst
D. Kondziella1, L.R. Damhave1, A. Wagner2, K. Hansen1
1Department of Neurology, 2Department of Neuroradiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

P1518
The therapeutic efficacy of herbal medicine for olivopontocerebellar atrophy versus genetic spinocerebellar ataxia 6
T. Okabe
Department of Integrated Traditional Medicine, University of Tokyo, Japan

P1519
The use of sulbactam treatment in ALS patients
N. Polat1, H.A. Idrisoglu2, A. Sazci2
1Merid Company, 2Department of Neurology, Medical Faculty of Istanbul, Turkey

P1520
The controversy behind Mills’ syndrome
E. Tufanoiu, A.M. Corfu
Neurology, Fundeni Clinical Institute, Bucharest, Romania