

**American Academy of Neurology Annual Meeting  
San Diego, California  
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Summary of Studies Relating to ALS**

**Acetylcholinesterase Antisense Oligonucleotides (EN101) as a Novel Treatment Strategy for ALS: A Mouse Model Study**

*Marc Gotkine, Gladis Gilinski, Leah Rozenstein, Oded Abramsky, Zohar Argov, Hanna Rosenmann, Jerusalem, Israel*  
The study investigated the effect of EN101 on a transgenic mouse model of ALS. Previous evidence indicated that acetylcholinesterase (AChE) is involved in ALS. However, AChE enzyme inhibitors result in up-regulation of production of “read-through” AChE, which could have detrimental effects. Therefore, it is expected that inhibiting AChE synthesis would be more beneficial. This can be done with antisense oligonucleotide technology. The study administered EN101 daily to the mouse model, comparing treated mice (N=11) to a control receiving saline (N=12). Disease onset was determined by weekly motor testing using a Rotarod device. Mice were also assessed daily for weight, clinical motor score and survival. Treatment was found to create a 13-day delay in onset and an 11-day delay in death compared to control mice. Therefore antisense oligonucleotides directed against AChE mRNA delay ALS progression in this model. This supports the theory that AChE is involved in the pathogenesis of ALS and that the inhibition of AChE synthesis could be used as a treatment.

**Age of SOD1 A4V Mutation Causing ALS and Founder Effect**

*Mohammad Saeed, Yi Yang, Han-Xiang Deng, Wu-Yen Hung, Nailah Siddique, Lisa Dellefave, Chicago, IL, Cinzia Gellera, Milan, Italy, Peter Andersen, Umea, Sweden, Teepu Siddique, Chicago, IL*  
This experiment traced the origin of the SOD1 A4V mutation North America, which causes 50% ALS-linked SOD1 mutations in North America, but is uncommon in Europe. Fifty-four North American and six European families with the mutation and 96 healthy individuals with different ancestries, with sporadic ALS and other SOD1 mutations were also genotyped. A breakdown of linkage disequilibrium (LD) was used to determine the ages of mutations. One mutation, A4V, was found to be associated with several SNPs. It was estimated that A4V was introduced into the Caucasian population roughly 400-500 years ago by Amerindians. A second form of A4V may have come to North America from Europe. Results also suggest that there was a genetic factor protecting American Indians from ALS which was not inherited by the Caucasian population.

**Aggregation of SOD1 Is Primarily Neuronal, Rather Than Glial in ALS Patients and Mouse Models with SOD1 Mutations**

*Han-Xiang Deng, Hong Zhai, Ronggen Fu, Chicago, IL, Arthur P. Hays, New York, NY, Teepu Siddique, Chicago, IL*  
This study examined the cellular distribution of SOD1 aggregates in ALS patients. SOD1 mutations are linked to about 20% of familial ALS cases, but the role of the mutation in the development of ALS is not well understood. Spinal cord sections from ALS patients and mouse models with specific SOD1 mutations were analyzed in a manner that localized the SOD1 aggregates. Aggregates were found in mouse glial cells, but not

human glial cells. The experiment found SOD1-immunoreactive aggregates to be primarily located in large neurons and their processes. Therefore these aggregates, not those in glial cells, may factor in the development of SOD1-mediated ALS.

**Analysis of the Cu/Zn Gene in a Catalan ALS Population. Should All Sporadic ALS Cases Also Be Screened for SOD1?** *Josep Gamez, Marc Corbera-Bellalta, Gisela Nogales, Nuria Rager, Elena Garcia-Arumi, Merce Badia-Canto, Antonio L. Andreu, Jose Alvarez-Sabin, Barcelona, Spain*

This study examined the prevalence of SOD1 mutations in a Catalan ALS population and the relationship between the genotype and phenotype. SOD1 mutations are the most commonly identified cause of ALS; however, the prevalence of the mutation varies according to ethnicity. Mutation frequencies were found for 30 FALS pedigrees and 94 sporadic ALS cases. The prevalence of SOD1 mutations in Catalan familial ALS was found to be similar to levels in Mediterranean countries but lower than in Belgian, Japanese, and Scottish populations. The mutation had a prevalence of 4.25% in subjects with sporadic ALS. Results could affect genetic counseling. Screening for SOD1 mutations in sporadic ALS cases should also be considered.

**Angiogenin Mutations Segregate with Familial and ‘Sporadic’ ALS** *Matthew J. Greenway, Dublin, Leinster, Ireland, Peter M. Andersen, Umea, Sweden, Carsten Russ, Boston, MA, Sean Ennis, Dublin, Ireland, Victor Patterson, Belfast, United Kingdom, Robert Swingler, Dundee, United Kingdom, Karen E. Morrison, Birmingham, United Kingdom, Andrew Green, Dublin, Ireland, Ravi Acharya, Bath, United Kingdom, Robert H. Brown, Jr., Boston, MA, Orla Hardiman, Dublin, Ireland*

This experiment examined the link between variants in the hypoxia-inducible gene angiogenin and ALS. A specific chromosome (14q11.2) had been identified as a region for ALS in Irish and Scottish populations. A single nucleotide polymorphism (SNP) (rs11701) in the angiogenin gene had been linked to ALS. In a study of 1629 ALS patients and 1264 controls from Ireland, Scotland, USA, UK and Sweden, the link with the SNP was confirmed in Irish and Scottish populations, but not in the other populations. Seven missense mutations were found in individuals with sporadic and familial ALS. An ALS-linked mutation was also found in one control. At least three of the mutations are expected to prevent enzyme activity. The results suggest hypoxia-inducible genes affect motor neuron degeneration and that controlling hypoxia responsive pathways could help manage neurodegeneration.

**Axonal Damage Markers in Cerebrospinal Fluid Are Increased in ALS** *Johannes Brettschneider, Ulm, BW, Germany, Axel Petzold, London, United Kingdom, Sigurd D. Süßmuth, Albert C. Ludolph, Hayrettin Tumani, Ulm, Germany*

This study tested the correlation between biomarkers for axonal degeneration in cerebrospinal fluid (CSF) and subtypes of ALS and whether biomarkers could help predict the progression of the disease. CSF levels in the tau proteins and neurofilaments of ALS patients, Alzheimer’s patients and age-matched controls were measured. CSF levels were found to be higher in patients with ALS than controls or Alzheimer’s patients. They were higher when there was predominant upper rather than lower motor neuron involvement. They were also higher when disease progressed more rapidly.

Therefore biomarkers relate to subgroup, rate of progression and could help measure future treatment strategies.

### **Behavioral Change in Patients with and without Cognitive Impairment in ALS**

*Susan W. Levine, Jonathan S. Katz, Robert G. Miller, San Francisco, CA*

This experiment compared behavioral abnormalities reported by caregivers in cognitively normal and cognitively impaired ALS patients. Frontal lobe pathology, which is known to occur in ALS can cause cognitive or behavioral impairment. In a test of cognitive impairment, 12 patients were found to be cognitively normal, 13 were not. There was no distinction in age and symptom duration between the two groups. New onset behavioral impairment and behavioral changes were more common in the CI group with apathy being the most common abnormality. The high rate of behavioral change in CI patients indicates that it may be a feature of frontotemporal pathology in ALS. Because it is also high in CN patients, changes may precede cognitive impairment, though this needs to be investigated further.

### **Behavioral Changes in ALS and Their Relationship to Cognitive Changes**

*Diane M. Mosnik, Houston, TX, Mariana Witgert, Tucson, AZ, Major Bradshaw, Paul E. Schulz, Houston, TX*

This study examined whether there are behavioral changes linked to ALS and if so whether they are associated with cognitive changes. 225 ALS patients underwent cognitive testing and were rated by family members on behavioral changes. Behavioral ratings were found to increase after the ALS diagnosis. Greater cognitive impairment was linked to higher behavioral ratings, apathy scores and dysexecutive ratings. The results indicate that there are frontally-mediated behavioral changes in ALS and that they are linked to cognitive impairments.

### **Changes in Metallothionein Expression in Amyotrophic Lateral Sclerosis**

*Isao Hozumi, Gifu, Japan, Mitsunori Yamada, Niigata, Japan, Yoko Uchida, Tokyo, Japan, Masahiko Sato, Gifu, Japan, Kazuhiro Ozawa, Hashima, Gifu, Japan, Aiko Kimura, Yuji Tanaka, Takashi Inuzuka, Gifu, Japan*

This study investigated the metallothionein (MTs) expression in spinal cords of autopsy samples as well as the immunoreactivity of MT-3 in spinal fluid of ALS patients to determine the role of MTs in the development of ALS. The expression of MTs was found to reflect the progression of ALS. Both MT-1/2 and MT-3 had reduced immunoreactivities in the spinal fluids of ALS patients compared to controls. The level of MT-3 in the cerebral spinal fluid also appeared to decrease over time; however the study was only able to chronologically follow one patient. Because MTs are known to be self-protective against reactive oxygen species, they may be used to treat ALS.

### **Cognitive Deficits, Emotional Lability, Quality of Life, and Depression in ALS**

*Augusto Gauthier, Alessandro Vignola, Turin, Torino, Italy, Valentina Pasian, Turin Italy, Andrea Calvo, Turin, Torino, Italy, Paolo Ghiglione, Turin, Italy, Roberto Mutani, Turin, Torino, Italy, Adriano Chio, Biella, Italy*

This study explored the impact of cognitive deficits on ALS patients' quality of life. Patients were given standardized tests for cognitive linguistic deficits, emotional lability

(rapid and extreme mood changes), depression, quality of life, mental and physical status. Results of the tests were generally related to the type of onset and bulbar symptoms. This study reinforced the importance of monitoring cognitive and linguistic deficits because of their ability to undermine quality of life and because of their effect on the important decisions facing patients throughout the course of their disease.

**Coping Style Is an Important Determinant of Quality of Life in Patients with Amyotrophic Lateral Sclerosis** *Leonard H. Van den Berg, Jan-Paul Van den Berg, Eline Lindeman, John H. Wokke, Utrecht, Netherlands*

This study explored the relationship between coping styles and quality of life in ALS patients, by interviewing 208 patients and their caregivers. Based on the Short Form Health Survey, 2 visual analogue scales, the Utrecht Coping List and the Caregiver Strain Index, patients and caregivers were found to have normal healthy coping mechanisms compared to standard norms. However, passive coping styles tended to correlate with lower qualities of life while an active approach and reassuring thoughts positively affected quality of life. Physical health did not seem to be affected by coping styles. These results suggest that psychological interventions to optimize coping styles would be helpful in enhancing quality of life for both patients and caregivers.

**A Cross-Sectional Study of Caregiver Time Use in Amyotrophic Lateral Sclerosis** *Adriano Chio, TorinoPiemonte, Italy, Augusto Gauthier, Alessandro Vignola, Andrea Calvo, Paolo Ghiglione, Anna A. Terreni, Roberto Mutani, Torino, Italy*

This study examined the care time required from ALS caretakers and its relationship to the patient's disability. This is important as time-dependence burden is the weakest Caregiver Burden Inventory domain. Using the Caregiver Activity Time Survey, caregivers were found to spend an average of 570 minutes per day caregiving, with the most time spent housekeeping, toileting and feeding. The time spent related to the overall extent of the patient's disability and to lower limb disability, especially in certain realms of care. The patient's age and duration of disease did not seem to affect care time. Results suggest that the caregiver aspect of the disease may serve as a measure of outcome for potential therapies.

**Deep Venous Thrombosis (DVT) in Amyotrophic Lateral Sclerosis (ALS)**

*Muhammad M. Qureshi, Charlestown, MA, Hui Zhang, Boston, MA, Merit E. Cudkowiez, Charlestown, MA, Elizabeth Raynor, Boston, MA*

This study examined the incidence of DVT in 501 ALS subjects involved in randomized placebo-controlled trials of topiramate, creatine and celebrex and its effect on laboratory results. The incidence of DVT was found to be more common in patients with difficulty dressing, bed turning, walking and climbing stairs (determined using ALSFRS). The Maximum Voluntary Isometric Contraction (MVIC) leg megascore declined more quickly in the DVT versus non-DVT group. Overall, DVT incidence was higher among ALS patients than the general population (2.7% versus 0.1%) and comparable to the hospitalized population (2.7% versus 0.8-1.3%). Based on these results, there is an increased risk of DVT in ALS subjects, especially those with impaired mobility. Therefore protective measures should be taken to prevent DVT in these patients.

**Detection of Upper Motor Neuron Degeneration in Amyotrophic Lateral Sclerosis by Diffusion Tensor Imaging** *John C. T. Wong, Luis Concha, Christian Beaulieu, Sanjay Kalra, Edmonton, AB, Canada*

This study aimed to overcome the limitations of physical examinations in evaluating upper motor neuron (UMN) degeneration in ALS using diffusion tensor imaging (DTI), an MRI technique that can test axonal integrity in vitro. The DTI was able to detect a degeneration of the corticospinal tract (nerves carrying voluntary motor commands from the brain to the spinal cord), the region of interest chosen on a coronal DWI image. The results of the test suggest that DTI can serve as an indirect measure of UMN damage. This could be used to expedite ALS diagnosis.

**Development and Evaluation of the ALSFRS-R as a Self-Administered Tool in Patients with ALS**

*Jacqueline Montes, Gilberto Levy, Buchsbaum Richard, New York, NY, Steven Albert, Pittsburgh, PA, Petra Kaufmann, Hiroshi Mitsumoto, Paul Gordon, New York, NY*

This study aimed to develop a self-administered version of the ALSFRS-R study, which predicts survival time based on changes in strength over time, in order to reduce clinic visits and improve retention in clinical trials. The self-administered versions were very reliable, compared with evaluator-administered versions, regardless of previous exposure to the assessment. Reliability was shown both for patients and caregivers.

**Dysregulation of the Hypoxia Response in CSF of Patients with ALS** *Caroline*

*Moreau, David Devos, Veronique Brunaud-Danel, Philippe Lassalle, Thierry Perez, Andre-Bernard Tonnel, Alain Destee, Luc Defebvre, Nicolas Just, Lille, North France*

This study compared levels of vascular endothelial growth factor (VEGF), erythropoietin (EPO) and prostaglandin (PGE-2), according to hypoxemia, in the cerebrospinal fluid (CSF) of ALS patients and neurological controls. VEGF levels were found to be lower in ALS patients than controls, but there was no correlation between the severity of hypoxemia (subnormal oxygen levels) and the level of VEGF. PGE-2 levels were higher in ALS patients. Within the ALS patients, EPO levels were higher in hypoxic patients than normoxic (normal oxygen levels) patients, while VEGF levels were lower. This suggests that hypoxic ALS involves a dysregulation of the hypoxia response and a decrease of VEGF165-dependent neuroprotection. Increased receptivity of EPO in hypoxic ALS suggests that there is a gene regulation pathway common to VEGF and EPO. The dysregulation of the hypoxia response may be mediated by another pathway possibly involving the interaction of VEGF and PGE-2.

**Effect of Respiratory Therapist on noninvasive Ventilation Use in Patients with**

**Amyotrophic Lateral Sclerosis** *Seth A. Kareus, Deborah F. Fewell, Susie Kagebein, Stacy A. Rudnicki, Little Rock, AR*

This study examined the effect of having a respiratory therapist (RT) in an ALS clinic, based on use of noninvasive ventilation (NIV), symptom control and survival. This was evaluated with retrospective assessment of NIV use in patients seen prior to hiring the RT (54%) and with the RT (83%). Prior to the RT a nurse performed vital capacity (VC) and the neurologist discussed NIV, with the addition of the RT, the RT performed VC, discussed NIV, provided education, and encouraged visits by NIV company to make

adjustments. The addition of the RT increased patient willingness to try NIV and to continue using it. This led to better quality of life and increased survival.

**Effects of Tube-Feeding on Quality of Life and Survival in Amyotrophic Lateral Sclerosis Patients** *Pierre Clavelou, Lemlih Ouchchane, Valérie Batel, Clermon-Ferrand, Auvergne, France, Corinne Bouteloup, Clermont-Ferrand, France, Gérard Besson, Grenoble, Rhone-Alpes, France, Philippe Couratier, Limoges, Limousin, France*

This study is assessing the effect of tube-feeding (TF) on quality of life and survival in ALS patients by observing patients in 17 French teaching hospitals and recording quality of life, anthropometry, ALS-FRS scales and respiratory function. Of 389 patients, TF was proposed for 81, with 51 refusing. TF led to increased “mobility” in the next six months, though there was an overall decline over time. Weight loss was found to have a slightly negative affect on survival, while early TF had a slightly positive trend. These preliminary results suggest that TF may positively affect quality of life. Completion of the study is expected to confirm the survival benefit of early TF.

**Electrical Impedance Myography as an Outcome Measure in ALS Clinical Trials**

*Seward B. Rutkove, Ronald Aaron, Elizabeth M. Raynor, Boston, MA, Jeremy M. Shefner, Syracuse, NY, Merit E. Cudkowicz, Charlestown, MA, David A. Schoenfeld, Denis Bron, Boston, MA, Karin H. Woodman, Brookline, MA, Carl A. Shiffman, Boston, MA*

This study examined the value of 50 kHz electrical impedance myography (EIM)—an atrophy sensitive technique that applies an electrical current to muscles and evaluates the resulting surface voltage pattern—in measuring the outcome of ALS trials. EIM was used to calculate daily rate of muscle decline which was comparable to that obtained using isometric quantitative muscle testing and ALS Functional Rating Scale. Thus EIM can effectively detect muscle deterioration and can do so painlessly, rapidly, without requiring patient effort, and is easily reproducible. It has the potential to be a valuable outcome measure in future trials.

**Evaluation of Sham Noninvasive Ventilation for Randomized, Controlled Trials in ALS** *Kirsten L. Gruis, Devin L. Brown, Ann Arbor, MI*

This study evaluated the potential of sham continuous positive airway pressure to act as placebo NIV. Forty ALS patients with forced vital capacity greater than 50% were given 30 seconds of either NIV or ineffective sham NIV and were asked if they believed their machine was “definitely pretend, probably pretend, definitely real, probably real” or if they were “uncertain.” Overall, treatment type had no effect on subjects’ responses. These results suggest that sham NIV would be a useful placebo control for NIV trials in ALS.

**Focality of ALS: II. 3-D Topography of Motor Neurons in Post Mortem Spinal Cords and the Neuropathologic Gradient of Degeneration** *John Ravits, Patrick Laurie, Brad Stone, Seattle, WA*

This study assessed the location of motor neurons in post-mortem ALS spinal cords. Post mortem spinal cords of ALS patients followed through the course of their disease were neuropathologically examined. Overall 41% of normal motor neurons were counted with

a range of 2% to 79%. The vertical distribution related to site of disease onset. A few patients had severe and pervasive motor neuron degeneration. Horizontally a spectrum of degeneration was present. Degeneration was more pronounced close to the onset region than in farther regions. Some patients had degeneration clustered around the anterior horn. Motor neuron degeneration appears to develop focally and move in 3-dimensions. Advancement into regions controlling respiration stops the disease at a point in time. Regions farther from the site of onset show the time frame of degeneration and molecular pathogenesis.

**Identification of Alsin Interacting Proteins** *Yong Shi, Chicago, IL, Kazutaka Shiomi, George Gorrie, Osman Mir, Teepu Siddique, Chicago, IL*

This study aimed to identify alsin interacting proteins in order to understand alsin function and its involvement in the development of ALS. Alsin mutations are known to cause a rare recessive form of juvenile ALS. Alsin VSP9 domain was found to interact with cytoskeleton proteins such as MAP1a tubulin  $\beta$  and cell cycle regulators such as Ras association domain family (which may case cell cycles to stop), and LMO4 (which regulates transcription). This suggesting that alsin may have a more complex function than currently known. It may be involved in cell division, cellular transport, and axonal guidance functions.

**Identification of Metabolic and Protein Biomarkers for Amyotrophic Lateral Sclerosis** *Lisa Paige, Durham, NC, Robert Bowser, F. Lutka, J. An, P. Ganchev, V. Gopalakrishnan, Pittsburgh, PA, Kristyn Newhall, Kim Kruczek, Emily Welsh, Charlestown, MA, Rima Kaddurah-Daouk, Durham, NC, Robert H. Brown Merit E. Cudkowicz, Charlestown, MA*

The objective of this study was to develop metabolic and protein biomarkers with diagnostic and therapeutic benefits to ALS, which would aid more rapid and accurate ALS diagnoses as well as identifying drug targets for treatment. Cerebrospinal fluid was analyzed for metabolite and protein levels associated with ALS. 16 metabolic biomarkers and 19 protein biomarkers were found to be altered in ALS patients. Metabolic biomarkers such as alpha-amino adipic acid had 83% sensitivity for identifying ALS. Proteomic biomarkers, such as transthyretin had 80% sensitivity and 91% specificity. Therefore metabolic and proteomic profiling of CSF can create biomarker panels, which may expedite ALS diagnoses, identify new drug targets and aid in evaluating drugs.

**Intravenous Plasmid DNA-Mediated Gene Transfer of IGF-1 Is Therapeutic for SOD1 Mouse Model of ALS** *Gyula Acsadi, Grosse Pointe, MI, Roumen A. Anguelov, Troy, MI, Xingli Li, Livonia, MI, Adam Cristescu, Macomb TWp., MI, Agnes A. Acsadi, Grosse Pointe, MI, Jon A. Wolff, Madison, WI*

This study assessed the ability of intravenous insulin-like growth factor (IGF-1) to alter the clinical course of SOD1 mice. Neurotrophic factors such as IGF-1 have been shown to promote survival and/ or the regeneration of motor neurons. It also increased the lifespan of SOD1 mice. The safer non-viral vector is preferable in human gene therapy than the viral vector. Injecting SOD1 mice with IGF-1 cDNA expression plasmid led to improved survival compared to control. The benefit was equal to or better than treatment with the viral vector. Motor performance deterioration was also slowed in treated mice.

This suggests that plasmid DNA-mediated intravenous gene transfer of IGF-1 was a beneficial treatment for the mice and has promise as a safe treatment of ALS.

**Is the Amygdala Affected in Amyotrophic Lateral Sclerosis?** *Heike I. Schmolck, Diane Mosnik, Paul E. Schulz, Houston, TX*

This study examined the involvement of a temporal lobe structure, the amygdala, in ALS. Subjects were shown faces and asked to rate their approachability—a test sensitive to amygdala lesions. ALS patients were found to rate many faces as approachable that controls deemed unapproachable. The result suggests amygdalar involvement. The inability to recognize threat expressed in facial clues may present a biological basis for the “ALS personality”—nice and cooperative with a low rate of depression.

**Measures and Impact of Cognitive Impairment In Patients with Amyotrophic Lateral Sclerosis** *Paul H. Gordon, Carolyn Doorish, Vanessa Battista, Melissa J. Lewis, Yuanjia Wang, Lewis P. Rowland, Lawrence S. Honig, Hiroshi Mitsumoto, Karen Marder, New York, NY*

This test related performance on a word generation task (FAS) to behavioral and cognitive screening tools, motor function and patient and caregiver well-being. ALS patients were assessed using the FAS, a modified Mini-Mental Status, the Beck Depression Inventory, the ALS Functional Rating Scale, and the Clinical Dementia Rating Scale. Caregivers assessed their own depression with the Beck Depression Inventory and patient function with the Frontal Behavioral Inventory. FAS performance was found to be related to cognitive and frontal behavioral impairment and shorter time between onset and diagnosis. This testing may be able to detect subtle frontal impairment. Rapidly progressive ALS may cause increased non-motor system degeneration. Behavioral changes also lead to caregiver depression, and increased severity can lead to depression in patients and caregivers.

**Microglial Activation Accelerates Disease Phenotype in CX3CR1 Null-SOD1<sup>G93A</sup> ALS Mice** *Erik P. Pioro, Volodymyr Kostenko, Astrid E. Cardona, Richard M. Ransohoff, Cleveland, OH*

This study tested whether a transgenic mouse model of ALS with the mutated human SOD1 G93A gene without a fractalkine receptor (making it null for the CX3CR1 gene) experiences ALS more severely than transgenic mice with the gene. The fractalkine receptor is known to suppress the activation of microglia, whose inflammation causes a loss of motor neurons. Mice with and without the gene were analyzed for behavior and survival. Lack of the gene resulted in greater microglial reaction, increased motor neuron loss, worse neurobehavioral outcomes and shorter survival. These results were more pronounced in males. More research is needed to elaborate on findings and develop treatments.

**Mutations in the Dynactin Gene and Amyotrophic Lateral Sclerosis** *Albert C. Ludolph, Anne D. Sperfeld, Jan Kassubek, Ulm, BW, Germany, Gabriele Stumm, Munich, Bavaria, Germany, Sumana Gopinath, Sidney, Australia, Magdalena Kuzma, Warsaw, Poland, Thomas Meyer, Christoph Münch, Berlin, Germany, Hubert Kwiecinski,*

*Warsaw, Poland, Garth Nicholson, Sidney, Australia, Reinhard Sedlmeir, Ulm, BW, Germany*

This study examined the spectrum of phenotypes associated with mutations in the dynactin gene in ALS. Mutations presented a wide range of phenotypes, including classical ALS patients and clinically uncommon patients. These phenotypes included patients with exclusive lower motor neuron disease or uncommon clinical and MRI signs. Some mutations were also found in controls. Therefore dynactin mutations appear to be associated with or overrepresented in patients with a range of ALS/MND phenotypes.

### **A Novel MRI Technique Demonstrates Thinning of Primary Motor Cortex in ALS**

*Devin R. Scott, Don C. Bigler, Mark D. Meadowcroft, Helen E. Stephens, Qing Yang, Zachary Simmons, Hershey, PA*

This study evaluated a new method of brain MRI for the diagnosis and monitoring of ALS, which was evaluated with a novel algorithm that can quantify cortical gray matter thickness. This technique was able to show the thinning of the primary motor cortex and may be useful both for the diagnosis and follow-up of these patients.

### **Oculomotor Apraxia and Cognitive Impairment Occur Together in ALS**

*Jonathan S. Katz, Susan W. Levine, Adam L. Boxer, San Francisco, CA, April McVey, Shawnee Mission, KS, Richard Barohn, Kansas City, KS, Robert G. Miller, San Francisco, CA*

This study described the link between ocular motility abnormalities and cognitive impairment in ALS patients. Patients with suspected cognitive abnormalities were given cognitive and ocular motor examinations looking for ocular apraxia (difficulty in maintaining pursuit movements, or quickly moving eyes from one position to another.) Ocular abnormalities including apraxia and severe supranuclear gaze palsy were found in patients with cognitive impairment and bulbar ALS, but were not found in any cognitively impaired patients without bulbar involvement or in any non-demented patients. The study showed the link between these conditions and suggests that ocular motility testing may be a useful screen for predicting cognitive deficits in ALS.

### **Optimizing the Detection of Central Motor Neuron Involvement in Amyotrophic**

**Lateral Sclerosis** *Shahran Attarian, Marseille, Paca, France, Annie Verschuere, Jean-Philippe Azulay, Jean Pouget, Marseille, France*

This study determined the sensitivity of the Transcranial Magnetic Stimulation (TMS) and the Triple Stimulation Technique (TST) as a means of better assessing Upper motor neuron involvement in ALS, evidence of which is often obscured by Lower motor neuron loss. The study found TST to be the best measurement, but concluded that the test should be performed on both upper and lower limbs in order to maximize diagnostic sensitivity.

### **Paraoxonase-1 Gly192Arg and Leu55Met and Paraoxonase-2 Ser311Cys**

**Polymorphisms and Risk for Sporadic Amyotrophic Lateral Sclerosis** *Agnieszka Slowik, Krakow, NY, Poland, Barbara Tomik, Dorota Partyka, Maciej T. Malecki, Pawel Wolkow, Krakow, Poland, Denise A. Figlewicz, Ann Arbor, MI, Andrzej Szczudlik, Drakow, Poland*

This study examined the effect of the Pon1 Gln192Arg PON1 Leu55Met and PON2 Cys311Ser polymorphisms on the development of sporadic ALS. A difference in

haplotype distribution was found between patients and controls, with the Arg-Cys-Leu haplotype significantly increasing the odds of developing sALS.

**Paraoxonase Gene Cluster is Associated with Sporadic Amyotrophic Lateral Sclerosis (SALS)** *Mohammad Saeed, Nailah Siddique, Wu-Yen Hung, Robert Sufit, Scott Heller, Teepu Siddique, Chicago, IL*

This test examined the association of the Paraoxanase (PON) gene cluster with sALS. This gene cluster was found to have a strong susceptibility variant for sALS, with the G allele being detrimental and the A allele protective.

**Performance of the ALSFRS<sub>r</sub> When Administered by Phone to Patients and Caregivers: Experience from the VA ALS Registry** *Edward J. Kasarskis, Lexington, KY, Kelli D. allen, Jennifer H. Lindquist, Cynthia J. Coffman, Eugene Z. Oddone, Durham, NC*

This study determined that the functional status of ALS patients could be determined by having a trained interviewer administer the ALSFRS<sub>r</sub>, telephonically to the patient, or the caregiver if the patient was unable. Results found the decline in ALSFRS<sub>r</sub> over 12 months to be virtually identical when rated by the patient or caregiver and to be comparable to recent studies.

**Phospholipase A2 Levels in G93A SOD1 Transgenic Mice** *Terry D. Heiman-Patterson, Jeffrey S. Deitch, Guillermo Alexander, Robin Yano, Timothy Cunningham, Philadelphia, PA*

The study examined the levels of phospholipase A2, a possible cause of the inflammatory response associated with ALS, secreted by SOD1 mice. SPLA2 levels in the serum and urine were increased both in early and endstage mice. This suggests that these enzymes play a role in the inflammatory damage in ALS and treating them with sPLA2 inhibitors could be beneficial.

**Prognosis of Amyotrophic Lateral Sclerosis in Southern Italy: Results from a Population-Based Registry, SLAP (Sclerosi Laterale Amiotrofica-Puglia)** *Stefano Zoccolella, Bari, Italy, Ettore Beghi, Milano, Italy, Guerrino Palagano, Angela Fraddosio, Vito Lepore, Bari, Italy, Vito Guerra, Castellana, Bari, Italy, Isabella Simone, Paolo Lamberti, Bari, Italy, Luigi Serlenga, Andria, Bari, Italy, Giancarlo Logroscino, Boston, MA*

This study used a population-based cohort of ALS cases from Puglia, Southern Italy, to evaluate survivorship and the prognostic value of clinical factors. Survival times were found to be similar to other population-based studies. Advanced age and bulbar onset of symptoms were found to indicate poor prognosis, while the subject's El-Escorial diagnostic category at the time of diagnosis was not a good predictor of survival.

**Prospective Study of Diet and Amyotrophic Lateral Sclerosis (ALS) within the CPSII Cohort** *Natalia Morozova, Marc Weisskopf, Boston, MA, Marjorie McCullough, Atlanta, GA, Cassandra Munger, Boston, MA Dugenia Calle, Michael Thun, Atlanta, GA, Alberto Ascherio, Boston, MA*

This study examined the effect of dietary factors including high fiber, high fat, coffee, tea and alcoholic beverages on the risk of ALS. Overall no relationship was found between high fat or high fiber foods and risk of ALS. However, there was increased risk associated with a high consumption of brown rice/whole wheat/barley, cold/dry cereals, decaffeinated coffee, wine and liquor and a decreased risk associated with high consumption of chicken, and tea. These results should still be interpreted very cautiously, but suggests a need for further studies on the link between diet and ALS.

**Quality of Care and Cost-Effectiveness of ALS Interdisciplinary Centers: The Quac**

**Study** *Gabriele Mora, Pavia, Lombardia, Italy, Adriano Chio, Torino, Italy, Virginio Bonito, Bergamo, Italy, Roberto D'Alessandro, Fabrizio Salvi, Bologna, Italy, Rudolph Schoenhuber, Bozen, Italy, Graziella Filippini, Daniela Testa, Vincenzo Silani, Milano, Italy, Guido Cavaletti, Monza, Italy, Mauro Ceroni, Monza-Pavia, Italy, Ettore Beghi, Milano-Monza, Italy, Giovanni Savettieri, Palermo, Italy, Giuliano Masiero, Milano Italy*

This study compared quality and cost of care in tertiary ALS centers and general neurology units. Patients enrolling in tertiary centers tended to be clinically worse. However, quality of life and satisfaction of care were higher and costs were lower. Therefore, tertiary centers were found to be more cost effective than general neurology units.

**Quantitative Magnetic Resonance and Histological Analysis of Primary Motor**

**Neuronal Loss in ALS** *Mark D. Meadowcroft, Don C. Bigler, Zachary C. Simmons, Michael B. Smith, Qing X. Yang, Hershey, PA*

The goal of this study was to evaluate and quantify MRI T<sub>1</sub> and T<sub>2</sub> image and parameter mapping differentials found in the primary motor cortex of ALS cadaver brains. These imaging methods were found to accurately quantify the contrast differentials in the motor cortex of ALS tissue. This differential is significantly different from other brain regions of interest and was evaluated and verified using histological staining.

**Repressible and Restricted or Unrestricted Spatial Expression of Cu/Zn Superoxide**

**Dismutase (SOD1) and Luciferase (luc) in Mice** *Lijun Wang, Chicago, Il, Kamal Sharma, Hanxian Deng, Teepu Siddique, Shujing Yang, Chloe S. Kim-Parker, Raymond P. Roos, Chicago, Il*

This study developed a mouse model with whose expression of the SOD1 mutation could be restricted in order to determine the effect of different duration of SOD1 expression in various cell types. They were able to develop mice with repressible ubiquitous or cell-type specific SOD1 gene and luc gene expression. This model should be helpful in determining whether ALS will occur with restricted spatial expression of the mutation and if repressing expression can reverse the ALS phenotype.

**Respiratory Rate As Predictor of Hypercapnia and Survival in Amyotrophic**

**Lateral Sclerosis** *Andrea Calvo, Torino, Piemonte, Italy, Paolo Ghiglione, Enrico Cavallo, Antonio Ilardi, Torino, Italy, Mario Zerbini, Federica Gamna, Roberto Torchio, Orbassano (TO), Italy, Adriano Chio, Torino Italy*

This study tested the reliability of respiratory rate (RR) as a marker of respiratory impairment in ALS patients. Patients with a high RR at initial measurement tended to have more severe respiratory involvement. When the RR is higher than 25, excess carbon dioxide may be present in the blood and blood gas should be analyzed. High RR is also associated with shorter survival.

**Riluzole and Amyotrophic Lateral Sclerosis Survival: A Population-Based Study in Southern Italy** *Stefano Zoccolella, Bari, Italy, Ettore Beghi, Milano, Italy, Guerrino Palagano, Angela Fraddosio, Bari, Italy, Vito Guerra, Castellana, Bari, Italy, Vito Lepore, Isabella L. Simone, Paolo Lamberti, Bari, Italy, Luigi Serlenga, Andria, Bari, Italy, Giancarlo Logroscino, Boston, MA*

This study examined the effect of riluzole, the only drug known to prolong ALS survival, on ALS survival in a cohort of incident cases. The test specifically focused on its efficacy treating bulbar-ALS and elderly patients, as it is still unknown if the drug's efficacy is limited to a certain stage of the disease or a subgroup of patients. Riluzole was found to prolong survival. The efficacy was proved in bulbar-onset and elderly patients, but not in limb-onset where the benefit was lost in prolonged follow-up.

**Riluzole Use in a Cohort of 501 Subjects with Amyotrophic Lateral Sclerosis (ALS)** *Muhammad M. Qureshi, Charlestown, MA, Hui Zhang, Boston, MA, Jeremy M. Shefner, Syracuse, NY, David A. Schoenfeld, Boston, MA, Merit E. Cudkowicz, Charlestown, MA*

This study examined the effect of riluzole on survival and outcome measures in ALS in subjects enrolled in 3 trials by the Northeast ALS Consortium testing creatine, topiramate and celebrex in ALS subjects. Subjects randomized to topiramate were excluded because treatment with riluzole could have accelerate the progression of ALS. The drug did not affect progression in muscle strength, pulmonary function and ALS-FRS. However the clinical trials were not randomized to riluzole use.

**Screening Mutations in the CHMP2B Gene in Familial Amyotrophic Lateral Sclerosis with Frontotemporal Dementia (ALS/FTD)** *Jianhua Yan, Chicago, IL, Nailah Siddique, Evanston, IL, Teepu Siddique, Chicago, IL*

This study examined the CHMP2B gene in 21 families with ALS and frontotemporal dementia for mutations to see if it might be the causative gene for this condition. No mutation in this gene were found in the 21 pedigrees examined, indicating that this mutation is not causative of ALS/FTD in this population.

**Selective Gene Ablation of Mutant SOD1 in Microglia Significantly Slows Disease Progression of ALS** *Koji Yamanaka, Severine Boillee, La Jolla, CA, George Kollias, Athens, Greece, Don W. Cleveland, La Jolla, CA*

This study examined in which cell types SOD1—a mutation whose expression causes motor neuron degeneration due to acquired toxic properties of mutant—generates toxicity to the motor neurons in ALS. Using a mouse model with a mutant SOD1G37R transgene than can be blocked in specific cell types using Cre recombinase. Removing expression of the mutant gene from motor neurons prolonged the age of onset and slowed the early phases of progression. Preventing expression in microglial cells and peripheral

macrophages slowed progressed, but did not effect age of onset. Therefore, microglia and/or macrophages are important in determining the progression of ALS.

**siRNA Mediated Interference of Motoneuron Death Triggered by Fas in SOD1**

**G93A ALS Mouse Model** *Federica Locatelli, Milan, MI, Italy, Stefania Corti, Dimitra Papadimitriou, Chara Donadoni, Sabrina Salani, Roberto Del Bo, Francesco Fortunato, Milan, Italy, Sandra Strazzer, Lecco Italy, Monica Nizzardo, Grazia Sardanu, Mereo Bresolin, Giacomo P. Comi, Milan, Italy*

This study investigated the in-vitro and in-vivo role of Fas-linked pathway in the motor neuron degeneration of SOD1 mouse model. Fas siRNA transfection reduced Fas expression on motor neurons in-vitro, increased cell survival and reduced expression of Fas-death mediators. siRNA infusion caused Fas down-regulation in spinal cord of SOD1 mice, decreasing cell death. Treated mice had reduced motor neuron death. Silencing the Fas pathway was found to increase motor neuron survival, which could lead to new strategies to treat ALS.

**Slower Disease Progression and Prolonged Survival in Contemporary ALS Patients: Is the Natural History of ALS Changing?**

*Adam Czaplinski, Basel, BS, Switzerland, Albert A. Yen, Pearland, Tx, Ericka P. Simpson, Stanley H. Appel, Houston, TX*

This study used the Kaplan-Meier life table method to analyze whether survival and disease progression in ALS have changed over the last 20 years. Contemporary patients were found to live significantly longer and have slower disease progression than the historical group. This seems to be unrelated to treatment. However further study is needed to determine if results are due to natural history of the disease or unmeasured aspects of improved care.

**A Study of Co-Variates of Fatigue in ALS** *Ericka Simpson, Albert Yen, Margaret P. Allred, Stanley Appel, Houston, TX*

This study explored fatigue in ALS to see if it is independent or linked to other features of the disease. Fatigue was found to be independent of disease progression and disability. It was also prevalent in patients without depression suggesting that fatigue is independent of such non-motor symptoms.

**Temporal Expression Profiles of Vascular Endothelial Growth Factor and Inducible Nitric Oxide Synthase in a Transgenic Mouse of Amyotrophic Lateral Sclerosis**

*Liang Lu, Birmingham, AL, Alvaro G. Estevez, White Plains, NY, Shin Oh, Peter H. King, Birmingham, AL*

This study examined the temporal expression profiles of VEGF (Vascular Endothelial Growth Factor) and iNOS (Inductible Nitric Oxide Synthase) in an SOD1 mouse model and connected the profiles with disease progression. As ALS progressed VEGF decreased and iNOS increased in the spinal chord of model mice, though not in wild-type mice. The loss of neuroprotection cause by the downregulation of VEGF may synergize with the toxic effects of iNOS and the byproduct, nitric oxide, to promote motor neuron degeneration.

**Transplantation of LeX+/CXCR4+ Adult Neural Stem Cells in the Spinal Cord of a Murine Model of Amyotrophic Lateral Sclerosis**

*Stefania Corti, Milan, MI, Italy, Frederica Locatelli, Dimitra Papadimitriou, Roberto Del Bo, Chiara Donadoni, Sabrina Salani, Milan, Italy, Sandra Strazzer, Lecco, Italy, Monica Nizzardo, Grazia Sardanu, Nereo Bresolin, Giacomo P. Comi, Milan, Italy*

This study investigated the ability of neural stem cells LeX+/CXCR4+ to contribute to spinal chord nerve growth and to alter the progression of ALS. These cells seem to be able to differentiate in motor neurons and prevent ALS in SOD1 mice. These stem cells may be a valuable source for neuronal replacement strategies of MN diseases.

**Utility of a Brief Screening Protocol To Identify Cognitive and Behavioral**

**Abnormalities in ALS Patients** *Jennifer M. Murphy, Vanessa Vanderpool, Catherine Lomen-Hoerth, San Francisco, CA*

This study evaluated the utility of a screening battery, which could be administered by bachelor's level staff, to identify ALS patients with cognitive and behavioral abnormalities. The screening battery seemed to successfully identify abnormalities in the population. Patients are currently being referred for neuropsychological evaluation, to determine the predictive utility of the screening.

**Weight Loss Is the Best Marker of Malnutrition in ALS: A Prospective Study**

*Paolo Ghiglione, Turin, Piemonte, Italy, Andrea Calvo, Stefania De Mercanti, Stefania Cammarosano, Anna A. Terreni, Concetta Finocchiaro, Rosalba Galletti, Adriano Chio, Turin, Italy*

This study assessed the markers of malnutrition and clinical outcome in a series of ALS patients. Weight loss or gain at each visit was compared to the healthy body weight determined at the initial visit and body mass index was also recorded. Body mass index was not a significant outcome parameter. Rate of weight loss as the disease progressed was the best marker of malnutrition, and should be included as a relevant outcome parameter in future studies.

**Wild-Type Microglia Are Less Neurotoxic Than Mutant SOD1<sup>G93A</sup> Microglia**

*Qin Xiao, Weihua Ahao, David R. Beers, Houston, TX, Albert A. Yen, Pearland, TX, Wenjie Xie, Jenny S. Henkel, Stanley H. Appel, Houston, TX*

This study investigated the relative neurotoxicity versus neuroprotection of microglia from SOD1 mice (which are expected to damage motoneurons) and wild-type mice (which are expected to protect motoneurons). Wild-type microglia were found to be less toxic and possibly neuroprotective. They may enhance the regulation of immune function, reducing microglial activation and motoneuron cytotoxicity.