Motor neurone diseases

EP4113

The diagnostic value of diffusion tensor MRI metrics in relation to the MND phenotype heterogeneity

F. Agosta1, E.G. Spinelli1,2, N. Riva2, M. Copetti3, S. Galantucci1, A. Chiò1, S. Messina4, S. Iannaccone6, A. Calvo1, V. Silani4, A. Falini7, G. Comi2, M. Filippi1,2,3

1Neuroimaging Research Unit, Institute of Experimental Neurology; 2Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan; 3Biostatistics Unit, IRCCS-Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG); 4Department of Neuroscience, University of Turin, Turin; 5Department of Pathophysiology and Transplantation, IRCCS Istituto Auxologico Italiano, University of Milan; 6Department of Clinical Neurosciences, 7Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: To investigate diffusion tensor (DT) MRI metrics as predictors of motor neuron diseases (MND).

Methods: Corticospinal tract (CST), corpus callosum (CC) and extra-motor tract DT MRI measures were obtained from 123 MND patients and 35 controls. C-indices were estimated using logistic regression analyses. Support vector machine (SVM) classification algorithm assessed MRI metric accuracy as predictors of MND diagnosis at individual patient level.

Results: MND patients showed CST and motor callosal damage (C-index range: 0.65–0.74). The most severe and widespread damage was found in pure upper motor neuron (UMN)/pyramidal ALS (C-index up to 0.81 for CST and 0.91 for CC). Classical, respiratory and bulbar ALS showed CST and callosal motor damage (C-index=0.70). In bulbar patients, uncinate and cingulum damage was found. No damage was found in pure lower motor neuron (LMN)-variants. In classical, respiratory and bulbar ALS, patterns of damage were confirmed in cases with disease duration <12 months. Severity and extent of white matter damage increased in the following order: pure UMN/pyramidal ALS>bulbar>classical/respiratory>pure LMN. The highest C-index (up to 0.94) was found for CC measures distinguishing pure UMN/pyramidal from pure LMN patients. SVM showed the highest diagnostic accuracy (0.93) in the comparison pure UMN/pyramidal vs. pure LMN. Disease severity and UMN involvement correlated with CST, eCC and motor callosal damage.

Conclusions: DT MRI provides sensitive objective measures of UMN and extra-motor burden at the individual level in MND patients. This study provides a roadmap for translation of MRI predictors of MND into daily practice.

Funding: #RF-2010-2313220.

Disclosure: Nothing to disclose

EP4114

Quick and non invasive sweat function assessment to evaluate small fiber neuropathy in Fabry disease

J.-H. Calvet1, B. Dussoy2, P. Sahuc3, L. Swider1, R. Froissard1, J. Pouget3, J. Franques3

1Impeto Medical, Paris; 2Nephrology, 3Neurology, 4Internal Medicine, 5Biology, La Timone, APHM, Marseille, France

Introduction: In patients with Fabry disease, small fiber dysfunction is more prominent than large fiber dysfunction and A-delta fiber function is more often impaired than C-fiber function. Sudoscan is a patented device designed to perform a quantitative evaluation of sweat gland function based on an electrochemical reaction between sweat chlorides and stainless steel electrodes in contact with the palms and soles. Several studies have demonstrated the high reproducibility and sensitivity of this objective, non-invasive and quick method. This study aimed to evaluate Sudoscan in Fabry disease.

Methods: 18 patients with Fabry disease and 18 age and sex matched controls were involved in the study. Patients were required to place their hands and feet on two large electrodes and then stand still for 2 mins. Results were expressed immediately as Electrochemical Skin Conductance (ESC, µS), the ratio between the current generated and the constant DC stimulus (lower than 4 V) applied on the electrodes.

Results: Good correlation was observed between hands and feet conductances both in controls and in Fabry disease (r=0.87, p<0.001). Hands and feet conductances were significantly lower in patients with Fabry disease compared to controls. This decrease was especially observed in patients with reported hypohidrosis (42±22 vs 74±11 µS, p=0.0014 and 48±27 vs 76±10µS, p=0.0056 respectively). No correlation was observed with renal dysfunction. No significant difference was found in sensory peroneal nerve amplitude between patients and controls.

Conclusions: Sudoscan could be used for the screening and the follow-up of patients with Fabry disease.

Disclosure: JH Calvet is Medical Director of Impeto Medical
EP4115

Evaluation of one year treatment with tafamidis in Portuguese patients with transthyretin familial amyloid polyneuropathy

T. Coelho1,2, I. Conceição3,4, M. Cardoso1,2, C. Monteiro1,5, C. Alves1, C. Rodrigues1, P. Pereira6, A.M. Silva1,5

1Familial Amyloid Polyneuropathy Clinical Unit, 2Neurophysiology Department, Hospital de Santo António, Centro Hospitalar do Porto, Porto, 3Department of Neurosciences, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, 4Translational and Clinical Physiology Unit, Instituto de Medicina Molecular, Faculty of Medicine, Lisbon, 5Neurology Department, Hospital de Santo António, Centro Hospitalar do Porto, Porto, 6Neurology Department, Hospital Garcia de Orta, Almada, Portugal

Introduction: Transthyretin (TTR) related Familial Amyloid Polyneuropathy presents as a severe sensory, motor and autonomic neuropathy. Tafamidis, an oral drug that stabilizes TTR and prevents amyloid deposition, was recently introduced in Europe to delay progression of neuropathy in ambulatory patients.

Objectives: To present Tafamidis efficacy and safety data after one-year treatment in the two Portuguese reference centers, in Porto and Lisbon.

Methods: Patients were evaluated at baseline, 6 months (M) and 12M. Adverse events and body mass index were registered. Renal, thyroid and liver functions were screened. Neuropathy Impairment Score (NIS) and the Norfolk Quality of Life (QoL) – Diabetic Neuropathy Total Score (Norfolk) were assessed, this last only at baseline and 12M. Patients were classified as responders if NIS change across 12M< 2, according to Dyck’s classification. Paired Student’s t test and ANOVA with repeated measures were used.

Results: 122 patients (67 males) completed a full 12M evaluation.

Body mass index and liver, renal and thyroid functions remained stable for 12M.

Mean NIS changed from baseline to 6M (2.45 vs. 2.51, p<0.01) and stabilized between 6M and 12M (2.51 vs. 2.54, p<0.1), showing a delay in the stabilization effect. Norfolk score improved (3.21 vs. 2.89, p<0.001) along one year.

Patients that were classified as responders (n=75, 61%) showed a significant NIS score decrease (improvement) between 6M and 12M (2.41 vs. 2.33, p<0.001).

Conclusion: Tafamidis prevented neurological deterioration and BMI and QoL decline in 61% of patients treated for one year. Stabilization effect was delayed 6M.

Disclosure: Isabel Conceição, Teresa Coelho, Ana M Silva, Cristina Alves, Cecília Monteiro and Márcio Cardoso served at the speakers bureau of Pfizer and received support from Pfizer to attend scientific meetings.

EP4116

Immunohistochemical studies of TDP-43 in skin of patients with sporadic amyotrophic lateral sclerosis

S. Ono

Neurology, Teikyo University Chiba Medical Center, Ichihara, Japan

Introduction: Several studies of skin in patients with sporadic amyotrophic lateral sclerosis (SALS) have shown unique morphological and biochemical alterations. The lack of bedsore formation even in the terminal stages in ALS patients is considered characteristic. Recently, a nuclear protein, 43-kDa TAR DNA-binding protein (TDP-43), was identified as a component of the ubiquitinated inclusions in SALS. Subsequently, TDP-43 immunohistochemistry demonstrated that SALS is a multisystem proteinopathy of TDP-43. It is unknown, however, whether TDP-43 positive structures are present in skin of SALS.

Methods: We have performed a quantitative immunoreactive study of TDP-43 in biopsied skins from the left upper arm of 18 patients with SALS and from 15 controls with other neurodegenerative diseases. Routine formalin-fixed paraffin-embedded 6 micrometer sections were immunostained according to standard techniques. A densitometric analysis was performed using an image analysis system.

Results: The proportion of TDP-43-positive cells in the epidermis in SALS patients is significantly higher (p<0.001) than in controls. There was a significant positive relationship (r=0.62, p<0.02) between the proportion and duration of illness in SALS patients. The optical density of TDP-43-positive cells in the epidermis in SALS patients is markedly stronger (p<0.001) than in controls. There was a significant positive relation (r=0.72, p<0.01) between the immunoreactivity and duration of illness in SALS patients.

Conclusions: These findings suggest that changes of TDP-43 in SALS skin are related to the disease process and that metabolic alterations of TDP-43 may take place in the skin of patients with SALS.

Disclosure: Nothing to disclose
EP4117  
iPSC-derived neural stem cells improve the phenotype of spinal muscular atrophy with respiratory distress type 1 (SMARD1)  
University of Milan, ‘Dino Ferrari’ Center, Fondazione Cà Granda, IRCCS Ospedale Maggiore Policlinico, Milano, Italy  
Introduction: Spinal Muscular Atrophy with Respiratory Distress Type 1 (SMARD1) is an infantile autosomal-recessive motor neuron disease characterized by diaphragmatic palsy and distal muscular atrophy; sensory and autonomic dysfunctions sometimes accompany the motor weakness. The disease results by mutations in the IGHMBP2 gene. We previously reported that primary neural stem cells (NSCs) can ameliorate the SMARD1 phenotype in mice even if several restrictions limit the the clinical translation of primary NSCs. The reprogramming of adult somatic cells into induced pluripotent stem cells (iPSCs) can provide an unlimited source of NSCs for therapeutic use  
Methods: We obtained iPS cell lines from human skin fibroblasts with a non-viral non integrating method based on the expression of reprogramming factors with episomal vectors. We used a protocol to differentiate iPSCs into neuronal stem cells. Hence the phenotype of these cells was analyzed by morphological, gene expression, and protein studies. Finally, iPSC-purified NSCs were transplanted by intraspinal cord injection into nmd mice, an animal model of SMARD1  
Results: NSCs from iPSCs are self-renewing and multipotent. They can differentiate in vitro into motor neurons and engraft into the spinal cord of SMARD1 animals, ameliorating their neuromuscular phenotype and significant extending transplanted nmd mice survival. iPSC-derived NSCs integrate appropriately into the anterior spinal cord, differentiate into the three neuroectodermal lineages, and exert a neuroprotective effect on endogenous motor neurons.  
Conclusions: Our data support the therapeutic potential of iPSC for the treatment of motor neuron disorders and other neurodegenerative diseases.  
Disclosure: Nothing to disclose  

EP4118  
C9orf72 hexanucleotide repeat expansion in Turkish ALS patients  
C. Iskender1, A. Gündoğdu Eken1, A. Özoğuz1, C. Akimoto2, H. Alstermark2, P.M. Andersen2, A.N. Başak1  
1Bogazici University, Molecular Biology and Genetics Department, Istanbul, Turkey, 2Umeå University Hospital, Umed, Sweden  
Introduction: The expansion of the GGGGCC hexanucleotide repeat in the non-coding region of the C9orf72 gene has been accepted as the leading cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Also several studies reported expansions in the C9orf72 gene as the cause of some neuropsychiatric disorders. Here, we aim to understand the wide clinical spectrum behind C9orf72 pathogenicity by focusing on clinical features of Turkish patients.  
Methods: In this study, we screened Turkish ALS patients for the expansion in the C9orf72 gene using repeat-primed PCR (RP-PCR), fragment analysis and Southern blotting. Our cohort consisted of 406 ALS patients, 95 of whom displayed the familial and the remaining 311 the sporadic form of the disease.  
Results: Among 95 fALS cases 13 patients, and among 311 sALS cases ten were found to be carriers of the repeat expansion. Nine patients with ambiguous results were subjected to Southern blotting to confirm the results obtained by RP-PCR.  
Conclusions: Although slightly lower than other populations screened so far, the frequencies of C9orf72 expansions in Turkish fALS and sALS cohorts are also high, being 13.7% and 3.2%, respectively. The ages of onset of the expansion carriers were variable ranging from 32 to 80 years; progression was fast in some cases. Furthermore, intrafamilial phenotypic heterogeneity was also observed in a sib pair carrying the expansion, in whom ALS with dementia vs. pure dementia was present. Altogether, our findings recapitulate the frequent occurrence and the heterogeneous clinical background of C9orf72 cases in the Turkish cohort.  
Disclosure: Nothing to disclose
**EP4119**

**RNA-based strategies leading to either an increase of SMN or modulation of disease pathways ameliorated spinal muscular atrophy phenotype**

S. Brajkovic1, G. Riboldi1, M. Ranieri1, M. Nizzardo1, C. Simone1, F. Rizzo1, M. Ruggieri1, S. Salani1, A. Dal Mas2, M. Bucchia1, E. Frattini1, G. Stuppia1, F. Magri1, N. Bresolin1, F. Pagani2, G.P. Comi1, S. Corti1
1University of Milan, Dino Ferrari Center, Fondazione Cà Granda, IRCCS Ospedale Maggiore Policlinico, Milan, 2International Centre for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy

**Introduction:** Spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disease caused by mutations of the survival motor neuron gene (SMN1) leading to infant paralysis and death. Currently, there is no effective treatment. The genetic correction of SMA induced pluripotent stem cells (iPSC) through antisense therapy is a promising strategy.

**Methods:** iPSCs were generated from human skin fibroblasts using non-viral non integrating episomal vectors. iPSCs were differentiated into motor neurons and their phenotype was analyzed by morphological, functional, gene expression, and protein analysis. RNA strategy based on antisense morpholino, shRNA and siRNA aiming at increasing SMN level or inhibiting Fas activation were tested.

**Results:** Motor neurons differentiated from SMA iPSCs displayed the disease-specific features characterized by fewer and smaller cells at late time periods in culture compared to wild-type iPSCs. After treatment with antisense morpholino or U1 shRNA leading to an increase of SMN expression, the SMA-iPSC phenotype was ameliorated. During motor neuron differentiation in SMA lines an increased Fas ligand-mediated apoptosis and caspase-8 activation were demonstrated.

**Conclusions:** SMA-iPSCs were confirmed to be a reliable in vitro disease model. In addition, strategies based on RNA modulation leading to either an increased expression of SMN or modifying disease pathways were demonstrated to be a promising therapeutic tool, which would be tested in in vivo models.

**Disclosure:** Nothing to disclose

**EP4120**

**ELP3-positive inclusions in motor neuron diseases**

Y. Fujita1, K. Okamoto2, S. Fujita3, Y. Ikeda1
1Gunma University Graduate School of Medicine, 2Geriatric Research Institute, Maebashi, 3Public Nanokaichi Hospital, Tomioka, Japan

**Introduction:** Recent studies have suggested that the allelic variants of elongator protein 3 (ELP3) are associated with amyotrophic lateral sclerosis (ALS). ELP3 is the catalytic histone acetyltransferase subunit of the elongator complex, which is a part of the RNA polymerase II complex and is involved in RNA processing. Our study was based on our hypothesis that ELP3 is involved in ALS pathogenesis.

**Methods:** We performed neuropathological studies with anti-ELP3 antibody in ALS patients. For this, we examined spinal cord sections from 10 common sporadic ALS (SALS) patients and 2 ALS patients with fused in sarcoma (FUS)-positive inclusions (FUS-ALS). These sections were immunostained with anti-ELP3, anti-TDP-43, and anti-FUS antibodies. Double-label immunofluorescence analysis was then performed on some sections by using anti-ELP3 and anti-TDP43 antibodies.

**Results:** In control cases, ELP3 immunoreactivities were primarily cytoplasmic in the anterior horn cells. ELP3-positive round and skein-like inclusions were noted in the cytoplasm of the anterior horn cells of SALS and FUS-ALS sections. ELP3-positive neuronal cytoplasmic inclusions (NCIs) were co-localized with TDP-43-positive and FUS-positive NCIs in SALS and FUS-ALS sections, respectively. However, cytoplasmic TDP-43-positive fine granules were not immunostained with ELP3 antibody. Furthermore, TDP-43-positive and FUS-positive glial inclusions (GCIs) were not immunostained with ELP3 antibody.

**Conclusions:** Our results suggest that ELP3 is a novel protein in ALS pathogenesis and that the component proteins of NCIs may be different from those of GCI in SALS and FUS-ALS.

**Disclosure:** Nothing to disclose
EP4121

Respiratory failure treated by NIV is not associated with a worst outcome during PEG insertion in ALS patients

A.-C. Héritier Barras, D. Adler, R. Iancu Ferfoglia, A. Truffert, J.-P. Janssens, CeSLA
University Hospitals Geneva, Geneva, Switzerland

Introduction: Enteral nutrition administered by percutaneous endoscopic gastrostomy (PEG) is probably effective in stabilizing body mass index in amyotrophic lateral sclerosis (ALS). Complications associated with PEG placement are increased when forced vital capacity (FVC) declines below 50% of predicted value. Non-invasive ventilation (NIV) can be administered during PEG insertion in patients with a FVC below 50%. This report aims at describing outcome after PEG insertions and comparing outcome in patients with or without NIV.

Methods: 20 ALS patients were offered a PEG between 2010 and 2013. Disease background, lung physiology, bulbar dysfunction, use of NIV, immediate complications and survival were analysed.

Results: Median age at time of PEG insertion was 68 years; 12 patients (60%) had a predominantly bulbar form. Patients (n=12, 60%) on NIV had a median FVC of 53% (IQR: 32-64%) of predicted value compared to FVC of 65% (IQR: 56-90%) for patients not on NIV (n=8) (p=0.04). Propofol sedation was used in all cases. Median length of stay in hospital after PEG was similar for both groups. No death was recorded in relation to PEG. Complication rate was similar in patients with and without NIV (table 1). Median survival post procedure was 362 days.

Conclusions: PEG can be inserted without additional peri-procedural complications in high risk ALS patients treated with NIV. Our complication rates are within the range of current published literature. Median survival after PEG was about one year and was independent of NIV use or presence of bulbar dysfunction at time of PEG insertion.

Disclosure: Nothing to disclose

EP4122

Accumulation of TDP-43 outside the central nervous system in individuals with or without amyotrophic lateral sclerosis

K. Okamoto¹, Y. Fujita², K. Makioka², M. Amari¹, M. Takatama¹
¹Department of Neurology, Geriatrics Research Institute and Hospital, ²Department of Neurology, Gunma University Graduate School of Medicine, Maebashi, Japan

Introduction: Transactive response DNA-binding protein of 43 kDa (TDP-43) has been identified as a major component of the pathological inclusions in most forms of frontotemporal lobar degeneration (FTLD) and in amyotrophic lateral sclerosis (ALS). Although TDP-43 is expressed ubiquitously in the nuclei of all cells, accumulation of TDP-43 outside the central nervous system (CNS) has not been reported, with the exception of the muscles of patients with protein-aggregate myopathies.

Methods: We examined general organs of nine patients with non-ALS, and four with sporadic ALS and one with FTLD-TDP. Paraffin sections were immunostained with antibodies against phosphorylated TDP-43 (pTDP-43), TDP-43 and ubiquitin. For enhancement, samples were autoclaved for 5 min before reaction with the antibodies, with the exception of the anti-ubiquitin antibody.

Results: Diffuse and granular accumulations of pTDP-43 and TDP-43 were observed frequently in the cytoplasm of renal tubular cells and less frequently in the cells of secretory glands, pancreas, adrenal gland, Leydig cells of testis, et al. Many TDP-43-positive cells were observed in the adrenal medulla, but these were negative for pTDP-43. However, majorities of pTDP-43-positive structures of the general organs also showed weakly positive immunoreactivities without primary antibodies after autoclave pretreatment. Immunoblotting of human kidney cytoplasmic lysate led to the detection of several bands, including a band at about 45 kDa.

Conclusions: This is the report to demonstrate the intracellular accumulations of pTDP-43 and TDP-43 outside the CNS in routine autopsied cases, however we must carefully distinguish the results from non-specific biotin reaction by other methods.

Disclosure: Nothing to disclose

EP4123

Abstract withdrawn
**EP4124**

**Magnetic resonance imaging brachial plexus alterations in ALS patients**

E.G. Spinelli\(^1,2\), S. Gerevini\(^3\), F. Agosta\(^1\), N. Riva\(^2\), E. Pagani\(^1\), G. Comi\(^2\), A. Falini\(^3\), M. Filippi\(^1,2\)

\(^1\)Neuroimaging Research Unit, Institute of Experimental Neurology; \(^2\)Department of Neurology, \(^3\)Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

**Introduction:** To investigate brachial plexus MRI abnormalities in amyotrophic lateral sclerosis (ALS).

**Methods:** Brachial plexus MRI scans were obtained from 18 ALS patients and 9 controls. Nerve roots and limb girdle muscles were evaluated for the presence of signal alterations (T2, T1 and STIR) and volume changes. Regions of interest (ROIs) of C5, C6 and C7 roots were delineated on axial, T2-weighted volumetric images. ROIs mean volume and T2 signal intensity were measured. Linear measures of adipose tissue thickness between trapezius and supraspinatus muscles were obtained from coronal T1-weighted images.

**Results:** At visual inspection, increased C5, C6 and C7 nerve root T2-signals and volumes were evident in ALS patients bilaterally. Suprascapulis, supra- and infraspinatus muscles T2 and STIR signal alterations and bilateral fat infiltration associated with muscle atrophy were found. ROI analysis showed that T2-signal intensity was higher in left C6 (p=0.05) and C7 (p=0.02) in patients compared with controls. Right C5 and bilateral C6 and C7 root volumes were higher in patients (right C5: p=0.04; right C6: p=0.006; left C6: p=0.01; right C7: p=0.003; left C7: p=0.001). Adipose tissue thickness between trapezius and supraspinatus muscles was higher in patients on the right side (p=0.024). A similar trend was observed on the left side (p=0.08).

**Conclusions:** T2-hyperintensity and increased volume of brachial plexus roots support a contribution of neuroinflammation to lower motor neuron and axonal degeneration in ALS. Denervation may explain muscle signal alterations. Increased adipose tissue between trapezius and supraspinatus muscles may represent an indirect marker of muscle atrophy.

**Disclosure:** FA funding for travel from Teva and speaker honoraria from Bayer, Biogen, Sanofi Aventis, SSIF. CG received compensation for consulting and/or speaking from Novartis, Teva, Sanofi, Genzyme, Merck Serono, Biogen, Bayer, Actelion, SSIF. MF received compensation for consulting and/or speaking from Bayer, Biogen Idec, Merck Serono, and Teva.

---

**EP4125**

**What is the difference between brachial amyotrophic diplegia and upper limb onset ALS? Clinical and neurophysiological manifestations**

B.-N. Yoon\(^1\), J.-J. Sung\(^2\), G.-W. Lee\(^2\), C.-K. Ha\(^1\), S.-H. Choi\(^1\)

\(^1\)Inha University Hospital, Incheon, \(^2\)Seoul National University College of Medicine, Seoul, Korea, Republic of

**Introduction:** When we encounter a patient who remains largely restricted to the upper limbs overt time, we should be concerned that the possible diagnosis is brachial amyotrophic diplegia (BAD) or upper limb onset ALS (U-ALS).

**Methods:** We reviewed the records of 385 patients who had a diagnosis as “motor neuron disease” or “amyotrophic lateral sclerosis” between 2006–2010. Seventy two patients had bilateral upper extremity weakness without involvement of lower-limbs, respiratory, and bulbar weakness at the first examination. All patients were classified according to the revised El Escorial research diagnostic criteria and were categorized according to operational definitions as BAD and U-ALS. Analysis of variance F tests for continuous variables and X² tests for categorical variables analyzed differences in baseline data among the diagnostic categories.

**Results:** At first examination, the site of onset, the lowest score of the weakest muscle, and fasciculation discriminated between eventual diagnostic group; patients with BAD were proximal muscle at onset and weaker more likely to have U-ALS. Fasciculation was 0% for BAD group, 70% for U-ALS (26/37). The ratio of men to women was 5:1 in the BAD group compared to 2:1 in U-ALS. Two or more upper motor neuron signs was 17% of BAD group and 35% U-ALS group. Wide spread denervation in EMG study was 75% for BAD group and 86% for U-ALS group.

**Conclusions:** Our findings underline the several clinical and electrophysiological features (Sex, involved site at initial onset, MRC grade, Fasciculations) that differentiate between BAD and U-ALS.

**Disclosure:** Nothing to disclose