Severe COPD may lead to cognitive impairment

Severe chronic obstructive pulmonary disease (COPD) is associated with lower cognitive function in older adults, according to research published in the *American Journal of Respiratory and Critical Care Medicine*.

Cognitive performance was compared in over 4150 adults with and without COPD and individuals with severe COPD had significantly lower cognitive function than those without, even after controlling for confounding factors such as comorbidities.

'Our findings should raise awareness that adults with severe COPD are at greater risk for developing cognitive impairment, which ... will likely further worsen their general health and quality of life,' said lead author Dr William W Hung, assistant professor at Mount Sinai School of Medicine, New York.

Dr Hung and colleagues obtained data from the Health and Retirement Study, a national prospective biennial survey of Americans aged 50 years and older. They included data from survey takers who had undergone cognitive testing in 1996 and again in 1998, 2000 or 2002.

Of the 4150 individuals included, 492 had COPD, and of those, about one-third (153) had severe disease. Using a 35-point cognition scale, the researchers found that scores among all patients with COPD declined on average by one point over the 6-year period between 1996 and 2002.

After further classifying those with COPD as having severe or non-severe disease, the researchers found that severity and cognitive decline were linked. Even after controlling for sociodemographic characteristics and other confounding factors, the mean cognition scores for those with severe COPD were significantly lower (0.9 points; P=0.01) than those without COPD.

Hung WW, Wisnivesky JP, Siu AL, Ross JS (2009) Cognitive decline among patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **180**: 134–7

Sugammadex rapidly reverses profound block

Leading figures in anaesthesia welcomed the availability of a novel relaxant binding agent and described its use in clinical practice at Euroanaesthesia 2009.

The fifth annual meeting of the European Society of Anaesthesiology was held in Milan from 6–9 June. Professor Jennifer Hunter, Professor of Anaesthesia at the University of Liverpool and Past Chairperson of the European Society of Anaesthesiology Scientific Programme Committee said the development of the selective relaxant binding agent sugammadex was a major innovation in anaesthesia.

Professor Jennifer Hunter, Professor of Anaesthesia, University of Liverpool

She added: 'Sugammadex reverses moderate or profound neuromuscular block rapidly. It allows us to do what we could never do before.'

Sugammadex is indicated for the routine reversal of the commonly used muscle relaxants rocuronium or vecuronium and for immediate reversal of rocuronium in adults. It is also indicated for routine reversal of rocuronium in children and adolescents. Professor Rajinder Mirakhur, Professor of Anaesthetics at The Queen's University of Belfast, Northern Ireland, said: 'The ability to reverse both moderate and deep levels of muscle relaxation during general anaesthesia was not possible before sugammadex.' Sugammadex was approved last year.

Speaking during a scientific session on sugammadex, Professor Hunter explained that although sugammadex reverses moderate neuromuscular block more quickly than neostigmine, 'the few extra minutes saved is not a convincing argument to use sugammadex routinely in this setting because of the cost differences between the two agents'.

She added that she used sugammadex in her own clinical practice to reverse profound neuromuscular block in major surgical cases and for immediate rescue reversal.

Professor Hunter said: 'We need more clinical experience to identify what its adverse effects are in the world of clinical practice compared to the effects reported in clinical trials.' The most commonly reported adverse reaction in clinical trials was a metal or bitter taste. Allergic-like reactions such as erythematous rash have also been reported.

Rhonda Siddall

Treatment available for Niemann–Pick C disease

Zavesca (miglustat) is the first and only licensed treatment available for people with Niemann–Pick type C disease. This rare genetic disease causes significant neurological deterioration that can be fatal and affects infants, children and adults.

Currently there is no cure for Niemann–Pick type C. Before miglustat patient management was restricted to symptom relief. Miglustat is licensed for the treatment of progressive neurological manifestations in adult and paediatric patients.

Neurological deterioration is the key feature of Niemann–Pick type C, which manifests in a variety of symptoms including: eye movement disorders, ataxia, dysphagia, dysarthria, dystonia and seizures. Intellectual decline, which often leads to dementia, is also common and in the final stages of the disease the patient is often bedridden.

Dr Ed Wraith, Royal Manchester Children's Hospital, said: 'For the first time we have an approved therapy for Niemann–Pick type C. The data on the effects of treatment with Zavesca obtained in a clinical trial and in a retrospective cohort study consistently showed a favourable clinical response. As a treating physician I am acutely aware of the importance of reducing progression of neurological symptoms.'

Predicting renal failure and death in vasculitis

The hypothesis that relapse in patients being treated for anti-neutrophil cytoplasmic antibody-associated vasculitis predicts a greater risk of end-stage renal disease and death has been disproved by an international study. A modified Birmingham Vasculitis Activity Score (BVAS), taking into account organ-specific disease activity, may be a more reliable prognostic indicator.

In the first of two poster presentations at the 14th International Vasculitis and ANCA Workshop, Lund, Sweden and Copenhagen, Denmark, Dr Michael Walsh from McMaster University, Hamilton, Ontario, Canada, reported that data from 370 patients in three major randomized trials were used to evaluate the association between relapses within 18 months of diagnosis and the development of end-stage renal disease or death.

A total of 88 patients experienced 92 relapses. Relapses were more common in patients with lower creatinine levels, those with a diagnosis of ear, nose and throat Wegener's granulomatosis at entry, and with lower toxicity treatment.

Fifty-three patients reached the clinical end point of end-stage renal disease or death. While a crude analysis suggested that this was associated with earlier relapses, when confounding factors were taken into account, this association disappeared (odds ratio 1.1, P=0.72).

The second poster reported data on 294 patients, revealing that conventional BVAS at relapse was not associated with end-stage renal disease or death. In the weighted model, however, gastrointestinal and neurological activity was positively associated with end-stage renal disease or death, while ear, nose and throat activity was negatively associated. The weighted BVAS correlated strongly with end-stage renal disease and death (odds ratio 2.46, P=0.004).

Dr Walsh concluded: 'Empirically calculated weights for disease activity during relapse may improve the prediction of hard clinical end points, supporting the concept that disease activity in different organs at relapse may foretell different prognoses in individual patients with anti-neutrophil cytoplasmic antibody-associated vasculitis.'

Stephen Pinn

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Azzalure offers new option for glabellar lines

A new formulation of botulinum toxin type A – Azzalure – provides a specially designed option for treating glabellar lines (vertical lines between the eyebrows) with an easy to use, customised dosage developed for aesthetic use.

The prescription treatment is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines seen at frown, in adult patients under 65 years, when the severity of the lines has an important psychological impact on the patient.

Clinical trials in 3500 patients have demonstrated Azzalure's efficacy and safety. The median time to onset of response was 2–3 days following treatment, with the maximum effect at 30 days. Placebo-controlled studies showed that the local muscle relaxant significantly reduced the severity of glabellar lines for up to 4 months, with one study showing significant effects after 5 months. Thirty days after injection, 90% of patients showed no or mild glabellar lines at maximum frown, compared to 3% of placebo-treated patients.

The most frequent treatment-related adverse events in clinical studies were mild to moderate headache and injection-site reactions, which occurred at a similar rate in patients treated with Azzalure to those randomized to placebo.

The local muscle relaxation achieved with the drug is fully reversible, with complete recovery of neuromuscular function after its effects have worn off. It is adapted from a previous botulinum toxin type A product, Dysport, which has a 20-year history of product consistency and safety.

Dr Hugo Kitchen, a member of the British Association of Cosmetic Doctors from Stratford-upon-Avon, said: 'Patients are telling me that improvements with Azzalure occur more quickly – sometimes within 24 hours. And the effects last longer, with an average of around 5 months. This has implications for cost savings.'

He has also found that he can use a smaller volume of the new agent to achieve similar effects as with other agents, which reduces the risk of affecting muscles not being targeted for treatment. 'Azzalure is also easy to use. The dose is easy to work out, and the drug is easy to draw up,' Dr Kitchen noted.

Susan Mayor

Yearly implant to treat prostate cancer

A new 12-month hormone therapy is available for men with advanced prostate cancer. The Vantas (histrelin) implant is a small and flexible device which is placed under the skin of the upper arm. It provides 50 mg of histrelin, released continuously over 12 months.

Filgrastim for chemotherapy or HIV infection-associated neutropenia

Filgrastim (Zarzio), a biosimilar recombinant granulocyte colony-stimulating factor, has been launched for the treatment of neutropenia associated with chemotherapy treatment or advanced human immunodeficiency virus (HIV) infection.

Bevacizumab and docetaxel in combination for metastatic breast cancer

More patients with metastatic breast cancer could benefit from a decision to allow bevacizumab to be combined with either docetaxel or paclitaxel chemotherapy. This license extension is important, as a higher proportion of metastatic breast cancer patients in the UK are treated with docetaxel.

European League Against Rheumatism (EULAR)
Copenhagen, 10–13 June

Early use of rituximab in rheumatoid arthritis improves outcomes

New data presented at EULAR suggest using rituximab earlier in the treatment of rheumatoid arthritis may be beneficial. Current guidance recommends that rituximab is used in people with severe active rheumatoid arthritis who are intolerant to or who have tried and failed disease-modifying drugs, including an anti-tumour necrosis factor (TNF) agent. But results from a new study could support the use of rituximab in the treatment of early rheumatoid arthritis.

Rheumatologist Professor John Isaacs, of Newcastle University's Institute of Cellular Medicine, said: 'These data show the efficacy of using rituximab earlier in the rheumatoid arthritis treatment pathway.' Rituximab is currently licensed for use in combination with methotrexate to treat adults with severe rheumatoid arthritis who have failed anti-TNFs.

The IMAGE study, presented by Dr Paul-Peter Tak from the Academic Medical Center at the University of Amsterdam in The Netherlands, showed that 2 x 1000 mg rituximab plus methotrexate achieved superior clinical and radiological responses than methotrexate alone in patients with early active rheumatoid arthritis who were naive to methotrexate. Lower doses of rituximab (2 x 500 mg) were also studied.

Dr Tak said: 'Our findings showed significantly improved clinical outcomes and inhibition of joint damage with rituximab at higher doses that could be seen by 6 months. The lower doses improved clinical but not radiological outcomes.'

ACR20, ACR50 and ACR70 responses were 80%, 64.8% and 46.8% in the higher dose rituximab group compared to 64.3%, 41.8% and 24.9% respectively in the placebo plus methotrexate group ($P<0.0001$). Mean change in modified total Sharp score was 0.359 in the higher dose rituximab group and 1.079 in the placebo+methotrexate group ($P<0.001$).

The percentage of patients with a change in modified total Sharp score was 63.5% *vs* 53.4% in the higher dose rituximab and placebo+methotrexate groups respectively ($P<0.05$). The percentage of serious adverse events was similar across the treatment groups.

Dr Edward Vital from the University of Leeds suggested that the difference in results between the doses could relate to ongoing synovitis. 'My guess is that in this study, patients treated at the lower dose still had residual disease.'

In a separate study presented at EULAR by Dr Vital, rheumatoid arthritis patients who had failed to respond to initial treatment with rituximab were successfully re-treated with a second course after 6 months.

Dr Vital said: 'Around a third of rheumatoid arthritis patients fail to achieve an adequate response the first time they are treated. Our study has shown that re-treating at a specific stage can enhance clinical responses to a level equal to those who fully respond to the rituximab course at first administration, providing hope for patients classified as non-responders.'

Rhonda Siddall

New anti-TNF maintains rapid improvements in rheumatoid arthritis

Two-year data presented at EULAR show that the new PEGylated anti-tumour necrosis factor (anti-TNF) agent certolizumab pegol maintains efficacy in rheumatoid arthritis when used as add-on therapy to methotrexate.

Certolizumab pegol showed improvements in rheumatoid arthritis symptoms as early as the first week of treatment and early inhibition of progression of structural joint damage in the RAPID 1 trial. Now, results from an open-label extension study to RAPID 1 show that treatment improvements were sustained for 2 years in patients maintained on certolizumab 400 mg every 2 weeks and methotrexate.

A separate analysis also presented at EULAR showed that patients receiving certolizumab whose symptoms were controlled as early as 6 weeks had significantly better control of symptoms after 1 year of treatment compared to patients whose symptoms responded later at 12 weeks.

Professor Edward Keystone, Mount Sinai Hospital, Toronto

RAPID 1 lead investigator Professor Edward Keystone of Mount Sinai Hospital, Toronto, said: 'It is important to know that a potential new treatment has a sustained effect.'

The 1-year results from RAPID 1, published last October in *Arthritis & Rheumatism*, showed that ACR20 response rates in patients receiving certolizumab pegol 200 mg and 400 mg were 58.8% and 60.8% respectively, compared with 13.6% for placebo in patients who had previously failed to respond to methotrexate.

Latest results from the 2-year open-label extension study show that ACR20 response rates in patients who completed treatment with certolizumab pegol 200 mg or 400 mg every 2 weeks were 68.2% and 69.5% respectively at 100 weeks. ACR50 response rates were 55.2% and 51.5% respectively. Serious adverse events occurred in a fifth of patients, with 7% affected by serious infections.

UCB submitted a marketing authorization application to the European Medicines Agency in June 2008 for the approval of certolizumab pegol in combination with methotrexate for treating moderate to severe rheumatoid arthritis in adults who have inadequate response to disease-modifying therapy. A company spokesperson said UCB expected the drug to be available by the end of this year.

Rhonda Siddall

EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR)
COPENHAGEN, 10–13 JUNE

COMET highlights sustained effect of etanercept and methotrexate

Two-year results from the COMET trial show that ongoing treatment of rheumatoid arthritis patients with a combination of etanercept and methotrexate led to better outcomes than treatment with methotrexate alone.

Presenting the results at EULAR, Professor Paul Emery, lead COMET investigator and Professor of Rheumatology at the University of Leeds, said: 'The major finding of this study is that the combination of etanercept and methotrexate produces a high rate of remission that is sustained over 2 years without significant additional risk.'

The study was designed to compare the clinical efficacy and safety of etanercept and methotrexate combination therapy with methotrexate alone on clinical disease activity and progressive joint damage in patients with early rheumatoid arthritis.

Professor Paul Emery, Professor of Rheumatology, University of Leeds

After 1 year, 50% of patients in the combined treatment group and 28% in the methotrexate-only group achieved a DAS28 remission. Subjects who completed a year of treatment with combination therapy or methotrexate monotherapy entered year two.

The original combination group either continued combination therapy or received etanercept monotherapy and the original methotrexate monotherapy group either received combination therapy or continued monotherapy in the second year of treatment.

After the second year of treatment, 57% of etanercept+ methotrexate-treated patients achieved clinical remission compared with 50% in the group that started on combination treatment but then went on etanercept monotherapy. Only 35% of the methotrexate-only group achieved clinical remission although when this group received combination treatment in the second year the remission rate went up to 58%.

However, Professor Emery added: 'Although delayed combination therapy was significantly more effective than methotrexate monotherapy with regard to clinical remission, it was not more effective in inhibiting progression of joint damage.'

Rhonda Siddall

Investigational treatment shows early promise

An oral JAK-3 (janus kinase) inhibitor shows promising efficacy in rheumatoid arthritis, according to interim results from a phase II dose-ranging study.

Presenting the results at EULAR, Dr Roy Fleischmann from the University of Texas, Dallas, said: 'The development of oral small molecule JAK inhibitors represents a new approach in the treatment of rheumatoid arthritis. These drugs offer the potential for more precise targeting than existing oral disease-modifying treatments in addition to a more convenient oral administration than biological treatments.'

Twelve-week results from the 6-month study showed that a quarter of active rheumatoid arthritis patients who had failed standard disease-modifying treatments such as methotrexate receiving either 10 mg or 15 mg twice daily of oral JAK-3 inhibitor CP-690,550 achieved an ACR70 score after 12 weeks of treatment. The investigational treatment was compared to the anti-tumour necrosis factor (TNF) drug adalimumab or placebo.

The percentage of patients achieving ACR 70 scores for adalimumab and placebo at 12 weeks was 3.8% and 5.1% respectively. CP-690,550 also achieved statistically significantly superior ACR 20 and ACR 50 scores at the 5, 10 and 15 mg doses studied. Dr Fleischmann said: 'This drug is clearly effective'.

The most frequently reported treatment-emergent adverse events with the JAK-3 inhibitor were urinary tract infections, diarrhoea, bronchitis and headache. Dr Fleischmann said plans for a phase III trial using the 5 and 10 mg twice daily doses were underway but no further details were available.

He added that if the phase III trial showed CP-690,550 was as efficacious as anti-TNF agents with a well-defined and manageable safety profile, the drug could be 'a major drug for the treatment of rheumatoid arthritis' as it is easier to administer and manufacture because it is a small molecule. 'It's likely to be cheaper than anti-TNF drugs,' he added.

Rhonda Siddall

Consensus disease index for Sjögren's syndrome

Thirty-nine international Sjögren's syndrome experts have developed the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). They identified 12 organ-specific 'domains' contributing to disease activity and classified these according to their severity.

The ESSDAI appears to be a promising clinical tool: once validated such a standardized index should facilitate both clinical practice and research.

Seror R, Ravaud P, Bowman S et al (2009) EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): development of a consensus systemic disease activity index in primary Sjögren's syndrome. *Ann Rheum Dis* **68**(Suppl3): 114