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with the 24th Dr. Janez Faganel Memorial Lecture

Ljubljana, 19–20 September 2008

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s 24. predavanjem v spomin dr. Janeza Faganela

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Ljubljana, Slovenia 19-20 September 2008 / Ljubljana, 19.–20. september 2008

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FOREWORD

Dear Colleagues,

In spite of recent advances in both the research and clinical domains of amyotrophic lateral sclerosis (ALS), the disease remains an incurable, fatal condition. On the other hand it is an inspiring challenge to researchers and clinicians alike. The Ljubljana ALS Team was established in autumn 2002 at the Institute of Clinical Neurophysiology, University Medical Centre Ljubljana. The team, led by Professor Janez Zidar, links together experts from different fields working in unison to provide care and support for patients with ALS. A few research projects have started in parallel making clinicians and researchers even more committed to this disease.

ALS is the topic of this year's Ljubljana autumn clinical neuroscience meeting taking place at the University Medical Centre, Ljubljana on 19–20 September 2008. The Symposium keynote speaker is Professor Nigel Leigh from King's College London presenting the 24th Dr. Janez Faganel Memorial Lecture entitled "ALS: Advances in the Laboratory and in the Clinic". In two days the meeting will cover various aspects of the disease, from neuroimaging and neurophysiology, to respiration, cognition, neurobiology, and – most importantly – treatment and care of the patients.

The meeting is mainly a bilateral event bringing together two groups of both young and also established researchers and clinicians: the Ljubljana ALS Team and the MND Team from King's College London. A few prominent speakers from other parts of Europe have joined them and it is great to see that the participants are coming not just from Slovenia, but also from neighbouring countries, making the meeting an important regional event.

The meeting is a result of the hard work of a group of dedicated colleagues and good friends from both Slovenia and the UK and I would like to thank them all for their input. The organisation of the meeting would be impossible without generous support from the British Council (The International Networking for Young Scientists Programme), the Slovenian Research Agency and also from numerous pharmaceutical companies. I'm deeply thankful to them all.

My hopes are that this meeting will strengthen the links between the groups and also create new opportunities and ideas for regional collaboration. I also hope that many new friendships will be made. With this in mind, I wish you an interesting and inspiring meeting, and a pleasant stay with us.

We wish you a very warm welcome to Ljubljana,

Blaž Koritnik

PROGRAMME

FRIDAY, 19 SEPTEMBER 2008

08:00–09:00 Registration of Participants

09:00–09:15 Opening of the Symposium

09:15–10:00 **The 24th Dr. Janez Faganel Memorial Lecture**

P.N. Leigh (*King's College London*): ALS – Advances in the Laboratory and in the Clinic

10:00–10:20 Coffee Break

10:20–12:25 **Neuroimaging and Neurophysiology** (*Chair*: P. Nigel Leigh)

10:20–10:45 Biba Stanton (*King's College London*): Functional MRI in ALS: What Have We Learned?

10:45–11:10 Camilla Blain (*King's College London*): Pathophysiology of ALS – Insights from DTI

11:10–11:35 Sheba Azam (*King's College London*), Blaž Koritnik (*University Medical Centre Ljubljana*): Is the Motor Cortex Hyperexcitable in Motor Neuron Disease? A Study Using Pharmacological fMRI

11:35–11:55 Jeremy D. Isaacs (*King's College London*): Sensory Neuropathy in ALS – Syndromic or Co-Incidental?

11:55–12:10 Petr Ridzoň (*Thomayer's Teaching Hospital, Prague*): Silent Period and Motor Evoked Potentials – Findings in ALS

12:10–12:25 Vesna Martić (*Military Medical Academy, Belgrade*): Repetitive Nerve Stimulation in a Patient with ALS – A Case Report

12:25–13:25 Lunch

13:25–15:05 **Cognition and Dementia** (*Chair:* Adriano Chiò)

13:25–13:50 Stella Tsermentseli (*King's College London*): Cognitive Change in ALS

13:50–14:15 Elka Stefanova (*Clinical Centre Serbia, Belgrade*): Executive Dysfunction in ALS

14:15–14:40 Vita Štukovnik (*University Medical Centre Ljubljana*): Executive Ability and Daily Living Performance in Patients with ALS

14:40–15:05 Rajka M. Liščić (*Institute for Medical Research and Occupational Health Zagreb*): ALS and FTLD: Cognitive Changes and Genetic Markers

15:05–16:20 **Respiration I** (*Chair:* Zorica Stević)

15:05–15:30 Jörg Steier (*King's College London*): Assessment of Respiratory Muscle Strength

15:30–15:55 Leja Dolenc-Grošelj (*University Medical Centre Ljubljana*): Role of Polysomnography in Assessment of Noninvasive Ventilation in ALS Patients

15:55–16:20 Lea Leonardis (*University Medical Centre Ljubljana*): Symptoms of Respiratory Function Insufficiency and Arterial Blood Gases Analysis as Prognostic Indicators in ALS

16:20–16:40 Coffee Break

16:40–18:15 **Respiration II** (*Chair:* Janez Zidar)

16:40–17:05 Mary Ann Ampong (*King's College Hospital, London*): Supporting ALS Patients Using Noninvasive Ventilation

16:40–17:05 Zorica Stević (*Clinical Centre Serbia, Belgrade*): Management of Respiratory Failure and Dysphagia in ALS Patients

17:05–17:30 Simon Podnar, Igor Rigler (*University Medical Centre Ljubljana*): Electromyography of the Diaphragm and Phrenic Nerve Conduction Studies in Patients with ALS

17:30–17:55 Marko Korošec (*University Medical Centre Ljubljana*): Sniffing-Related Cortical Motor Potentials in ALS – A Preliminary Report

17:55–18:15 Blaž Koritnik (*University Medical Centre Ljubljana*): Investigating the Central Control of Respiration in ALS – A Pilot fMRI Study

20:00 Symposium Dinner (Ljubljana Castle)

SATURDAY, 20 SEPTEMBER 2008

09:00–10:00 **Basic Research** (*Chair:* Maja Bresjanac)

09:00–09:35 Albert C. Ludolph (*University of Ulm*): Translational Research in ALS

09:35–10:00 Boris Rogelj (*King's College London*): TDP-43 in Sporadic and Familial ALS

10:00–11:15 Treatment and Care I (*Chair: Bruno Giometto*)

10:00–10:25 Aleksandar Radunović (*Royal London Hospital, London*): Clinical Care of Patients with ALS

10:25–10:50 Emma Willey (*King's College London*): Multidisciplinary Approach in ALS

10:50–11:15 Aleš Pražnikar (*University Medical Centre Ljubljana*): Rehabilitation Medicine in ALS

11:15–11:35 Coffee Break

11:35–13:10 **Treatment and Care II** (*Chair:* Albert C. Ludolph)

11:35–12:10 David Oliver (*University of Kent, Canterbury*): Palliative Care in ALS

12:10–12:25 Tatjana Žargi (*Slovenian Hospice Association, Ljubljana*): Hospice ALS Patient – A Case Study

12:25–12:50 Adriano Chiò (*University of Torino*): Quality of Life and Depression in the Patient-Caregiver Scenario in ALS

12:50–13:10 Vid Zgonc (*University Medical Centre Ljubljana*): Demographic and Phenotypic Characterisation of Our ALS Patients

13:10–13:15 **Closing of the Symposium**

14:00–late Social Event (British Council Participants)

The 24th Dr. Janez Faganel Memorial Lecture
ALS: ADVANCES IN THE LABORATORY AND IN THE CLINIC

P. N. Leigh
MRC Centre for Neurodegeneration Research, King's College London and King's MND Care and Research Centre, Department of Clinical Neuroscience, Institute of Psychiatry, London, UK

ALS (MND) appears now a more complex disease than it did two or even one decade back, but new insights have been plentiful. From the perspective of the clinical scientist, some key (and inter-related) questions can be posed:

1. What is the core definition of ALS and what does that tell us about pathogenesis?
2. What does the natural history and epidemiology of ALS tell us about the biology of the disease?
3. What is selective vulnerability in relation to ALS, and is it a useful concept?
4. What insights have we gained from genetic studies and what have genetic studies told us about the causes of sporadic ALS?
5. What have we learnt from ALS trials and what might be key elements of a strategy to find effective therapies?

There are some partial answers, many more questions, and a pressing need for ambitious, long-term collaborations between basic and clinical scientists.

WHAT IS THE CORE DEFINITION OF ALS AND WHAT DOES THAT TELL US ABOUT PATHOGENESIS?

The molecular pathology of ALS indicates common pathways and generic mechanisms, despite a wide range of genotypes and phenotypes. According to the El Escorial Criteria, 'Proven ALS' is defined by cellular pathology. This includes the presence of characteristic ubiquitin-immunoreactive (Ub-IR) inclusions in lower motor neurons (LMNs), now widely accepted as the definitive hallmark. However, Ub-IRs are consistently associated with p62 (and now TDP43) across the spectrum of sporadic and familial ALS. Where there is ALS, we find typical Ub-IR inclusions. Does this indicate that these protein aggregates are mechanistically involved? Is TDP43 telling us something fundamental about motor neuron degeneration? Both protein aggregation and disruption of splicing mechanisms are emerging as key themes in neurodegeneration, and targets for therapy.

WHAT DOES THE NATURAL HISTORY AND EPIDEMIOLOGY OF ALS TELL US ABOUT THE BIOLOGY OF THE DISEASE?

Through the landmark epidemiological studies of ALS undertaken here in Scotland and other population-based cohorts we know that incidence and prevalence are rather similar in Western countries. The only consistent risk factors are increasing age, male sex, and family history. Clearly, finding new ALS genes is of fundamental importance. But understanding the biological basis of prognosis (survival) in terms of phenotype in sporadic and familial ALS is crucial. As we move into the era of large scale genome wide association studies, careful definition of these and other phenotypes will be of great interest, and all samples will require (verifiable!) data on onset, survival and phenotype.

WHAT IS SELECTIVE VULNERABILITY IN RELATION TO ALS AND IS IT A USEFUL CONCEPT?

Maybe, but the notion that ALS is a 'pure' degeneration of upper motor neurons (UMNs) and LMNs is not tenable, and arguably too much attention has focused on the supposed 'Achilles heel' hypothesis. True, degeneration of LMNs is what shortens life, and anterior horn cells have some interesting susceptibilities to excitotoxin-mediated damage. But large neurons are easy to study compared to small neurons, and we found significant loss of GABAergic interneurons in extra-motor areas in ALS, and imaging and cognitive studies have amply confirmed that extra-motor involvement is the rule rather than exception, and not just as end-stage disease. In this context, the association between MND and dementia has been 'rediscovered' and in some series cognitive abnormalities have been detected in > 50% of patients. More rigorous and conservative approaches to cognitive evaluation are needed but there is no doubt that frontotemporal pathology is more common

than formerly appreciated, and that we are beginning to understand the genetic, cellular, molecular and clinical implications of these phenotypes. Interestingly, SOD1 Familial ALS (SOD1-FALS) subjects may be less likely to have cognitive changes than non-SOD-FALS cases, suggesting that the notion of a continuous spectrum of ALS through 'pure' motor neuron degeneration to frontotemporal lobar degeneration (FTLD) with ALS (FTLD-ALS) and FTLD without ALS, may be incorrect. Several gene loci are linked to ALS with FTLD but as yet the causative gene lesions are unknown. Almost always the underlying molecular pathology of frontotemporal involvement with MND is that of ubiquitin and TDP-43 immunoreactive (IR) intracytoplasmic (and in some familial forms, intranuclear) inclusions. The role of tau remains enigmatic. Despite the likely importance of altered tau in the Guam form of ALS, such cases show Ub- and TDP-43-IR inclusions in motor neurons, not tau-positive inclusions. Motor neurones do not 'do' abnormal tau, it seems, even in the rare cases of motor neurone degeneration associated with tau gene mutations.

WHAT INSIGHTS HAVE WE GAINED FROM GENETIC STUDIES AND WHAT HAVE GENETIC STUDIES TOLD US ABOUT THE CAUSES OF SPORADIC ALS?

Fourteen years has elapsed since the discovery of SOD1 gene mutations that account for ~20% of familial ALS cases, and 2–3% of apparently sporadic cases. Recently mutation in TDP43 have been identified in FALS and in some apparently sporadic cases, linking a striking pathological hallmark with causative mutations. Interestingly, TDP43-IR inclusions are absent or less common in SOD1 familial ALS (FALS) than in sporadic ALS (SALS) or non-SOD1-FALS. This (and the relative absence of cognitive change in SOD1-FALS compared to non-SOD1-FALS) urges caution in equating SOD1-ALS with SALS - although Don Cleveland has provided data implicating a common molecular signature for SOD1-FALS and SALS. This issue is of key importance for translational research, as is the concept of non-cell autonomous mechanisms of cell death. Activation of the innate inflammatory system is present in MND and neurodegenerative disorders, and glial cells seem to contribute significantly to the neuronal death process. Gene defects in other motor neuron disorders highlight altered transport of mitochondria as a possible mechanism underlying or contributing to axonal degeneration. Many other possible mechanisms are mooted but we may be moving closer to a consensus on the key mechanisms, although new genes, and new models, may upset these notions. From the clinical viewpoint, finding generic mechanisms that might be susceptible to treatment must be the priority. At present the 'best bets' probably include neuroinflammation, axonal transport and energy (mitochondrial) defects, protein aggregation, intracellular trafficking changes, and of course cell death mechanisms- and all are likely to be inter-related and inter-dependent. Meanwhile, the 16q FALS gene has been identified but is not yet published.

The major challenge, however, for the next decade is to identify the cause(s) of sporadic ALS. A start has been made in this direction with the first published genome wide association studies. At present, we cannot be sure that any of the published associations are definitely related to risk or causation. Hopefully we have learnt some lessons – chiefly the requirement for large well characterised samples with replication samples in-built, and stringent statistical analysis.

WHAT HAVE WE LEARNT FROM ALS TRIALS AND WHAT MIGHT BE KEY ELEMENTS OF A STRATEGY TO FIND EFFECTIVE THERAPIES?

Only one phase 3 trial (the riluzole study published in 1996) has been convincingly positive, with only a small effect on survival. Meta-analyses indicate that the effect was real, and that there may have been a small effect on function. Yet we still do not know how riluzole works. We do know through the NNIPPS (Neuroprotection and Natural History in Parkinson Plus Syndromes) trial that the effect on survival in ALS is not (alas) translated to PSP or MSA. So riluzole does not have a generic neuroprotective effect. We might conclude that we would be unwise to abandon survival as an arbiter of efficacy. Paradoxically, we should beware of equating survival with function in trials. They are related, of course, but the relationship is complex. ALS patients (and thus functional measures of deterioration) are very susceptible to adverse drug effects. A recent example may be the North American minocycline trial – maximum tolerated dose may not be the best option for neuroprotection. The selection of agents for trials has been idiosyncratic, and (inevitably, given our ignorance of mechanisms) determined more by the enthusiasm or bias of particular investigators or companies than rational processes. Perhaps more rigorous criteria for moving from cellular and animal models to man might be agreed to avoid time-wasting studies. We urgently need a new approach to phase 2 studies that includes dose finding. Normally this relies on functional measures that have high variance and are relatively insensitive to change. Ideally, we need to identify biomarkers that will indicate whether the supposed target has been modified. Examples would include inflammatory markers as indicators of the actions of minocycline and other putative anti-inflammatory agents, and proteomic or metabonomic markers of cell damage. Most likely, CSF analyses will be required. New imaging techniques may contribute.

I believe that we are on the threshold of new phase in ALS research. Understanding of the mechanisms of SOD1 ALS may at last be crystallising into more focused hypotheses, and treatments are being developed to modify this form of the disease. New ALS genes have been identified, and the prospects for success in sporadic ALS through genome wide association studies – although far from certain– are encouraging. Biomarker work is taking off, and even imaging may catch up with mechanisms in the next decade. We must have tools to study the human brain in life, and to develop an effective experimental medicine approach to neurodegenerative disorders if we are to integrate laboratory science with clinical practice to find effective treatments.

Acknowledgements

The King's MND Care and Research Centre is supported by the MND Association and by King's College London and King's College Hospital NHS Foundation Trust. PNL has received research grant support from the MRC, Wellcome Trust, ALS Association (ALSA), UK Department of Health, MND Association, and Tim Perkins family (MND Research Fund).

In the last 5 years PNL has held consultancies with and/or has received research grants in relation to clinical trials from Sanofi-Aventis, GlaxoSmithKline, ONO Pharma, Novartis, Exonhit, Teva, Trophos, Oxford Biomedica, and Evotec.

FUNCTIONAL MRI IN ALS: WHAT HAVE WE LEARNED?

B. Stanton, V. Williams, A. Simmons, P. N. Leigh
King's College London, Institute of Psychiatry, London, UK

BACKGROUND

Functional MRI has been widely used to study changes in motor and extra-motor pathways in ALS. Increased activation during motor execution has been consistently demonstrated, and hypothesised to reflect adaptive changes or damage to inhibitory pathways. However, differences in task difficulty for patient and control groups confounds the interpretation of these findings. We have performed a series of fMRI studies of motor execution and motor imagery to test specific hypotheses about the observed changes in cortical function in ALS.

HYPOTHESES

1. Patient with ALS show increased cortical activation during a motor task compared to both healthy controls and patients with muscle weakness due to peripheral lesions.

2. Patients with ALS show increased cortical activation during motor imagery compared with healthy controls.

3. fMRI demonstrates altered function of extra-motor regions in ALS.

METHODS

fMRI was used to measure activation during two block design paradigms contrasting execution and imagery of right hand movements against rest. Sixteen patients with ALS, seventeen healthy controls and nine patients with peripheral lesions took part in the study. The groups were matched for age and gender and the two patient groups were matched for their degree of upper limb weakness. Analysis used a non-parametric approach to perform hypothesis-driven comparisons between the groups.

RESULTS

During the motor execution task, patients with ALS showed increased cortical activation bilaterally (extending from the sensorimotor cortex posteriorly into the inferior parietal lobule and inferiorly to the superior temporal gyrus) when compared to peripheral lesion patients and controls. In addition, ALS patients showed reduced activation in the dorsolateral pre-frontal cortex (DLPFC) extending to anterior and medial frontal cortex.

Contrary to our hypothesis, patients with ALS showed reduced activation during the motor imagery task in the left inferior parietal lobule and in the anterior cingulate gyrus and medial pre-frontal cortex.

CONCLUSIONS

The findings of the motor execution study suggest that increased activation during motor tasks in ALS does not reflect confounding by task difficulty or a non-specific adaptation to chronic weakness, but is likely to be specifically related to upper motor neuron pathology in ALS. The contrasting reduction in cortical activation during motor imagery may reflect the disruption of normal motor imagery networks by ALS pathology outside the primary motor cortex. Our experience in ALS may have wider implications for the use of fMRI as a tool to study the pathophysiology of neurodegenerative disorders.

PATHOPHYSIOLOGY OF ALS INSIGHTS FROM DTI

C. Blain[1], B. Stanton[1], V. Williams[1], D. Shinhmar[1], S. Brunton[1], A. Leemans[2], D. Jones[2], A. Simmons[1], P. N. Leigh[1]

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[2] CUBRIC School of Psychology, Cardiff University, Cardiff, UK

BACKGROUND

The majority of ALS cases are regarded as sporadic, although it is recognized that complex genetic factors may be involved. In sporadic ALS (sALS) there is heterogeneity in the distribution of motor and extra-motor damage within the brain and rate of disease progression. Patients homozygous for the D90A SOD-1 mutation (homD90A ALS) have a stereotyped phenotype, causing them to be uniquely suited to studying genotype/phenotype interactions in ALS. Diffusion tensor MRI (DTI) allows quantification of axonal damage within cerebral white matter tracts, providing a method of studying the pathophysiology of ALS in vivo. Using DTI we investigated differences in axonal damage between sALS and ALS patients with the homD90A mutation.

HYPOTHESES

1. On whole brain DTI analysis, sALS patients would show more widespread axonal damage (particularly extra motor), than homD90A ALS patients.
2. Diffusion tensor tractography (DTT) would demonstrate more severe damage to the intracranial portion of the corticospinal tract in the sALS patients than the genetic group.
3. Correlations would be demonstrated between diffusion measures and clinical scores.

METHODS

Seven homD90A ALS patients, 21 sALS patients and 21 healthy controls underwent whole head DTI (1.5 Tesla). Voxel based analyses were performed comparing FA across the whole brain between the three groups. Using DTT, the corticospinal tracts were dissected out bilaterally, allowing FA and MD to be calculated along their entire length. Diffusion measures were related to disease duration and scores of disease severity.

RESULTS

In the whole brain analyses, homD90A ALS patients showed less widespread degeneration of both motor and extra-motor pathways than those with sALS, despite similar disease severity. In addition DTT revealed significantly greater damage to the intracranial portion of the corticospinal tract in sALS patients compared to HomD90A ALS patients. In both these studies, diffusion measures were correlated with the degree of upper motor neuron involvement assessed clinically and with overall disease severity.

CONCLUSIONS

DTI can be used to investigate and quantify in vivo differences in the patterns and extent of motor and extra-motor intracerebral axonal damage in sporadic and genetic forms of ALS. Our results indicate that genotype influences the distribution of cerebral pathology in ALS.

IS THE MOTOR CORTEX HYPEREXCITABLE IN MOTOR NEURON DISEASE – A STUDY USING PHARMACOLOGICAL fMRI

S. Azam[1], B. Koritnik[3], M. Mehta[2], S. C. R. Williams[2], P. N. Leigh[1]
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[3] Institute of Clinical Neurophysiology, University Medical Centre Ljubljana, Ljubljana, Slovenia

BACKGROUND

In motor neuron disease (MND) functional studies have shown altered intracortical inhibition and excitation. Excess glutamate induced corticomotor excitability has been proposed as a possible mechanism for this imbalance. More recent anatomical studies showing a global loss of GABAergic interneurones and an alteration in the GABAA receptor mRNA expression pattern in pyramidal cells have highlighted that GABAergic mediated inhibition may also play an important role in the pathophysiology of MND. Midazolam (MZ), a selective GABAA agonist allows us to probe the functional status of post-synaptic GABAA receptors, allowing us to investigate the role of the GABAergic system in MND. Increased motor effort in MND patients, and subsequent cortical reorganisation as an adaptive phenomenon where greater effort is exerted in carrying out a motor task may explain some of the altered cortical activation. Therefore in this study we have examined the effects of MZ on motor task activation, controlling for effort.

METHODS

Using functional imaging (fMRI) we studied 12 patients with MND as defined by the El-Escorial Criteria of definite, probable or possible MND and two control groups: 12 healthy volunteers (HV), and 12 patients with multifocal motor neuropathy (MMN) matched for weakness with the MND group. A visually paced motor task was performed, requiring responses of 5%, 10%, 20% and 30% of maximum grip strength thereby controlling for effort. Subjects were scanned while they received an intravenous challenge of normal saline and on a separate visit an infusion of MZ. Image pre-processing and statistical analysis were carried out using SPM5. Regions of interest (ROI) were defined to extract representative data for the contralateral motor cortex, ipsilateral cerebellum and bilateral subcortical areas.

RESULTS

BOLD signal changes in cortical and subcortical motor networks during motor task under control conditions were comparable between all groups. In contrast to previous studies, we did not see a greater increase in BOLD signal in the cortex of MND patients compared to HV. Following MZ, direct group comparisons revealed a decreased BOLD response in the contaralateral motor cortex (sensorimotor, premotor and supplementary motor areas) in HV, but not MND or MMN. In contrast, after MZ, the BOLD response was increased in the putamen of all groups.

CONCLUSION

The use of a graded motor task matched to individual maximum grip strengths may be a more precise way of providing comparable data on cortical activation between groups in whom motor effort can play an important role in observed results. Suppression of BOLD signal in the motor cortex of HV is likely to be a direct result of post-synaptic GABAA receptor mediated inhibition or due to an indirect reduction of glutamatergic output from the motor cortex. The increase in BOLD signal in the subcortical areas following MZ in all three groups may reflect a compensatory response from parallel motor loops when the task is made more "difficult". The lack of cortical BOLD signal suppression following MZ in the MND group and in the MMN group who have importantly been matched for weakness, may reflect further compensatory changes due to increased motor effort. In the MND group this means that during a motor task GABAA receptor mediated effects seen are likely to be a compensatory response to effort.

SENSORY NEUROPATHY IN ALS – SYNDROMIC OR CO-INCIDENTAL?

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[4] National Hospital for Neurology and Neurosurgery, London, UK

Although an increasing body of evidence suggest that ALS is a multi-system neurodegenerative disorder, sensory involvement is still thought not to be a significant feature of the disease. In our cohort of over 1000 patients with ALS we have identified five who had clinical and/or neurophysiological evidence of sensory neuropathy. Sensory nerve biopsy of three cases demonstrated mild or moderate loss of larger myelinated fibres, some reduction in myelin and in two cases, regeneration clusters. These findings are in accord with clinical, neurophysiological, pathological and animal studies suggesting that peripheral sensory neuronopathy and/or axonopathy can occur in ALS and may be relatively common. Wider knowledge of this association might help avoid diagnostic delay or unnecessary treatment in a minority of ALS patients who present with sensory features.

SILENT PERIOD AND MOTOR EVOKED POTENTIALS – FINDINGS IN ALS

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Amyotrophic lateral sclerosis (ALS) is degenerative disease involving in various forms central and peripheral motoneurons. Pyramidal tract – or otherwise lesion of central motoneuron, can be investigated using Motor evoked potentials (MEP). Silent period (SP) in MEP represents function of descendent inhibitory spinal tract and cortical inhibitory interneurons.

In our group of 46 patients with ALS we investigated MEP and SP in upper and lower extremities in the time of assessment of diagnosis. We used machines Magstim 200 and Medelec Synergy.

In our ALS group we noticed variability of thresholds for cortical stimulation, sometimes absence of evoked cortical potentials. Silent period were absent in 21% of ALS patients on upper extremities and in 36% patients on lower extremities.

Acknowledgement

This study was supported by grant IGA MZ CR NR/8491-4.

REPETITIVE NERVE STIMULATION IN A PATIENT WITH ALS – A CASE REPORT

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Lower content of acetylcholine in reinnervated nerve endings is a possible reason for decremental responses to repetitive nerve stimulation in patients with amyotrophic lateral sclerosis. Electrophysiological features suggesting other disease processes should be considered when the decrement on repetitive stimulation exceeds 20% on repetitive stimulation.

We present a patient with fluctuating muscle weakness increased by exertion of facial muscles, in which maximal decrement on repetitive nerve stimulation was 45%. By pharmacological and immunological testing, myasthenia gravis was not confirmed.

At the beginning, after detailed clinical investigations and neurophysiological testing, multifocal motor neuropathy was suspected, and because of that the patient was treated by humane immunoglobulins. Clinical deterioration after the treatment and appearing of pathological reflexes reflecting corticospinal tract degeneration suggested the diagnosis of amyotrophic lateral sclerosis.

COGNITIVE CHANGE IN ALS

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Amyotrophic lateral sclerosis (ALS) was traditionally believed to spare cognitive functions, but is now known to involve a range of cognitive impairments suggesting that ALS is a multisystem neurodegenerative disorder. Cognitive and behavioural symptoms have been described for over a century, and there is evidence that ALS and frontotemporal dementia (FTD) overlap. Although there is a clear link between some forms of ALS and FTD, the prevalence and characterization of mild cognitive dysfunction in classic ALS still remain unclear. Cognitive impairment occurs in sporadic and familial forms of ALS; Patients may present with cognitive deficits before, after, or at the onset of motor neuron disease. The most consistently reported cognitive changes in ALS relate to dysfunction in components of the executive system whereas abnormalities in language and memory are rare but increasingly reported. Neuroimaging studies have also shown extra-motor cortical degeneration corresponding to levels of frontal executive impairment on neuropsychological testing. The purpose of this talk is to review the evidence on cognitive deficits in ALS. The potential clinical and theoretical implications of cognitive impairment in non-demented ALS patients will be also discussed. Understanding of this condition will lead to better care for patients and provide valuable insights into the pathogenesis of neurodegeneration.

EXECUTIVE DYSFUNCTION IN ALS

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BACKGROUND

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease that has sporadic and inherited forms. Cognitive and behavioural symptoms have been described for over a century. Cognitive decline in ALS is characterised by personality change, irritability, obsessions, poor insight, and pervasive deficits in frontal executive tests.

OBJECTIVE

To investigate the profile of cognitive impairment in patients with ALS.

METHODS

Forty-nine ALS patients and 25 healthy controls underwent a comprehensive neuropsychological assessment including: Mini Mental State test; Raven Progressive Matrices Letter Fluency Test; Category Fluency Test (Animal Naming Test); Boston Naming Test; Cambridge Automated Neuropsychological Battery (CANTAB). The affective status was estimated with Apathy scale and Hamilton Rating Scale For Depression (HDRS).

RESULTS

The most striking impairment was found on tests of verbal fluency– indicating executive dysfunction. Also, the significant difference was shown on Boston Naming Test, as sign of deficit in spontaneous confrontation naming. The difference among groups found on tests of Spatial Work Memory (strategy score) ($p < 0.05$) and on Stockings of Cambridge (initial thinking time) ($p < 0.01$) indicates deficits in planning, attention and working memory. Behavioural changes, especially on apathy scale was found ($p < 0.01$). There was significant difference on HDRS, but according to DSM IV criteria, none of the patients fulfilled the diagnosis of depression.

CONCLUSIONS

Understanding of cognitive impairment in ALS will improve care for patients and their families and provide valuable insights into the pathogenesis of neurodegeneration.

EXECUTIVE ABILITY AND DAILY LIVING PERFORMANCE IN PATIENTS WITH ALS

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Amyotrophic lateral sclerosis (ALS) was traditionally thought to affect solely the lower and upper motor neurons. Recent studies suggest that the pathogenic processes of ALS are more extensive, involving a wider dysfunction of cortical grey and white matter with clinical correlates in the impairment of cognitive abilities. Cognitive deterioration has until recently been associated almost exclusively with a subgroup of 3–5% of ALS patients with frontotemporal dementia. However, a number of latest neuropsychological investigations demonstrated selective impairments of the executive and memory functions in nondemented ALS patients (25–75%). The relevance of these results for everyday life, however, still remains in question, thus demonstrating the need for the development and use of an ecologically valid test (1).

The purpose of this preliminary study was to assess the prevalence of cognitive dysfunction in ALS and also dysfunction's impact on patients' daily activities. We evaluated 16 patients with ALS, according to El-Escorial Criteria of "possible", "probable" or "definite" ALS, and with a mean age of M = 59.6 (SD = 7.3) on a battery of standardized neuropsychological tests as well as a specially designed and ecologically valid test of executive functions called Medication Scheduling task – MST (2). With MST, patients are asked to coordinate multiple rules in order to create a safe daily schedule of medications.

Both, standardized neuropsychological measures as well as the ecologically valid measure of executive functions, revealed important deficits in cognitive performance of ALS patients. Using the cut-off value of the 15th percentile to mark the deficient activity (3), we found that most patients demonstrated the same kind of impaired activity, i.e. placing incorrectly the pills to the medical schedule and neglecting to follow the rules while executing the MST task. The MST task's high demand for cognitive control, including the ability to coordinate multiple tasks and/or multiple sources of information, the application of strategies to a novel problem and the ability to monitor incoming information for relevance to the task at hand, seems to present great difficulties to patients with ALS and could possibly interfere with the planning and executing of their daily activities. Further explorations of patients' daily living performance are needed. Knowing whether or not an ALS patient has cognitive impairment brings up important considerations regarding the management of the patients, including a higher degree of involvement and supervision on the part of their caretakers.

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ALS AND FTLD: COGNITIVE CHANGES AND GENETIC MARKERS

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BACKGROUND

Amyotrophic lateral sclerosis (ALS) may be accompanied by cognitive impairment; when present, it is mainly in the form of frontotemporal impairment. Frontotemporal lobar degeneration (FTLD) is a focal, non-Alzheimer form of dementia, clinically characterized as either behavioral or aphasic variants (1). The overlap between dementia and ALS is demonstrated by the presence of cognitive, behavioural, executive dysfunction and change of personality in up to 50% of ALS patients (2). Behavioural features are mostly due to changes in serotoninergic and catecholaminergic system (3).

OBJECTIVE

To identify genetic correlates of cognitive changes with the emphasis on executive function in ALS patients.

MATERIALS AND METHODS

In a prospective study, two tests of executive functions (Controlled oral word association – FAS test; Tower of London (TOL)), were applied on 16 ALS patients (10 male, 60.5 ± 5.8 years), as defined by El Escorial Criteria. All subjects also completed the Dementia Rating Scale II (DRS-II). 1021 C/T polymorphism of DBH gene, 102 C/T polymorphism of 5-HT2A receptor gene, val66met polymorphism of COMT gene and val 158/108met polymorphism of BDNF gene were correlated with a cognitive tests.

RESULTS

ALS patients carrying GG, GA and AA genotype of the BDNF gene polymorphism were 73%, 20% and 7%, respectively. The frequency of GG, GA, AA genotype for COMT gene polymorphism was 33%, 53% and 14%, respectively. The DBH gene polymorphism distribution was 47%, 47% and 6% for CC, CT and TT genotype, respectively. The frequency of CC, CT, TT genotype for 5-HT2A gene polymorphism was 30%, 60% and 10%, respectively. 57% of patients showed deficient word generation capability. 21% of patients were impaired on TOL Total move score and 33% of patients on TOL Total rules violation score. 40% of patients were impaired at DRS II Conceptualization subtest and 20% of patients on DRS-II Memory subtest. No significant ($p>0.05$) relationship between genes polymorphism and variables of executive functional tests was found (4).

CONCLUSIONS

The preliminary findings reveal a tendency for executive deficit in ALS. There is a potential genotype-specific influence in ALS for executive functions. Further studies on a larger sample, however, are needed in order to confirm it.

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ASSESSMENT OF RESPIRATORY MUSCLE STRENGTH

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The respiratory muscles are an important part of the respiratory system. Normal respiratory muscle function is needed for sufficient ventilation. Weakness of the respiratory muscles eventually results in respiratory failure. Tests of respiratory muscle strength, in particular the diaphragm, are therefore an integral part of the approach towards patients with motor neuron disease.

There are various tests of respiratory muscle strength that have different advantages. The most useful assessment starts with noninvasive estimations. Tests of general inspiratory muscle strength are maximum inspiratory pressures (PImax), measured with a mouth-occlusion technique, and sniff nasal pressure (Sniff Pnasal). Such tests are easy to perform and high results exclude severe inspiratory weakness. However, low results in volitional tests do not necessarily confirm weakness, but might be caused by poor effort. The measurement of sniff oesophageal pressure (Sniff Poes) is more invasive and is measured with an oesophageal balloon catheter. It is more precise than Sniff Pnasal measurements. Usually Sniff Pnasal should be within 90–100% of Sniff Poes, but, if the nose is blocked, the pressures are lower. More specific for diaphragmatic strength evaluation is the measurement of transdiaphragmatic pressure (Sniff Pdi). For such measurement, a gastric balloon catheter is needed in addition to an oesophageal balloon catheter. Sniff Pdi is the difference between gastric and oesophageal pressure and therefore exclusively measures the gradient across the diaphragm. However, all these manoeuvres are volitional and only high values can exclude weakness, low values do not necessarily confirm it. Out of a group of 39 patients with a clinical diagnosis of unilateral diaphragm paralysis (UDP) we found that only 17 had the diagnosis confirmed by specific diaphragm tests while the 22 had either no weakness at all or bilateral diaphragmatic involvement (1). Nonvolitional tests of diaphragm strength are therefore useful. Magnetic stimulation of the phrenic nerves with the simultaneous measurement of transdiaphragmatic pressure (Pdi) allows the function of each hemidiaphragm to be tested independently of patient effort. The phrenic nerve can be stimulated (twitch Pdi), using anterolateral (bilateral or unilateral), cervical (bilateral) or anterior (bilateral) approaches. Such techniques are helpful in the diagnosis of unilateral or bilateral diaphragm weakness in sedated or ventilated patients on the intensive care unit. However, the measurement of twitch Pdi requires expensive equipment and appropriate expertise. A combination of tests to increase diagnostic precision can help to support or revise a diagnosis of muscle weakness. For example the combination of the two noninvasive tests PImax and Sniff Pnasal increases the accuracy of diagnosing inspiratory muscle weakness (2).

Which test should be used depends on clinical circumstances. Respiratory muscle strength in patients with motor neuron disease (3) is an important predictor of ventilatory failure and should therefore be an integral part of the clinical assessment.

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ROLE OF POLYSOMNOGRAPHY IN ASSESSMENT OF NONINVASIVE VENTILATION IN ALS PATIENTS

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INTRODUCTION

Respiratory weakness in patients with ALS causes dyspnoea and orthopnea, but can also present only with symptoms of nocturnal hypoventilation (1, 2, 3). Clinical symptoms and signs along with pulmonary function tests may not be sensitive enough (forced vital capacity) or not in routine assessment (sniff nasal pressure) to recommend starting noninvasive ventilation (1). As sleep disturbance may be one of the earliest signs of respiratory insufficiency in ALS patients the aim of our study was to perform the whole-night polysomnographic (PSG) recording to objectively asses the effectiveness of noninvasive ventilation on sleep.

METHODS

One hundred and twenty-four (n = 124) patients with ALS were followed in our ALS Center from October 2002 to July 2008. They were seen at regular 3 months intervals when symptoms and signs of respiratory insufficiency were searched for and forced vital capacity and/or arterial blood gases were measured. When the first symptoms or signs of respiratory insufficiency appeared the noninvasive respiration was discussed and PSG was recommended.

RESULTS

In 34 (27%) of our patients (38% with bulbar onset, 2 pts with family history of ALS) overnight PSG was performed. In 20 patients sleep architecture was disrupted together with night hypoventilation and the use of noninvasive ventilation was indicated. 19 patients accepted BiPAP and underwent the second overnight PSG using the noninvasive ventilation (mean time from diagnosis to noninvasive ventilation was 32 months in pts with spinal and 28 months in pts with bulbar form). However only 7 patients (5.6% (5 pts with bulbar and 2 pts with spinal form)) tolerated the BiPAP well and used it on a regular basis (more than 4 hours per night). In these patients (n = 7) better sleep architecture with more slow wave sleep (27 ± 0.02 min/52 ± 0.02 min (p = 0.07)) and longer REM sleep (10 ± 0.00 min /33 ± 0.01 min (p = 0.002)) with less night oxygen desaturation (mean SaO_2 (91 ± 0.03%/94 ± 0.01% (p = 0.02)) were found. Patients using BiPAP also reported better sleep quality and less daytime sleepiness.

CONCLUSION

PSG objectively shows disruption of sleep architecture as one of the earliest signs of respiratory insufficiency in ALS patients. It may help in identification of early respiratory impairment and assess effectiveness of noninvasive ventilation therapy.

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SYMPTOMS OF RESPIRATORY FUNCTION INSUFFICIENCY AND ARTERIAL BLOOD GASES ANALYSIS AS PROGNOSTIC INDICATORS IN ALS

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INTRODUCTION

Many patients with amyotrophic lateral sclerosis (ALS) develop symptoms of respiratory insufficiency during the time of the disease and for the majority respiratory failure is the cause of the death (1). We were interested in usefulness of symptoms of respiratory insufficiency and/or abnormal results of the daytime arterial gas analyses as indicators (AGA) for initiation of non-invasive mechanical ventilation (NIV) and if they are predictive for survival.

METHODS

Clinical and laboratory data of 82 patients with ALS, who were followed by our ALS clinic since October 2002 and died before July 2008, were analyzed retrospectively. Patients were regularly followed at 3-month intervals. We questioned them about the symptoms of respiratory insufficiency (dyspnoea, orthopnoea, morning headaches, nightmares, disturbed sleep), and performed arterial gases analyses. The last AGA was on average performed 65 days before death (range: 1–702 days, SD 130). Patients with respiratory infections or lung disease were excluded from study.

RESULTS

Mean age at the disease onset was on average 70 years (SD 11). Fifty-three patients reported symptoms of respiratory insufficiency which started 23 months after the disease onset (range 0–108 months, SD 22) and died on average 9 months later (SD 9). These patients had slightly longer survival (29 months from the disease onset (SD 21)) compared to those without respiratory problems (mean 25 months, SD 14), but the difference was not significant ($t = 0.89$, $p = 0.38$). Thirteen symptomatic patients and/or those with increased p_{CO_2} saturation underwent a NIV trial but only seven of them used it for at least 4 hours per night (good compliance). They, on average, survived for 312 days (range 52–485 days, SD 150) after the onset of respiratory insufficiency. Those who did not comply with NIV, survived for 258 days (range 3–1347, SD 279). The difference was not significant ($t = 0.50$, $p = 0.62$). At least two arterial gas analyses were performed in 48 patients. Only 48%, 67% and 27% of patients had abnormal p_{CO_2}, p_{O_2} and oxygen saturation, respectively, at any time of the disease course. Symptoms of respiratory insufficiency most commonly preceded AGA abnormalities and much less frequently occurred concurrently or afterwards. AGA abnormalities could even not be detected at all. First abnormalities in p_{CO_2}, p_{O_2} and oxygen saturation were found 160, 297 and 108 days before death, respectively. NIV tolerant and intolerant patients had similar survival (143 compared to 150 days on average) when measured from the first abnormal p_{CO_2} result. Similar non-significant differences were found also, when low p_{O_2} values and oxygen desaturation were used as starting point of survival measurements. Mean age at the disease onset was at 70 years (SD 11).

CONCLUSION

In our small group of patients, the occurrence of symptoms of respiratory insufficiency and arterial gases abnormalities did not affect survival and are therefore unlikely to be useful as only indicators for NIV initiation.

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SUPPORTING ALS PATIENTS USING NONINVASIVE VENTILATION

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For patients with ALS who develop breathing difficulties the decision to consider noninvasive ventilation can pose additional difficulties and dilemmas.

There has been an increase in the numbers of patients wishing to consider ventilatory support. Evidence that it improves quality of life and in some cases prolongs survival is growing.

Improvements in technology, and a greater awareness of the benefits of noninvasive ventilation, have increased the number of patients wishing to access ventilatory support. As the symptoms of ALS progress, complex symptom management is essential alongside ventilatory support in order to maximise the quality of life for the patient.

This session is based on my experience in supporting patients, their carers and the professionals involved throughout the course of the disease, including monitoring for breathing difficulties, information giving, helping with decision making, symptom management and supporting patients until the end of life.

MANAGEMENT OF RESPIRATORY FAILURE AND DYSPHAGIA IN ALS PATIENTS

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INTRODUCTION

Symptomatic treatment primarily based on noninvasive ventilation (NIV) and percutaneous endoscopic gastrostomy (PEG) provides longer survival and better quality of life of ALS patients.

AIM

To determine frequency of PEG placement and/or NIV in ALS patients and their influence on duration of ALS.

METHODS

A total of 242 (91 female and 151 male) ALS patients were initially diagnosed between 2003 and 2007 at the Institute of Neurology in Belgrade, Serbia. Sixty five had a bulbar and 177 had a spinal onset of the disease. Among them, a group of 31 (16 female and 15 male) patients, 16 with spinal and 15 with bulbar onset, was formed either with placed PEG or used NIV, due to dysphagia and/or respiratory insufficiency (FVC below 65%, $Pa_{CO2} > 6.0$ kPa).

RESULTS

From the group of 211 ALS patients 136 (64.5%) died during the period from 2003 till the end of 2007. In the same period, 21 (67.7%) died in the group of 31 patients with PEG and/or NIV. There was no statistically significant difference between these two groups in the mean duration of the disease. We also did not register the statistically significant difference in the mean duration of the disease between the group of ALS patients with PEG (3.25 ± 0.52 years) and the group without PEG (3.71 ± 0.55 years). The mean duration of the disease was longer in the group of patients with PEG and/or NIV (4.2 ± 0.5 years) which was statistically significant in comparison with the group without PEG and/or NIV (3.0 ± 0.1 years, $p < 0.05$).

CONCLUSIONS

Only a small number of ALS patients in Serbia (12.8%) were with PEG and/or they used NIV. The results of this study show that much has to be done to prolong the life of our ALS patients improve their quality of life.

ELECTROMYOGRAPHY OF THE DIAPHRAGM AND PHRENIC NERVE CONDUCTION STUDIES IN PATIENTS WITH ALS

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In patients with restrictive ventilation failure of unknown aetiology neuromuscular disorders always need to be considered. In suspected lesions to the phrenic anterior horn neurons or motor axons or to the diaphragm electrodiagnostic investigation, including phrenic nerve conduction studies and needle examination of the diaphragm muscle, can be useful. Phrenic nerve conduction studies are usually done using a supramaximal (80–100 mA, 0.1–0.2 ms long) electrical stimulation applied by a surface electrodes in the supraclavicular fossa (just above the clavicle, between both heads of the sternocleidomastoid (SCM) muscle) (1), and with a pair of self adhesive recording electrodes on the thorax (the active electrode (G1): 5 cm above the xiphoid process, the reference electrode (G2): 16 cm from G1, on the chest margin (2)). Phrenic nerve M-wave parameters describing axonal loss (amplitude (mV), and area (mVms)), or demyelination (latency and duration and (ms)) can be measured. Needle examination of the diaphragm muscle is usually done by a standard concentric EMG needle inserted into the medial recess of the 7th, 8th or 9th intercostal space (3). During slow advancement of the needle electrode through the tissue EMG signal is carefully observed and listened. Rhythmic bursts of low amplitude MUPs during inspirations disclose that tip of the electrode reached the diaphragm (3). At that point EMG activity during normal breathing is observed. In addition, motor unit potential (MUP) parameters can be measured (quantitative MUP analysis), and compared to normative limits (1).

Respiratory electrodiagnostic studies are valuable also in patients with suspected ALS, because some of these patients present with respiratory insufficiency. Furthermore, respiratory failure limits the life span of these patients. However, in this population apart from lower motor neuron (at high cervical or thoracic levels) upper motor neuron involvement may cause of respiratory failure. Phrenic nerve conduction studies and needle examination of the diaphragm muscle, however, evaluate mainly only the lower motor neuron function. Low amplitude or area of the phrenic nerve M-wave point to few remaining functional diaphragm muscle fibres, and therefore to a advanced stage of the disease in the respiratory domain. The needle EMG studies may be of some prognostic value and aid in long-term planning of respiratory management in patients with ALS. Abundant spontaneous denervation activity with a decreased number of relatively normal-sized MUPs points to acute denervation and rapidly developing disease with poor reinnervation. In contrast, little spontaneous denervation activity with a decreased number of large MUPs indicates a more slowly progressive denervation and better reinervation. Respiratory electrodiagnostic findings need to be combined with electrodiagnostic findings obtained in other trunk and limb nerves and muscles to diagnose ALS.

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SNIFFING-RELATED CORTICAL MOTOR POTENTIALS IN ALS – A PRELIMINARY REPORT

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BACKGROUND

Respiratory insufficiency is by far the most frequent cause of death in amyotrophic lateral sclerosis (ALS). Neural control of breathing depends on a central drive to the respiratory muscles. Affection of the latter, which is in clinical setting most difficult to assess in isolation, may contribute to respiratory deficiency in ALS. A possible way to study the central mechanisms for the control of voluntary breathing is through different respiratory manoeuvres, e.g. sniffing and coughing. Movement-related cortical potentials (MRCPs) mainly reflect functioning of the supplementary, premotor and primary motor areas that are involved in sniffing as well.

OBJECTIVE

To determine whether MRCPs evoked by sniffing (sniffing-related cortical potentials – SRCPs) can serve as a useful marker of cortical respiratory drive dysfunction. We hypothesised that SRCP amplitude is reduced in ALS due to neuronal loss. We were also interested if sizes of SRCPs correlate with overall and specific respiratory functional scores and results of pulmonary function tests.

METHODS

Eight patients (48–75 years; 4 with definite and 4 with probable ALS according to El-Escorial criteria) and 10 healthy control subjects (21–26 years) were studied. None of the patients had symptoms or clinical signs of respiratory insufficiency. Both groups performed self-paced sniffing manoeuvre every 5–10 seconds, patients with 20% and controls with 30% of maximal sniff nasal inspiratory pressure. Onset of sniff nasal inspiratory pressure was used for back-averaging of electroencephalogram (10-10 system, 32 electrodes). MRCPs on right index finger flexion was used as a comparison. The maximum amplitudes of SRCPs and MRCPs as well as amplitudes at 500 ms and 100 ms before and at the time of sniff/finger flexion (0 ms) were measured. Grand average was calculated for each task. A three-way mixed ANOVA and Pearson's correlation coefficient were used for statistical analysis.

RESULTS

On grand average, MRCPs and SRCPs of ALS patients were larger compared to controls, but the differences were not statistically significant. No correlation was found between sizes of individual SRCP components' and age, overall and specific respiratory and upper limb subdivisions of Norris and ALS FSRr scores, and results of pulmonary function tests.

CONCLUSIONS

The findings are in contrast with our hypothesis. A tendency toward increased SRCPs and MRCPs may suggest that degeneration of upper and lower motor neurons in ALS is paralleled by processes that compensate for such loss. Plastic changes possibly involve recruitment into the response of additional generator cells within and adjacent to the motor cortical areas that are not called upon in physiologic circumstances (e.g. by reduction of neuronal cell inhibition). The drawbacks of our study are small number of patients that do not include those with clinically overt respiratory dysfunction, large interindividual variability of SRCPs, and non-matched control group.

INVESTIGATING THE CENTRAL CONTROL OF RESPIRATION IN ALS – A PILOT fMRI STUDY

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BACKGROUND

How the brain controls breathing is still not completely understood (1). In recent years, functional magnetic resonance imaging (fMRI) has been used to study voluntary breathing in healthy subjects (2). Respiratory failure due to progressive respiratory muscle weakness is the usual cause of death in ALS. Maximal sniff nasal pressure measurement was the single respiratory test combining linear decline, sensitivity in mild disease, and feasibility in advanced disease. Therefore it appears well suited to assess the decline of respiratory muscle strength, the risk of respiratory failure and to provide prognostic information in ALS patients (3). Upper motor neuron abnormalities could add to the respiratory dysfunction in ALS.

HYPOTHESES

We hypothesised that fMRI during sniffing would reveal sniffing-associated brain activation patterns both in healthy subjects and in ALS patients, and that ALS patients would show reduced cortical activation compared to healthy subjects.

METHODS

Six ALS patients and five healthy subjects were studied. Static inspiratory and expiratory mouth pressure and maximal sniff nasal pressure were measured. Imaging was performed on a 3T Siemens Trio scanner. In each subject, 221 functional scans were acquired. Nasal pressure and chest movements were measured during scanning. An event-related experimental design was used. A submaximal sniff manoeuvre was performed every 20 s. Image pre-processing and statistical analysis were done using the SPM5 software. A random effects group analysis was performed ($p < 0.01$ uncorrected).

RESULTS

A bilateral cortical and subcortical sensorimotor network was found to be activated during sniffing in both groups. Compared to healthy subjects, ALS patients showed reduced activation bilaterally in the prefrontal cortex, and to a lesser extent also in temporal and occipital lobes and cerebellum. Increased activation in ALS patients was found in left temporal lobe only.

CONCLUSIONS

Using fMRI during sniffing, it is possible to visualise the cortical sensorimotor network associated with voluntary control of breathing both in healthy subjects and in ALS patients. The reduced prefrontal activation suggests that a central neural component to the respiratory dysfunction could exist in ALS. Some clinical observations support this hypothesis (4). Reduced prefrontal activation was also described in ALS patients using fMRI during hand movements (5).

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TRANSLATIONAL RESEARCH IN ALS

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The need for new therapeutic, including pharmacological approaches for ALS/MND is undebated. However, in the past 10 years a number of experimentally promising therapeutics and candidate drugs met with failure in cost-intensive human clinical trials.

On first sight this experience is surprising since the field of ALS/MND seems to be well-prepared for translational research because a number of in vitro models and in vivo rodent models exist for anterior horn cell disease. Also, a priori, since the field of ALS/MND pioneers the field of neurodegenerative diseases with regard to translational medicine a number of new and unexpected experiences were unavoidable. Today, we have identified some major reasons which obviously played a negative rate for the success of translational medicine in ALS/MND in the past decade. If these problems are resolved, the path to more effective therapeutics seems to be more clearly defined than ever.

Which are the major insights which need to be given attention in the future?

1. Like the majority of neurodegenerative diseases ALS/MND was defined as a clinical-neuropathological syndrome by our forefathers. It is getting increasingly clear that this syndrome has multiple aetiologies, potentially not only genetic ones. Therefore, there is an urgent need for validation of the common aspects of the pathogenesis of selective motor neuron degeneration, independent from the various etiological factors ("target validation").
2. There is an urgent need to clarify recent results which seem to suggest that intervention could be stage-specific, in other words drugs for prevention of disease might differ from those influencing the course of the disease itself.
3. Preclinical experimental animal – in particular rodent – studies need rigorous methodological standardization, approaching the standards of human clinical trials.
4. The step from in vitro to in vivo studies is a major hurdle and far from being understood and standardized.
5. The step from experimental rodent studies to human candidate drugs requires additional expertise, in particular with regard to the development of biomarkers, mirroring the specific effect of the drug and the natural history of anterior horn cell disease.

To avoid major financial loss for the field, these issues need to be resolved in the forthcoming years to build the basis for successful translational research, including drug development in ALS/MND.

TDP-43 IN SPORADIC AND FAMILIAL ALS

B. Rogelj, J. Sreedharan, C. Vance, V. Tripathi, S. Ackerley, T. Hortobagy, C. E. Shaw
MRC Centre for Neurodegeneration Research, Department of Clinical Neuroscience, Institute of Psychiatry, King's College London, London, UK

For nearly 20 years the neuropathological hallmark of ALS has been polyubiquitinated skein-like and globular inclusions in the perikaryon and proximal axon of motor neurons in the brain stem and spinal cord. These have recently been shown to colocalise with a 25kDa, C-terminal, detergent-resistant fragment of TAR DNA binding protein TDP-43. These inclusions are present in ~90% of ALS cases and a subset of frontotemporal lobar degeneration cases now termed the "TDP-43 proteinopathies" (1–3). TDP-43 is predominantly a nuclear protein but in those neurons with the most striking cytoplasmic inclusions there is a marked reduction in nuclear TDP-43, suggesting that it has been sequestered in the cytoplasm and that miss-localisation may play a role in pathogenesis.

We have recently identified a TARDBP mutation (the gene encoding TDP-43) in a single familial ALS kindred (4). The mutation is predicted to result in a single amino-acid substitution of methionine for valine at residue 337. We also identified two sporadic MND missense mutations (Q331K and G293A) in neighbouring amino acids. The only two mutations studied showed increased tendency to protein cleavage and were toxic to the embryonic chick spinal cord neurons causing apoptosis and developmental delay.

Fourteen missense mutations have now been reported in familial and sporadic MND (3, 5–7). All but one of the mutations, reside in the C-terminal domain.

The finding of rare mutations in TARDBP in familial and sporadic ALS does implicate a mechanistic role for TDP-43 cleavage, mislocalisation and aggregation in ALS and FTD. These pathogenic mutations should provide important biological tools that will enable us to develop more informative cellular and animal models of ALS.

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CLINICAL CARE OF PATIENTS WITH ALS

A. Radunović
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Amyotrophic lateral sclerosis (ALS; motor neuron disease) is a well-delineated but nonetheless clinically and pathogenically heterogeneous syndrome. In most cases, ALS and its variants are easily recognised by neurologists but diagnostic errors occur in about 10 percent of patients and delays in the diagnostic process are common. Accurate and prompt diagnosis, sensitive communication of the diagnosis, close involvement of the patient and family, and an active, positive care plan are prerequisites of good management. A multidisciplinary approach to care may prolong survival and probably improves quality of life. Riluzole improves survival by a few months but has a marginal effect on the rate of functional deterioration whereas noninvasive ventilation both prolongs survival (often by many months) and improves or maintains quality of life.The role of palliative care, broadly defined, is likely to expan but the evidence for the effectiveness of some interventior (e.g., gastrostomy) is weak. The diagnosis, managemen and coping with impaired function and end-of-life will b discussed in the light of our own experience, expert opir ion, existing guidelines, and clinical trials. The presenta tion also highlights the need for research into the efficac of gastrostomy, factors influencing access to noninvasiv ventilation and palliative care, as well as communicatio in patients unable to speak or on long-term ventilatior and the impact of cognitive impairment on quality of lif of patients and care-givers. Finally, it also suggests tha the plethora of existing evidence-based guidelines shoul be distilled into a single internationally agreed guidelin of best practice.

MULTIDISCIPLINARY APPROACH IN ALS

E. Willey
King's MND Care & Research Centre, Institute of Psychiatry, London, UK

Although Amyotrophic Lateral Sclerosis (ALS) is currently incurable, it is not untreatable, and multi-disciplinary care has become an accepted cornerstone of management (1). Correct early diagnosis and introduction of palliative care and specific therapy can have a profound influence on the care and quality of life of the patient and may increase survival time (2). This is in contrast to the common misconception that in the absence of a cure 'nothing can be done'.

Involvement of the multi-disciplinary team in supporting patients diagnosed with ALS allows greater flexibility of response to patient needs and promotes individualised care, essential in a disease characterised by uncertain patterns of progression and deteriorating function. Interventions such as gastrostomy and noninvasive ventilation are used to palliate symptoms and require a network of healthcare professionals, social care and support groups, working in co-ordination to support clinical, educational and psychosocial needs of patients and carers (3). Timeliness of intervention can raise difficult practical and ethical questions about individual choice, quality of life and end of life decisions.

In the UK, MND care centres supported by the MND Association and a network of regional of multidisciplinary teams are established and work to promote and support the development of local care. Their effectiveness depends on excellent channels of communication, and a coherent philosophy of care (1). Health professionals in hospital and community settings face different challenges, and multi disciplinary team input may be identified as both a help and as a hindrance, depending on effective communication and acceptance of overlapping roles (4).

This talk will define the essential elements of multi-disciplinary care; discuss organisation and effective delivery drawing on experience from the model of care developed at King's MND Care & Research Centre. There are various models of care in existence depending on local history of service organisation, funding and patient population/ geography. Commitment to communication, collaboration and the nomination of a single point of contact or key worker is recommended good practice.

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REHABILITATION MEDICINE IN ALS

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that poses a myriad of clinical, personal and social problems. ALS is clinically manifested predominantly by upper motor neuron signs and symptoms in limb and trunk musculature like spasticity, central paresis, loss of dexterity, desinhibition of pathological reflexes; lower motor neuron signs and symptoms like atrophy, weakness, loss of tendon reflexes, lowered muscle tone, fasciculation; and bulbar signs and symptoms like dysarthria, dysphagia, siallorhoe, emotional lability,... Fatigue, dementia, pain, sleep disorders, depression or cachexia could contribute to severity of clinical picture in some patients with ALS. At the moment there is no causal treatment that would significantly change the prognosis of the patients with ALS. The disease course relentlessly progresses to respiratory compromise. Rehabilitation medicine (also in neurology) bases its interventions on disordered function ("lack of activity") in order to lessen the disability of the individual patient ("lack of participation"). According to International Classification of Functioning, Disability and Health (ICF, WHO) functioning and disability are viewed as a complex interaction between the health condition of the individual and the contextual factors of the environment as well as personal factors – "the person in his or her world". Rehabilitation principle treats these dimensions of health as interactive and dynamic in each patient with ALS. By doing so, rehabilitation team that consists of rehabilitation specialist or neurologist, physical and occupational therapists, speech language pathologists, dietitians, psychologists, social workers, rehabilitation nurses and case managers evaluates and treats loss of function due to motor, psychological and/or social consequences of ALS. The need for anticipation and for a quick response of the health system makes rehabilitation of patients with ALS specific. The main goals are to prolong independence, prevent complications and improve quality of life. Therefore, rehabilitation medicine offers active approach in addressing the disease, improves the quality of life and prolongs the survival in patients with ALS as part of complex multidisciplinary team management as a gold standard of today's management of patients with ALS.

PALLIATIVE CARE IN ALS

D. Oliver
Wisdom Hospice, Rochester, and University of Kent, Canterbury, UK

As there is at present no cure for ALS the treatment of the patient should be palliative care from the time of diagnosis (1). There is the need for a co-ordinated multidisciplinary approach. The various aspects of care should be considered:

- Physical
  There are many symptoms that may be suffered by the patient and careful assessment by the multidisciplinary team is essential (2):

Pain	73%
Dyspnoea	85%
Dysphagia	87%
Drooling	23%
Emotional lability	23%
Insomnia	50%
Constipation	53%

  Opioid medication can be helpful, when used appropriately, in the management of symptoms – in particular pain, dyspnoea and insomnia (3).

- Emotional concerns
  Patients with ALS may have fears of the diagnosis, disability, dependence and death and dying

- Family concerns
  There may be concerns within the family about the diagnosis, isolation, communication, finances, sexuality and death and dying.

- Spiritual aspects
  These may be expressed as "why me" or the deeper concerns and fears of dying and death. These aspects include religious issues but maybe wider than these issues alone.

- Terminal care
  As the patient deteriorates there is an increased need to assess and work together as a team to ensure that crises are anticipated, communication is encouraged between all involved – patient, family and professionals and other carers (4). This should also allow support of both the patient and family and the professional carers.

Symptoms need to be managed effectively and medication should be available for a crisis or sudden deterioration – in particular:
- Morphine for pain and distress
- Midazolam for sedation and muscle relaxation
- Glycopyrronium or Scopolamine for secretions and respiratory distress

The aim of palliative care for ALS is to reduce the effects of the disease and enable the patient and family to live as full a life as possible

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HOSPICE ALS PATIENT – A CASE STUDY

T. Žargi
Slovenian Hospice Association, Ljubljana, Slovenia

This case study is presenting importance to address an open truth based relation in the couple, reducing pressure and anger on both sides, and relations with health care professionals, protecting the patient's rights and dignity, respecting his will – how he doesn't wont to be treated – and understanding his personal needs trough the open dialogue, when coping with life threatening disease.

On suggestion of the Institute of Clinical Neurophysiology social worker, University Medical Centre Ljubljana, our Hospice started to follow for 10 months a 63 years old patient, after his wife called for our help. In May 2004 diagnosed ALS disease, two years later at Hospice introduction, the patient was hardly moving, unable to talk, using only one hand to communicate by his computer. Due to dysphaghia, PEG was placed for effective alimentation, but the patient prefers to take the food orally. Frequent salivation and the fear of suffocation during the night were great burden for him. The help from assisted ventilator was also refused. His wife took over all the difficult care by herself.

Living in a home setting with family – wife and two adult sons – he was trying to avoid any hospitalisation. For degradation of the patient, responsibilities and working pressure, his wife nearly burnt out. At that time family and the patient were convinced to win the battle with his illness, using several complementary and alternative methods and drugs.

Hospice team made a plan how to improve the primary care, and allow his wife to find some time for herself, therefore a Hospice nurse introduced other sources of care and 3 Hospice volunteers to stay with him almost every day during the week.

Reaching a deeper connection with the patient, our Spiritual Care professional, on his demand, a dialogue on life balance, euthanasia and his life values were addressed. Supporting his fears and difficult acceptance of complete control of his daily living and life decisions until the last days, he died peacefully at his home with his wife at bedside.

The family dynamic was guided by Family coordinator to acceptance and connection among all members, important for the patient. In collaboration with the Institute specialists, symptom management was sensitively followed by Hospice stuff, considering the patient consents.

Hospice goal was achieved creating the space for acceptance and peaceful dying, patient opening to his wife, surrounded by loving people and reaching the holistic healing, realising how dying is much more than a medical issue.

QUALITY OF LIFE AND DEPRESSION IN THE PATIENT-CAREGIVER SCENARIO IN ALS

A. Chiò
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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder of adult life, characterized by a progressive loss of motor function (upper and lower limb mobility, speech, swallowing, respiration). The progressive loss of independence that occurs as a result leads to an increasing need for help with every day life activities from informal or paid caregivers. Family caregivers are largely involved in this care, and bear an increased physical, psychological and emotional burden. Despite the severe impairment of physical function and the prospect of death, ALS patients have a relatively good 'existential' or 'personal' or 'individual' quality of life (QoL) and a low rate of depression throughout the whole course of the disease. Conversely, their caregivers show a progressive rise in depression and decline of QoL paralleling the increased subjective burden of care. Caregivers' burden of care is mostly related to personal and social restrictions and psychological and emotional problems. Coping strategies are different in ALS patients and caregivers, and these differences should be acknowledged by health professionals in planning support interventions. Respiratory problems have a particularly strong impact on the patient-caregiver couple, since mechanical ventilation causes a deep burden on caregivers, reducing their QoL, increasing their responsibilities related to managing the ventilator, and constituting an increased financial burden. From the moment of the first communication of diagnosis caregivers go through a grieving process; this grief needs to be addressed because it influences their well-being, increasing the risk of psychological and emotional disturbances, and compromising the care of their patients.

DEMOGRAPHIC AND PHENOTYPIC CHARACTERISATION OF OUR ALS PATIENTS

V. Zgonc, L. Dolenc Grošelj, B. Koritnik, L. Leonardis, S. Ristić-Kovačič, V. Štukovnik, I. Zidar, J. Zidar
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Knowledge of clinical and epidemiological data on ALS patients assist physicians to identify prognostic factors of the disease what helps patients and their relatives to schedule their activities during disease course.

Our aim was to analyse the available demographic and phenotypic disease characteristics from our ALS database that includes patients referred from October 2002 to July 2008.

We identified 124 patients (45% men, 55% women). Mean age at disease onset was 62 years (range 35–81, SD = 10 years), 63 years (SD = 10) in women and 61 years (SD = 11) in men. The disease started as spinal form in 58%, and as bulbar form in 27%. Fifteen percent of patients could not be unequivocally classified in either of these two categories. Four patients (3%) had familial form of the disease. According to El Escorial diagnostic criteria (EDC) at the time of first referral, 26% of patients had definite, 40% probable, 12% possible, and 22% suspicious form of ALS.

Walking problems in 77% of patients started on average 10 months after admission (range 0–96, SD = 17). Forty percent of them were unable to ambulate independently on average 25 months after admission (range 2–105, SD = 23). Twenty-eight percent of patients were unable to feed themselves, what on average happened 23 months after the diagnosis (range 5–69, SD = 16). Fifty-eight percent had speech problems that started on average after 11 months (range 0–102, SD = 19), 32% became anarthric (on average after 21 months, range 5–72, SD = 15). Swallowing problems had 62% of patients, on average 16 months (range 0–110, SD = 21) after disease onset and in 27% percutaneous endoscopic gastrostomy (PEG) was performed (on average after 25 months after making the diagnosis, range 5–96, SD = 21). Breathing problems that on average started 25 months after admission (range 2–108, SD = 24) had 52% of patients, and 11% opted for noninvasive ventilation, on average 30 months after the diagnosis was made (range 7–110, SD = 26) while only 2 patients were tracheotomised. Among most frequently used drugs were riluzole (36% of patients) and glycopyrrolate (22% of patients), both drugs being registered in Slovenia since 2005, followed by antidepressants (21% of patients) and quinidine (12% of patients).

Sixty-five percent of patients from our register had already died. The median survival time from symptom onset was 28 months (range 3–111, SD = 19) with the median age of death at 66 years (range 45–82, SD = 10). The median survival time after admission was 13 months (range 1–39, SD = 10). In those with PEG, the median survival time after this intervention was 7 months (range 0–23, SD = 7).

The survival curves for the following variables were calculated by Kaplan-Meier method and compared with the log-rank test. The hazard ratio was calculated for each variable. The variables were: male vs. female from the first symptom onset, male vs. female from the time of referral to our clinic, patients with bulbar vs. spinal forms of the disease, median delay between the symptom onset and time of diagnosis (less or more than 15 months), median age at the onset of first symptom (older and younger than 62 years), median grade of ALS Functional Rating Scale score at the time of referral (below and above 31 points), and median Norris ALS Disability Scale score at the time of referral (below and above 80 points). The significantly better survival was identified only for patients with longer diagnostic delay (over 15 months; log-rank chi square = 23.23, $p < 0.0001$, HR (95% CI) = 3.7) and in a younger age group (< 62 years at the time of the first symptom, log-rank chi square = 9.98, $p < 0.0016$, HR (95% CI) = 2.1).

Our database, that is regularly updated, was not designed to serve for the descriptive epidemiological studies and is insufficient in many other aspects as well. Its main aim was to support other possible clinical studies that nevertheless necessitate a prospective collection of separate sets of data.

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1986 Diagnostics in Neuromuscular Disorders
K.-G. Henriksson (*Linkøping, Sweden*): Muscle pain in neuromuscular disorders and primary fibromyalgia

1987 2nd Yugoslav Symposium on Neurourology and Urodynamics
J. K. Light (*Houston, Texas, U.S.A.*): Neurogenic bladder in patients with spinal cord injury

1988 Symposium on Quantitative Electromyography
E. Stålberg (*Uppsala, Sweden*): Electromyography – reflection of motor unit's physiology in health and disease

1989 Symposium on Sensory Encephalography
A. M. Halliday (*London, Great Britain*): The widening role of evoked potentials in clinical practice

1990 Symposium on Assessment of the Upper Motor Neuron Functions
A. M. Sherwood (*Houston, Texas, U.S.A.*): Brain motor control assessment

1991 Symposium on Neurophysiological Monitoring
V. Deletis (*New York, N.Y., U.S.A.*): Intraoperative monitoring of evoked potentials – current status and perspective

1992 International Symposium on Evaluation and Treatment of Severe Head Injury
E. Rumpl (*Klagenfurt, Austria*): Neurophysiological evaluation of severe head injury patients

1993 Symposium on Neurophysiological Evaluation of the Visual System
H. Ikeda (*London, Great Britain*): Mammalian retinal neurotransmitters – as seen through the eyes of a neurophysiologist

1994 Symposium on Extrapyramidal Disorders
J. Jankovic (*Houston, Texas, U.S.A.*): New horizons in dystonia
and
The First Lecture of the Slovene Basal Ganglia Club:
G. Stern (*London, Great Britain*): Amara lenta tempera risu

1995 Symposium on Multiple Sclerosis
W. I. McDonald (*London, Great Britain*): The clinical and pathological dynamics of multiple sclerosis

1996 Symposium on Update in Neurogenetics
L. P. Rowland (*New York, N.Y., U.S.A.*): Molecular genetics and clinical neurology

1997 Symposium on Cognitive Neuroscience
G. Barrett (*Farnborough, Great Britain*): Cognitive neurophysiology, a tool for studying the breakdown of mental processes

1998 9th European Congress of Clinical Neurophysiology, Ljubljana
J. Trontelj (*Ljubljana, Slovenia*): SFEMG – Sensitive optics in space and time

1999 Symposium on Electrophysiology of Hearing
A. Starr (*Irvine, California, U.S.A.*): Mysteries of the cochlea

2000 Symposium on Movement Disorders, "The Alpine Basal Ganglia Club"
A. J. Lees (*London, Great Britain*): The relevance of pleasure/reward dopamine circuits to Parkinson's disease

2001 EC-IFCN Ljubljana 2001 Regional EMG Refresher Course
E. Stålberg (*Uppsala, Sweden*): The role of conventional and advanced electromyography in clinical neurology

2002 International Symposium on Clinical and Electrophysiologic Diagnostics of Epilepsy
P. Chauvel (*Marseille, France*): High-resolution electroencephalography in clinical neurophysiology: applications to epilepsy and evoked potentials

2003 Symposium on Intraoperative Neurophysiology
V. E. Amassian (*New York, N.Y., U.S.A*): Essentials of neurophysiology of the motor system

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M. Billiard (*Montpellier, France*): Excessive daytime sleepiness: clinical impression versus final diagnosis

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2006 International Symposium on Spinal Cord Motor Control "From Denervated Muscles to Neurocontrol of Locomotion"
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2007 XVIth International SFEMG and QEMG Course and IXth Quantitative EMG Conference
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2008 Symposium on Amyotrophic Lateral Sclerosis
P. N. Leigh (*London, Great Britain*): ALS: Advances in the laboratory and in the clinic

INVITATION TO THE SYMPOSIUM 2009

Dear Colleague,

Neuropathic pain is increasingly gaining in importance in neurological and neurophysiological practice, especially so with growing possibilities of pharmacological treatment. The next year traditional Ljubljana autumn neuroscience meeting with the 25th Dr. Janez Faganel Memorial Lecture will take place on 9–10 October 2009, and will deal with clinical neurophysiology in investigation of pain, with special interest in neuropathic pain. I am pleased to announce that Professor Giorgio Cruccu from Rome, Italy, will give the Memorial Lecture with the title *Clinical Neurophysiology of Pain*.

Besides lectures, short communications are planned. Everybody with interest and experience in this field is cordially invited to actively participate in the meeting.

With best regards,

Zoran Rodi

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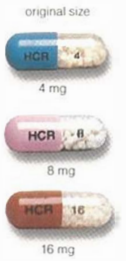

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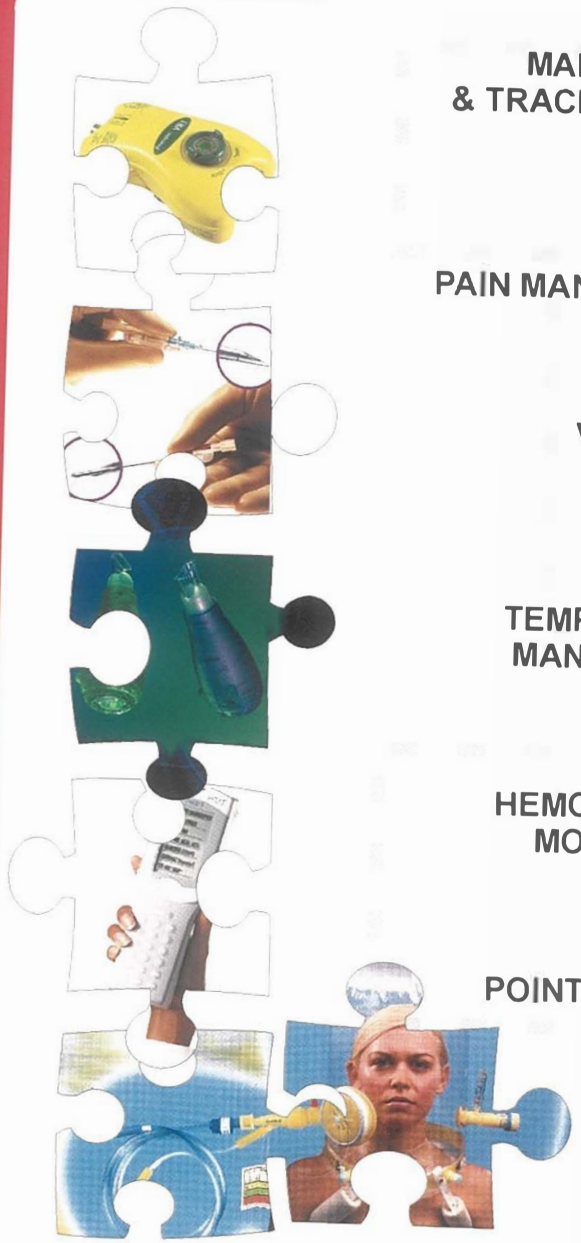


AIRWAY MANAGEMENT & TRACHEOSTOMY CARE

PAIN MANAGEMENT

VASCULAR ACCESS

TEMPERATURE MANAGEMENT

HEMODYNAMIC MONITORING

POINT OF CARE

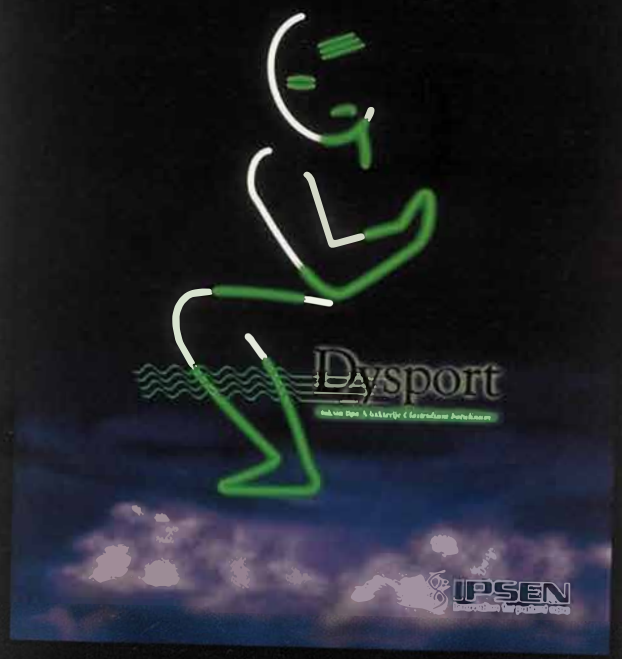
auremiana d.o.o. - Partizanska cesta 109 - 6210 SEŽANA Slovenija - +386 (0)5 7070 200 - +386 (0) 5 7070 210 - info@auremiana.com - www.auremiana.com

Dysport®

toksin tipa A bakterije Clostridium botulinum

Toksin botulin, tip A, periferni mišični relaksant za zdravljenje:

- Spazmodičnega tortikolisa
- Hemofacialnega spazma
- Blefarospazma
- Spastičnosti pri otroški cerebralni paralizi



PharmaSwiss
Choose More Life

Tulip®
atorvastatin

40 mg
film coated tablets

Tulip® atorvastatin, 10, 20 and 40 mg film coated tablets

Short Summary of Product Characteristics

THERAPEUTIC INDICATIONS: Hypercholesterolaemia: as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia, including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia, when response to diet and other nonpharmacological measures is inadequate. METHOD OF ADMINISTRATION: The usual starting dose is 10 mg once a day. The maximum dose is 80 mg once a day. Each daily dose of atorvastatin is given all at once and may be given at any time of day with or without food. CONTRAINDICATIONS: in patients with hypersensitivity to the active substance or to any of the excipients of this medication, with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal, with myopathy, during pregnancy, while breast-feeding, in women of child-bearing potential not using appropriate contraceptive measures. SPECIAL WARNINGS AND PRECAUTIONS FOR USE: *Liver effects:* Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of TULIP® is recommended. TULIP® should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. *Skeletal muscle effects:* Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated CPK levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION: The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics including erythromycin, azole antifungals, or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. Other interactions: nefazodone, HIV protease inhibitors, inducers of cytochrome P450 3A4 (e.g. rifampicin or phenytoin) , digoxin, oral contraceptives, colestipol, antacid , warfarin, phenazone, cimetidine. UNDESIRABLE EFFECTS: The most commonly expected adverse events are mainly gastrointestinal, including constipation, flatulence, dyspepsia, abdominal pain and usually ameliorate on continued treatment. Most common are: constipation, flatulence, dyspepsia, nausea, diarrhea, allergic reactions, insomnia, headache, dizziness, paraesthaesia, hypoesthesia, skin rash, pruritus, myalgia, arthralgia, asthenia, chest pain, back pain, peripheral oedema. NATURE AND CONTENTS OF CONTAINER: Blister packs containing 30 and 90 film-coated tablets containing 10, 20 or 40 mg of atorvastatin. MARKETING AUTHORISATION HOLDER: Lek farmacevtska družba d. d., Verovškova 57, Ljubljana, Slovenia. DATE OF REVISION OF THE TEXT: March 2007.
Full summary of product characteristics is available from Lek d. d.

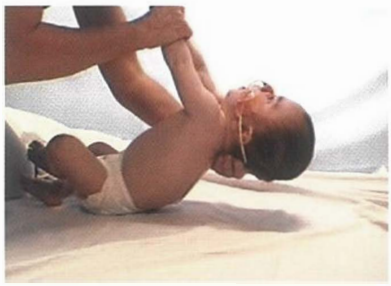
lek
a Sandoz company

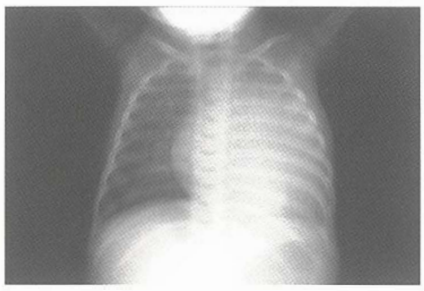
Lek Pharmaceuticals d.d., Verovškova 57, 1526 Ljubljana, Slovenia • www.lek.si

Early diagnosis of Pompe disease -
leads to better management

DO YOU RECOGNIZE SYMPTOMS OF POMPE DISEASE?

A progressive, multisystem, debilitating and often fatal muscular disease





Lisosomal enzyme deficiency (acid alpha-glucosidase) results in progressive glycogen accumulation that eventually may lead to irreversible muscle damage and ultimately death

SYMPTOMS OF POMPE DISEASE

Infantile onset

- Profound and rapidly progressive muscle weakness
- Hypotonia
- Floppy baby
- Head lag
- Delayed motor milestones
- Frequent respiratory infections
- Progression to respiratory insufficiency
- Marked cardiomegaly/cardiomyopathy
- Death due to cardiorespiratory failure

Late onset

- Progressive proximal muscle weakness (esp. trunk and lower limbs)
- Muscle pain
- Gait abnormalities
- Difficulty climbing stairs
- Frequent falls
- Scapular winging
- Respiratory failure/insufficiency
- Respiratory infections

Myozyme®
(alglucosidase alfa)

FIRST AND ONLY SPECIFIC TREATMENT FOR POMPE DISEASE

**Pompe disease -
the only congenital neuromuscular
disease with available treatment**

genzyme

Representative Office of Genzyme Europe B.V., Hektorovićeva 2/VI, Grand Centre, 10 000 Zagreb, Croatia

Torrex PHARMA Chiesi

People and ideas for innovation in healthcare

ATIMOS - formoterol

BUDIAIR - budezonid

CITALOPRAM TORREX - citalopram

CUROSURF - naravni fosfolipidi - poraktant α

FENTANYL TORREX - fentanil

FOSTER - beklometazon/formoterol

GABITRIL - tiagabin

INOTOP - dobutamin

ISOFLURAN - izofluran

MIDAZOLAM TORREX - midazolam

MOCLOBEMID TORREX - moklobemid

PAMITOR - pamidronska kislina

REVIA - naltrekson

SUFENTANIL TORREX - sufentanil

Torrex Chiesi Slovenija, d.o.o. Trdinova 4 1000 Ljubljana
T (01) 43 00 901 F (01) 43 00 900 E info@torrex-chiesi.com

Ugled je povezan z zaupanjem

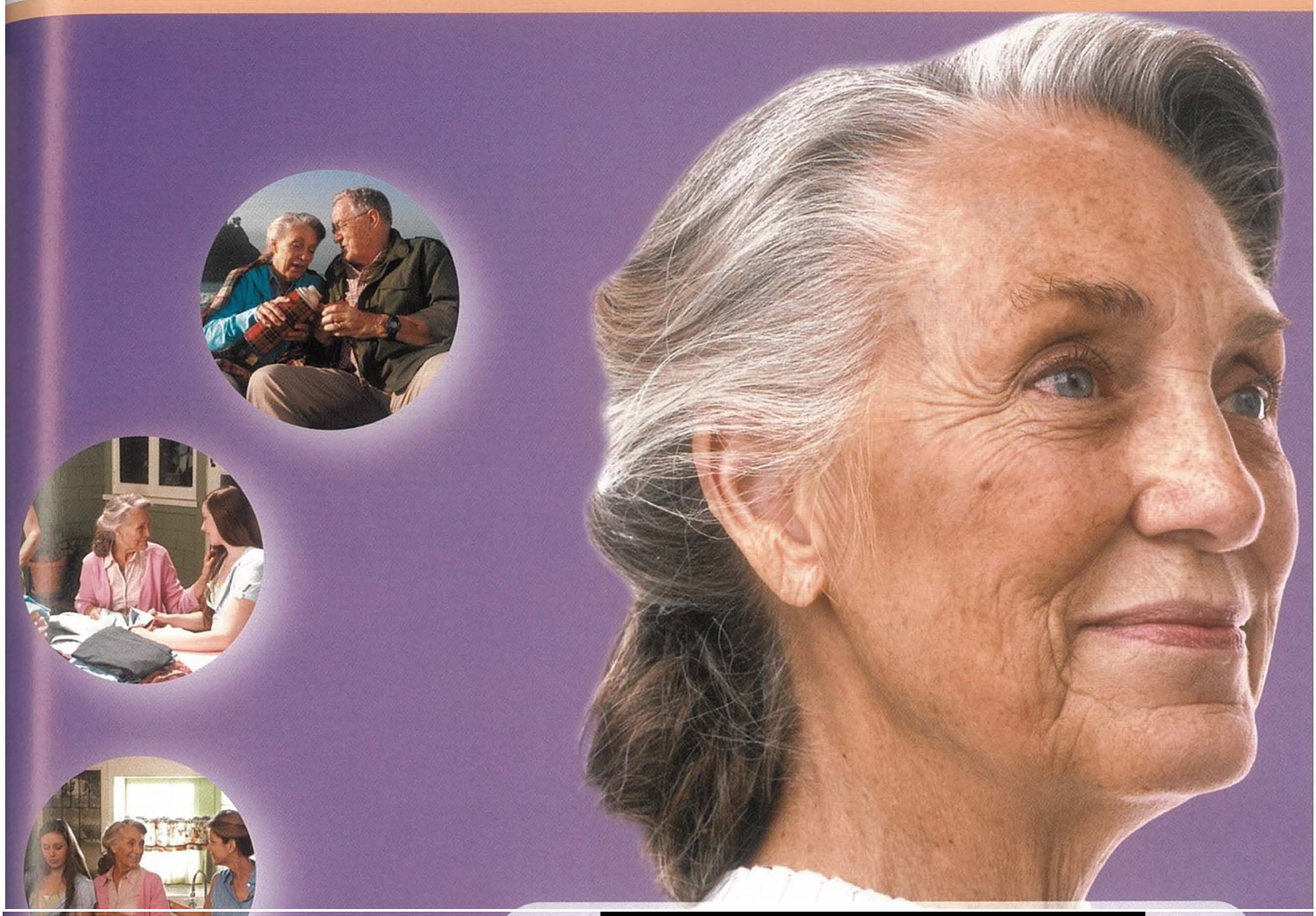
Sledimo poslanstvu Creda in
ustvarjamo inovativno prihodnost.

Iz Creda Johnson & Johnson, 1943:
"Menimo, da smo najprej odgovorni zdravnikom, sestram in bolnikom, materam in očetom ter vsem drugim, ki uporabljajo naše izdelke in storitve.
Ko poskušamo zadostiti njihovim potrebam, mora biti zelo kakovostno vse, kar naredimo ..."

JANSSEN-CILAG
Farmacevtski del Johnson&Johnson d.o.o.

JAC-SLO-A-009-050908

Nova oblika zdravljenja Alzheimerjeve bolezni



Vidna učinkovitost

EXELON®
transdermalni obliž
rivastigmin