



Annals of Delirium

March 2010

Editorial

Welcome to the first newsletter of the European Delirium Association, the EDA – the Annals of Delirium. These are exciting times with the EDA soon to “go official” by gaining charitable status. Following this we will be inviting clinicians and interested scientists to become members. The EDA has great potential and plans to make significant progress in the field of delirium scientifically and clinically, on an international scale for all our patients!

This first newsletter is in keeping with our chrysalis state. There is a keen desire to produce a quality journal on delirium with a high impact factor but the resources are not (yet!) available and probably that will be the case for some time. And so it is of course with delirium in general... In 1959 Engel and Romano bemoaned the lack of skills clinicians had in diagnosing delirium, the lack of interest and failure to recognise its importance. 50 years later and many of us are still struggling with this on a daily basis. However the tide is turning and this Cinderella of syndromes is about to put the glass slippers on!

The Annals will start by communicating what is important, and what we think you will be interested in. For this first edition Dr John Holmes looks back at the last Annual Congress and forward to the next. Professor Alasdair MacLulich outlines the discussion in a Congress workshop on research on the pathophysiology of delirium. Agreeing on certain standard assessment tools and collaborating on more challenging techniques would benefit the

field. We offer expert comments by Dr Schieveld on a rare review of paediatric delirium and an educational article on delirium statistics from Dr Adamis prompted by a recent publication. I’m suggesting recent papers in the field of delirium that may be of interest including one from a medical physics journal.

We hope this newsletter will be published quarterly. You are welcome to send in your contributions to our letters page. Please send us any news that is happening in your own area and let us know details of any relevant meetings or conferences.

I would like to dedicate this first newsletter to my father who suffered delirium during his final illness.

Valerie Page

Editor

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EDA, Leeds, 8-9 October 2009

The EDA held its 4th Annual Scientific Congress on Delirium at the Metropole Hotel in Leeds, UK on the 8th and 9th October 2009 and ably facilitated by staff from the Andrew Sims Centre. The 99 delegates and speakers were welcomed as "delirium freaks", yet the excellent content of the programme made it clear that to be interested in delirium should not be considered freakish or abnormal; delirium is a problem at the very heart of healthcare, and should be of interest to all.

The congress had a mixture of keynote addresses, invited speakers, new research presentations from submitted abstracts, interactive workshops and a total of 21 posters. On the first day, the first session focused on delirium in intensive care settings; that was followed by new research presentations before a stimulating and thought-provoking keynote on improving delirium detection from Dave Meagher. Lunch was followed by a session on genetics and paediatric delirium, and after tea we heard cutting-edge research on inflammatory hypotheses of delirium, followed by parallel workshops. An EDA Board Meeting held at the end of the day's proceedings made some important steps towards formal membership and subscriptions, making the EDA less virtual and more real-life, and there were important discussions about links with other similar organisations worldwide. The congress dinner was a useful networking opportunity, and was followed by some, though not all, by a trip round the hostels of Leeds, providing some useful and interesting insights into Yorkshire life.

Day two kicked off with a view of delirium care in the USA from Barbara Kamholz and more, high quality, new research presentations. After the morning break, a session on delirium services was followed by easily the most important talk of the congress, when Rachel White was able to share with delegates her moving and powerful story of the episode of delirium that she experienced whilst unwell in an intensive care unit. This really brought home the importance of delirium not just to healthcare systems, but to individuals and carers. It also highlighted the importance of qualitative as well as quantitative methodologies, an importance reflected in the content of the new research presentations and posters. Then to lunch, followed by observations on experimental designs in delirium studies and more interactive workshops. In a final plenary session, winners of our prestigious awards, the best research presentation (Laura Brown) and best poster (Valerie Page) were announced to great acclaim. Finally, the congress was closed by our President, Jouko Laurila, who announced the next EDA congress, in Amsterdam on the 11th and 12th November 2010 (watch this space for programme information). Delegate feedback from the Leeds meeting was very good - let's hope that the feedback from Amsterdam is even better - Good luck Sophia and the scientific committee!

John Holmes
Leeds

Re: Expert opinion commentary regarding:

From: Jan N.M. Schievel, M.D., Ph.D

Consultant in pediatric neuropsychiatry, Maastricht University Medical Center+ Department of Psychiatry and Psychology. Division of Child and Adolescent Psychiatry and Psychology. The Netherlands

"Delirium: An Emerging Frontier in the Management of Critically Ill Children"

By: Heidi A.B. Smith, MD, MSCIA,* , D. Catherine Fuchs, MD, Pratik P. Pandharipande, MD, MSCIC, Frederick E. Barr, MD, MSCID, E.Wesley Ely, MD, MPH
Crit Care Clin 25 (2009) 593-614

There exist very few papers regarding paediatric delirium in critical illness. A PubMed search at November, 2009, yielded only 7 English language papers, and this is one of these, published in July 2009. It was written by the famous group from Vanderbilt University, Nashville, TN, U.S.A., initiated by Wes Ely, pulmonologist-intensivist. Amongst the multidisciplinary teammates are e.g. Heidi Smith, paediatrician -intensivist, Cathy Fuchs, child and adolescent psychiatrist and Pratik Pandharipande, anaesthesiologist-intensivist. It gives a thorough, and indeed expert opinion, overview of all the different aspects and problems regarding the issue of Pediatric Delirium (PD). There are only two points at which I must disagree with this important paper:

- 1) The PAED items 1, 2, and 3 are in my opinion perfectly suitable in the case of a hypoactive delirium (but also in the case of hyperactive) and the items 4 & 5 especially also in the case of

hyperactive delirium. 2) our ICM case series (n= 40) regarded NOT only hyperactive delirium: 9 of these were hypoactive ones. These cases also were referred to our Consultation Liaison service because of disturbance in emotion and or behaviour: "This is now not my child anymore".

I do agree with their remark that the PAED items are subjective, but then: in a critically ill child or infant at the PICU every change in baseline mental/ psychological functioning - the 6th vital sign! - is an expression of PD (until proven otherwise - see also our algorithm). And who knows the child's/infant's mental functioning best ? Ask any mother (or dedicated caretaker-nurse) and they will answer: ME! And so in this respect the mother or dedicated caretaker - nurse is in my humble opinion THE gold standard (and not even a very experienced pediatric neuropsychiatrist). That is why we also embrace the PAED items, especially < age of 5 years. But not only there: I dare to generalize and to state, although unproven, that "This is now not my beloved brother / sister /father / grandmother", etc. in the ICU exclaimed by the relative is also very comparable with delirium and with high scores at the PAED items.

The authors conclude: "Delirium is a syndrome of acute brain dysfunction that commonly occurs in critically ill adults and most certainly is prevalent in critically ill children all over the world. The dearth of information regarding the incidence, prevalence and severity of PD stems mainly from the fact that there is no validated tool yet for daily routine use at the bedside at the PICU" and I fully agree. Work is in progress in the USA as well as here to tackle this major issue.

Editorial note:

The Pediatric Anesthesia Emergence Delirium (PAED) scale Dr Schievel refers was designed to detect emergence delirium post-operatively in children as young as 2 years. The PAED scale has five items, each scored 0 to 4 according to severity and the scores are added up. Items 1 - 3 relate to eye contact, awareness of environment and purposeful actions. Items 4 and 5 ask if the child is restless and/or inconsolable.

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Survival analysis in delirium studies

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A recent study by Shintani et al (2009) explores the biased results when delirium as time-dependent (time-varying) and time-independent variable in the Cox proportional hazard model (PH) was used for analyzing the effects of delirium on mortality and length of stay. The authors found that when delirium used as time-independent variable this leads to considerable errors.

To my knowledge this is the first study which addresses the violation of the assumptions of the Cox PH model in delirium studies, although numerous papers (the earliest in medical research maybe this of Crowley and Hu 1977) have illustrated the use of time-varying covariates and discussed some of the problems in different research disciplines. For more examples in other research areas see the editorial (Linde-Zwirble 2009), Andersen (1992), Suissa and Ernst (2009) for a study in COPD, Renoux and Suissa (2008) for a study of the effectiveness of interferon beta in multiple sclerosis, Bellera et al (2008) for studies in breast cancer, and Zhou et al (2005) for drug effectiveness evaluation.

Why the results are different when the "delirium" variable is treated as time-independent in one analysis from those when the delirium is treated as time-dependent (time-varying) variable?

Before that, few definitions and a little theory.

Definitions:

- a) Time-independent variables are the variables which considered fixed predictors (or explanatory or independent) measured at study baseline and they assumed constant across the time.
- b) Time-dependent variables are predictors whose values may vary with the time. In fact a variable is considered as time-dependent if the differences between variable values from two different subjects maybe changing across the time.

Examples:

Gender and race are time-independent or fixed variables, they stay unchanged during the study period. Age as well is a time-independent variable. A patient's age is increased by one year but the difference in age between two patients remains unchanged. However for long term studies and especially when new subjects are included after one or more years the age maybe is a time-dependent variable. Similarly delirium status vary across time so it is a time-dependent variable, but if for any reason we are interest only in delirium subjects and we have excluded all the non delirious subjects from our sample, delirium in this case is a time-independent variable.

Thus to characterize a variable as time-independent or time-dependent, we need to considered not only the "nature" of the variable but also the study's design.

Furthermore the time-dependent variables are divided in three categories: a) "defined", b) "internal" and c) "ancillary" (some times referred as "external"). See textbooks in survival analysis (e.g. Kleinbaum and Klein 2005, Tableman and Kim 2004). The reason for distinguishing among defined, internal, and ancillary variables is that the computer commands required to define the variables for use in an extended Cox PH (see below) are different for the different variables types, depending on the computer program used.

"Defined" time-dependent variables are usually in the form of the product of a time-independent variable multiplied by time or some function of time $g(t)$ (eg $\log(\text{TIME})$ or $\ln(\text{TIME})$). For instance, the variable gender is a time-independent variable (unchanged during time) but the variable gender X TIME or gender X $\log(\text{TIME})$ is a "defined" time-dependent variable.

"Internal" time-dependent variable is the variable in which the values change over time for any subject under the study. The reason for a change depends on "internal" characteristics or behaviour specific to individual. Clearly an example for this is delirium status or severity of delirium. Other examples maybe severity of illness, cytokines, blood pressure, results of blood tests etc.

Finally a variable is called "ancillary" time-dependent variable if its value changes primarily because of external characteristics of the environment that may affect several subjects simultaneously. If we considered that the ICU environment is a deliriogenic factor or that have effects on mortality, or length of stay, and subjects going in and out of ICU, then we need to consider this variable as well. In this case the variable "in and out of ICU" is an ancillary time-dependent variable.

Why do we need to distinguish among time-independent and time-dependent variables?

The primary reason is that when we use the Cox PH for survival analysis we need to meet its assumption that: The hazards ratio is constant across time. If this assumption cannot be met the Cox PH model is inappropriate. However there are alternatives if this assumption is not meet, like to analyse by stratifying on the exposure variable and to obtain Kaplan-Meier curves for each exposure separately, or to fit different Cox PH models at different time points where the hazard ratio remains constant between time intervals, or more often to use a modified Cox PH model that includes time-dependent variables which is called extended Cox PH model.

How we can check that our analysis has met the Cox PH assumption?

There are several approaches (for details see textbooks in survival analysis) but more often we use:

- a) graphical approaches
- b) Goodness of fit tests (e.g. Harret and Lee test)
- c) Using time dependent covariates (extended Cox PH) by including one or more time-independent variables and their product by any function of time. E.g. if the PH assumption is being assessed for delirium status an extended Cox model can be used to included the variable "delirium" X TIME in addition to "delirium" variable. [Note here that the variable "delirium X TIME" is a defined time-dependent variable and the extended Cox model must be used]. If the coefficient of the product (delirium X TIME) is significant we can concluded that the PH assumption is violated for the "delirium" variable and in that case the variable "delirium" is a time-dependent variable.

d) Comparison of two models, one Cox PH model and one extended Cox PH model. This can be done by using the likelihood ratio test which compare the differences between the log likelihood statistic (-2lnL) for a Cox PH model and the log likelihood statistic for the extended Cox model. This approach also can be used as the previous one for more than one variable. For instance considered an extended Cox PH model which contains the exposure "delirium" as a time-independent variable (as a main effect) and the variable "delirium X TIME" a time-dependent (as an interaction effect), and one reduced Cox PH model which includes only the main effect "delirium" as time-independent variable. The likelihood ratio statistic is the difference between log likelihood statistic for the full model (extended Cox model) and the reduced (Cox PH model). In mathematical notation:

$LR = -2\ln LR - (-2\ln LF)$, F=full model (extended), R=reduced model (PH).

This difference will have an approximate χ^2 distribution with one degree of freedom. If the result of the test for the PH assumption is significant then the extended Cox model is preferred to PH model (thus the exposure variable delirium can be considered as a time-dependent variable)

So why did Shintani et al found different results when they use delirium as a time-independent vs. time-dependent variable? Because they used an incorrect model which possible violates the Cox PH assumption, against a correct model the extended Cox PH model.

Their paper reminds us that effective control for survival bias in delirium studies, and general, relies on correct use of study design and analysis.

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Workshop on the pathophysiology of delirium

Alasdair MacLulich and Barbara van Munster

This workshop focused on two main issues in this area of research. We first had a discussion on what the main conceptual issues and research questions are in the field. We then went on to talk about methodological Issues.

We had a wide-ranging discussion on defining the main research areas. The central issue was thought to be: what are the acute changes in the central nervous system associated with the clinical syndrome of delirium? Other important issues identified were as follows. Because delirium is mostly precipitated by non-CNS disease processes, for example peripheral inflammation, it is clear that we need to develop a better knowledge of signalling pathways from the periphery to the CNS. Good candidates in delirium include pro-inflammatory cytokines, stress hormones and direct vagal signalling. Alongside understanding these peripheral signalling mechanisms, we also need to understand more about the CNS vulnerability to such signals.

Epidemiological studies have shown the importance of age, cognitive impairment, cardiovascular disease, and other risk factors, in increasing risk of delirium. However there are clear gaps in our understanding of what makes some individuals more susceptible than others in terms of specific features of the CNS, such as particular forms of neuropathology or genetic variations. Another major issue is that we need to investigate the mechanisms of the apparent permanent decline in cognitive and other mental functions seen in many people who have recovered

from delirium. Presently it is unclear if the insults which precipitated the delirium are causing or accelerating neurodegeneration separately from any processes directly causing delirium, or whether the process underlying delirium itself has longer term damaging effects.

We also spoke in detail about methodological issues. The group acknowledged that the considerable challenges in the field, particularly around consent and also because the condition itself makes many kinds of research techniques difficult to implement. We noted that there are very few neuroimaging studies in delirium. We wondered whether we were perhaps being too cautious in attempting to perform neuroimaging; one workshop member reminded the group that neuroimaging is commonly done in many other unwell and unstable patient groups such as those with traumatic brain injury and stroke. We thought it might be possible to advance the field by thinking of ways in which some subgroups of patients with delirium could undergo neuroimaging. Another potential use of neuroimaging is in understanding specific anatomical, molecular and functional features of CNS vulnerability, and also in longitudinal studies by examining the neuroimaging correlates of longer-term mental status decline. The use of blood biomarker measurement is well-established but there are very few studies of cerebrospinal fluid in delirium. The latter could be extremely informative with respect to the central research question of acute CNS changes in

delirium. We discussed approaches to the challenge of getting CSF specimens. These include performing lumbar punctures for research reasons alone (not employed recently probably because of ethical restrictions); analysis of specimens taken in the course of clinical care such as in patients with suspected CNS infection or vasculitis; and taking specimens in the course of lumbar puncture for spinal anaesthesia. The latter has recently been used in patients with hip fracture, who suffer a higher rate of delirium. Another potentially valuable measurement modality is EEG. Advances in technology mean that acquisition of such measurements could be achieved with much simpler apparatus more suitable for this patient group. We also discussed the potential for animal model research in delirium. The group considered that delirium is potentially highly tractable with respect to animal models because the condition is rapid onset, severe, and potentially reversible. With the advent of rodent models of neurodegenerative disease, new paradigms which more closely model delirium in older humans (who mostly have existing CNS pathology) appear feasible and are currently under-utilised.

Finally, we discussed the value of sharing methods among different research groups around the world, in particular the use of standard measures of delirium and other outcome measures. We thought that many biomarker measurements are standard, and that particular research groups might have expertise which could readily be shared with others who don't have on-site access to the methods. Additionally, because pathophysiology studies are generally difficult to do, multicentre studies would allow a larger sample sizes and clearer results to be generated. There was general agreement that collaborations would move the field forward.

News & Meetings

International

EDA Annual Congress: 5th Scientific Meeting 2010

November 11 – 12

Amsterdam

Keynote Speakers

Sharon Inouye, Wes Ely and Alastair MacDonald

Aimed at all health care professionals and researchers interested in delirium

For further details see www.europeandeliriumassociation.com

UK

ICU Delirium Study Day. Tuesday June 15th.

Watford General Hospital, Watford.

Aimed at all ICU health care professionals.

Lectures by Dr Valerie Page, Dr Dan Conway and Mark Borthwick.

CME applied for. £30.

For further details contact: Alison East alison.east@whht.nhs.uk or Sarah Lafbery sarah.lafbery@whht.nhs.uk Tel UK 01923 217610

The 9th Liaison Psychiatry for Older People Conference-
Directions & Developments 2010

Date: Wednesday 12 May 2010 to Thursday 13 May 2010

Location: Hilton Leeds City Hotel, Neville Street, Leeds LS1 4BX

Keynote speaker: Professor Alistair Burns, National Clinical
Director for Dementia, Department of Health

www.lpop.org.uk

Editors Choice: Did you see?

1. Case Scenario: Postoperative Delirium in Elderly Surgical Patients. Jean Mantz et al. *Anesthesiology* 2010; 112: 189-95. Provides an excellent overview of all we should know of delirium and it uses the word logorrhoea!

2. Critical Care Medicine February 2010; 38
This edition of Critical Care Medicine, the Intensive Care Journal from the USA, there are 2 original papers and no less than 3 commentaries on delirium in intensive care. One commentary starts with a quote "We are drowning in information but starved for knowledge" - John Naisbitt

* Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomised, placebo-controlled trial. Girard et al. *CCM* 2010; 38: 428-37

* Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicentre, randomised, double-blind, placebo-controlled pilot study. Devlin et al. *CCM* 2010; 38: 419-27

* Delirium: The struggle to vanquish an ancient foe. Young and Flanagan. *CCM* 2010; 38: 693-94

* Why all the confusion about confusion? Joffe, Coursin and Coursin. *CCM* 2010; 38: 695-95

* Free your MIND and the rest will follow: Decoding delirium in the intensive care unit. Balas, *CCM* 2010; 38: 697-98

3. Motion analysis in delirium: a discrete approach in determining physical activity for the purpose of delirium motion subtyping. Godfrey et al. *Medical Engineering and Physics* 2010; 32: 101-10

A novel technique for determining motoric subtypes.

4. Neuroleptic dose in the management of delirium in patients with advanced cancer. Hui et al. *Journal of Pain and Symptom Management*; 2010: 186-96

A retrospective study with a sobering message.

Letters and content for future editions of Annals of Delirium

You are invited to submit - reports, opinions or commentaries. Please forward to

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