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Short Communications

Seasonal variation in the occurrence of delirium in patients admitted to medical units of a general hospital in Italy

Gallerani M, Manfredini R. Seasonal variation in the occurrence of delirium in patients admitted to medical units of a general hospital in Italy.

Objective: Delirium syndrome is common in the hospitalised population. However, data on its aetiological factors are scarce. Clinical observations suggest a relationship between delirium occurrence and seasons. The aim of study was to determine whether a seasonal variation exists in the occurrence of delirium events in-hospital patients.
Methods: The study included all admissions to the medical units of the Hospital of Ferrara, Italy, between January 2002 and December 2010. On the basis of date admission, cases have been analysed for seasonal variation (four 3-month intervals by seasons) by means of conventional statistics. Moreover, cases categorised into twelve 1-month intervals were also analysed by means of a validated chronobiologic inferential method (single cosinor) to search for cyclic variability.
Results: During the analysed period, the hospital database contained 74 379 records referring to 42 625 subjects (52.7% females). Delirium diagnoses were 1300 (1.7% of total sample), 668 of whom in females (51.4%) and 632 in males (48.6%). Events of delirium were more frequent in winter and autumn (26.6 and 26.5%, respectively) than in spring (23.5%) and summer (23.4%). Chronobiological analysis yielded a significant peak of delirium events in January, when considering both the total raw number of cases and the percent of admissions.
Conclusions: The study seems to indicate in patients hospitalised in medical units, a higher rate of occurrence of delirium in autumn-winter, similar to that reported for acute medical diseases. The role of possible underlying favouring or triggering factors deserves further research.

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Significant Outcomes

- Delirium represents a not negligible finding in a large cohort of hospital admissions to medical units (1–2%).
- Autumn and winter months show a higher frequency peak of delirium events (26.6 and 26.5%, respectively) compared with spring and summer months (23.5 and 23.4%, respectively).
- Chronobiological analysis yielded a significant cyclical variability of delirium events, characterised by a significant peak in January, both for total number of cases and percent of admissions.

Limitations

- As this study is performed on hospitalised patients and is based on International Classification of Diseases, Ninth Revision, Clinical Modification discharge codes, it is exposed to underestimation risk.
- As this study is limited to patients admitted into medical units, these findings cannot be generalised to general population nor to the overall population admitted to a general hospital.

Introduction

The syndrome of delirium is characterised by an acute onset of disturbances of consciousness, attention and global changes in cognition. It is a common neuropsychiatric syndrome in the elderly, characterised by concurrent impairments in cognition and behaviours. The aetiologies for delirium are often multifactorial and secondary to underlying medical illnesses and/or due to medication effect. The diagnosis of delirium is often missed in elderly patients, and this condition may be labelled as depression or dementia. If untreated, delirium may have devastating consequences, with high rates of morbidity and mortality (1–6).

Available evidence indicates that early detection, reduction of risk factors and better management of this condition can decrease its morbidity rates. On one hand, the multifactoriality of causes potentially generating delirium, and on the other, the observation that general morbidity of elderly people varies according to seasonal factors, may suggest the possible existence of seasonal differences regarding the occurrence of delirium syndrome (7).

This study aimed to determine whether a seasonal variation exists in the occurrence of delirium in patients admitted to hospital medical units.

Methods

This study was conducted with the approval of the local institutional committees for human research.

The analysis included the data record of all consecutive admissions to the medical units of the Hospital of Ferrara, Emilia-Romagna region of Italy, between 1 January 2002 and 31 December 2010. Each hospital discharge form contains information of each subject: surname and name, sex, date of birth, date and department of hospital admission and discharge, main and up to 15 accessory discharge diagnoses and most important diagnostic procedures, based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We considered the ICD-9-CM codes used to identify patients with delirium, either as principal or accessory diagnosis, and in particular: presenile dementia with delirium (code 290.11), senile dementia with delirium (code 290.3), vascular dementia with delirium (code 290.41), acute delirium (code: 293.0) and subacute delirium (code 293.1). The following codes have been excluded from the analysis: alcohol withdrawal delirium (code: 291.0), alcohol-induced psychotic disorder with hallucinations (code 291.3), alcohol withdrawal (code 291.81) and drug-induced delirium (code 292.81).

The total sample was divided into subgroups by gender, age (<60, 60–74 and ≥75 years), most frequently found associated risk conditions for delirium (urinary tract infections, *Escherichia coli* infections, volume depletion, Alzheimer disease and senile brain degeneration, cerebral atherosclerosis, heart failure, injury and trauma) and patients' hard outcomes (dead during hospitalisation or discharged alive).

On the basis of date of admission, all cases have been analysed for seasonal and monthly variation. For seasonal analysis, total cases were categorised into four intervals by seasons (spring: 21 March–20 June, summer: 21 June–20 September, autumn: 21 September–20 December and winter: 21 December–20 March), and the distribution of admissions was tested for uniformity by the chi-squared goodness of fit test. Furthermore, to explore the possible presence of cyclical repetitivity, an inferential analysis was performed by applying partial Fourier series on monthly data with an internationally validated Chronolab software (8). This method selects the harmonic, or combination of harmonics (cosine waveforms), that best explains the temporal variance of the data. The percentage of the overall variance attributable to the approximated cosine function (percent of rhythm) serves as the estimate of the goodness of fit, with the F-test statistic applied to the variance accounted by the single or multiple cosine curve approximation versus straight-line approximation of the time series data to accomplish a test of the null hypothesis – zero amplitude. The parameters calculated for the chosen period (τ) cosine approximation of the time series data were as follows: the Midline Estimated Statistic of Rhythm (the rhythm-adjusted mean for the time period analysed), amplitude (one-half the difference between the absolute maximum and minimum of the fitted approximation) and peak (acrophase) and trough (bathyphase) time referenced to 00:00 h, 31 December. Significance levels were assumed for $p < 0.05$. Finally, raw data of monthly admissions were adjusted for the different number of days of the month, using the average number of admissions per month. This analysis is available using the method by Barnett and Dobson, Analysing Seasonal Health Data, Springer, 2010 (free download at: http://cran.r-project.org/web/packages/season/season.pdf).

Results

During the analysed period, the hospital database contained 74 379 admissions to medical units (39 348 or 52.9% females) referring to 42 625 different subjects (22 476 females, 52.7%). The main characteristics of the sample population are summarised in Table 1. Delirium diagnoses were 1300 (1.7% of total

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Table 1. Main characteristics of a sample of 42 625 consecutive subjects hospitalised to medical units, of whom 749 with diagnosis of delirium, according (by ICD-9-CM) to the discharge records

	Patients			
	All events ($n = 74\,379$)	Controls ($n = 73\,079$)	Delirium ($n = 1300$)	p
Subjects	42 625 (100)	41 876 (98.2%)	749 (1.8%)	
Female gender	39 348 (52.9)	38 680 (52.9%)	668 (51.4%)	0.272
Age (mean/SD)	70.9 ± 16.4	70.9 ± 16.4	71.4 ± 16.2	0.256
Deyo Index	4.26 ± 2.49	4.25 ± 2.49	4.60 ± 2.28	<0.001
Hospital length of stay days	9.6 ± 11.6	9.6 ± 11.6	9.8 ± 11.5	0.508
Number of diagnoses	3.7 ± 2.2	3.6 ± 2.2	4.85 ± 2.2	<0.001
Number of procedures	2.1 ± 1.99	2.09 ± 1.98	2.35 ± 1.9	<0.001
Mortality rate	5594 (7.5%)	5494 (7.5%)	100 (7.7%)	0.796
Mean age of death	78.6 ± 12	78.6 ± 11.9	79 ± 11.9	0.686

sample), 668 of whom in females (51.4%) and 632 in males (48.6%). Of the 1300 delirium events, 260 of 15 210 (20% of total) were observed in patients aged <60 years, 364 of 20 572 (28%) in patients aged 60–74 years and 676 of 38 607 (52%) in patients aged ≥75 years ($\chi^2 = 0.158$, $p = 0.924$).

During the observation period, 5594 deaths (7.5% of total) occurred in patients with no delirium diagnosis, whereas 100 deaths occurred in patients presenting a delirium diagnosis (7.7%, $\chi^2 = 0.056$, $p = 0.0427$).

The raw yearly number of delirium diagnoses was not significantly different during the analysed period, with the highest percentage (1.9%) in 2002 and 2009, and the lowest (1.5%) in 2007 ($\chi^2 = 9.253$, $p = 0.321$).

As for season, hospital admissions were most frequent in winter (19 102, 25.7%) and least so in summer (17 635, 23.7%). Events of delirium were 346 (26.6%) in winter, 305 (23.5%) in spring, 304 (23.4%) in summer and 345 (26.5%) in autumn (Fig. 1). Pattern of delirium events is not statistically different from that of total admissions ($\chi^2 = 2.518$, $p = 0.644$), even when considering seasonality ($\chi^2 = 2.598$, $p = 0.626$). Again, although in the presence of a general trend for a summer low (with the only exclusion of volume depletion – code 276.5), no statistically significant differences in seasonal pattern were found for the considered subgroups admissions (Table 2). Chronobiological analysis yielded a significant peak of delirium events in winter (Fig. 2, Table 3) and particularly in January.

Discussion

Many and different aetiological factors may be potentially responsible of the genesis of delirium, for example, the higher frequency of traumas during colder periods, i.e. hip fractures, viral and other

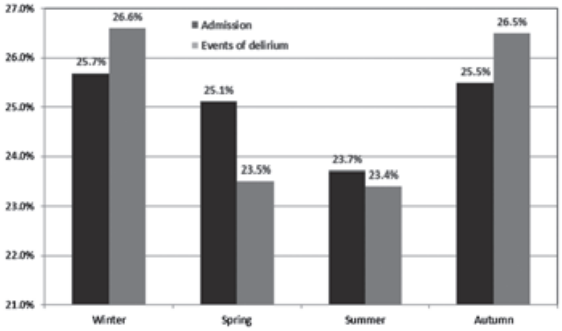

Fig. 1. Seasonal distribution of delirium syndrome admission or in-hospital events (Ferrara Hospital, years 2002–2010).

infectious diseases, cardiovascular and cerebrovascular diseases and any change in occurrence and in the balance of all the underlying factors may play a potential triggering role in the delirium syndrome generation. Our study seems to indicate a higher rate of occurrence of delirium in winter among patients hospitalised in medical units, which is higher than expected from the seasonal increase in general morbidity. These results agree with the only available study in literature (7), which retrospectively analysed medical records of 5218 old patients hospitalised in medical wards between 1991 and 1997, and found in 312 patients with delirium at admission, and 234 that developed delirium during their hospitalisation, a seasonal variation, with higher rates in winter than in summer months (12 vs. 4%, $p < 0.001$).

On one hand, it is known that elderly people have a higher sensitivity to the seasonal light-dark cycle changes, possibly as a result of the age-related deterioration in the circadian time-keeping system. Most of the delirium symptoms, wandering, confusion, disorientation, hyperactivity, restlessness and aggression, worsen in the late afternoon/evening time (sundowning syndrome) and are often seen in patients with cognitive impairment (6,9). In northern Italy, winter months are characterised by shorter days and longer nights, and this may play an influencing factor in the occurrence of delirium in elderly people. However, a further subanalysis of our total sample into dichotomised categories by light-dark cycle (spring-summer, with ≥12 day-light hours vs. autumn-winter, with ≤12 day-light hours) did not show any significant difference.

On the other hand, patient's medical comorbidities could play an additional role. Acute medical diseases, i.e. community-acquired pneumonia (10), exacerbations of chronic obstructive pulmonary diseases (11), acute myocardial infarction (MI) (12), heart failure (13,14), pulmonary embolism (15), cerebrovascular accidents and stroke (16,17), are all characterised by peaks in winter. It has been observed, for example, that approximately 53% more cases of

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Table 2. Seasonal distribution of hospital admissions for delirium syndrome (total subjects and higher frequency subgroups)

	n	Winter	Spring	Summer	Autumn	Chi-squared test for non-uniformity	*p*
All cases	74 379	19 102 (25.7%)	18 681 (25.1%)	17 635 (23.7%)	18 961 (25.5%)	36.021	<0.001
Delirium events	1300	346 (26.6%)	305 (23.5%)	304 (23.4%)	345 (26.5%)	2.590	0.626
Urinary tract infection, site not specified (code 599.0)	3808	998 (26.2%)	970 (25.5%)	873 (22.9%)	967 (25.4%)	1.692	0.639
Escherichia coli infections (code 041.4)	988	263 (26.6%)	237 (24.0%)	238 (24.1%)	250 (25.3%)	0.925	0.819
Volume depletion (code 276.5)	995	239 (24.0%)	262 (26.3%)	257 (25.8%)	237 (23.8%)	4.696	0.195
Alzheimer's disease and senile degeneration of brain (codes 331.0–331.2)	2652	664 (25.0%)	646 (24.4%)	640 (24.1%)	702 (26.5%)	2.312	0.510
Cerebral atherosclerosis and other generalised ischemic cerebrovascular disease (codes 430–437.1)	15 219	3846 (25.3%)	4019 (26.4%)	3529 (23.2%)	3826 (25.1%)	16 517	0.001
Congestive heart failure, unspecified and heart failure, unspecified (codes 428.0–428.9)	3704	945 (25.5%)	946 (25.5%)	889 (24.0%)	924 (24.9%)	0.919	0.821
Injury and trauma (codes 800–959)	3274	813 (24.8%)	837 (25.6%)	763 (23.3%)	861 (26.3%)	2.347	0.504

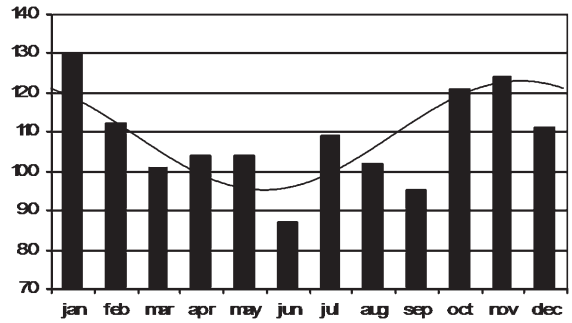

Fig. 2. Monthly distribution of delirium syndrome total events. Superimposed is the best fitting curve.

MI were reported in winter (18), heart failure deaths were 20% above average in January (19) and the relative risk of venous thromboembolism was 14% more in winter and 19% more in January (20). Urinary infections deserve a brief consideration apart: seasonal peaks in summer have been reported (21,22), but high consumption of antibiotics is significantly higher in winter (23).

Our study has some limitations. First, it refers only to hospitalised patients, and in particular in those admitted to medical units, and is based on discharge codes, with a high underestimation risk. It is known that delirium is consistently underdiagnosed in clinical practise (6), and about one-third to two-thirds of delirium goes unrecognised (3,5,6). In particular, hypoactive delirium subtypes are frequently undiagnosed (4). Reasons for underdiagnosis include the lack of awareness of the clinical features of delirium and its fluctuating nature, the overlap with dementia, the lack of formal cognitive assessment as a routine and the failure to consider either the possibility of the condition or its consequences (5,6). Thus, this could help to explain why the observed incidence rate of delirium is definitely lower than that effectively present according to literature data (24). However, in studies based on Diagnosis-Related Groups (DRG), delirium was coded in 0.8% of the cohort (25), which is significantly lower than our results. Economic considerations underlying the DRG codification (and not only professional skills) play a pivotal role when planning ICD-9-based studies. Even in this study, the number of diagnoses reported in the discharge sheets is lower than that found in other epidemiologic studies. However, this bias is supposed to be

Table 3. Chronobiologic analysis of monthly frequency of delirium syndrome admission or in-hospital events (total cases and subgroups)

	n	Amplitude ± SE	Acrophase (peak)	*p*
Total	74 379	205.43 ± 76.50	December	0.071
Delirium events	1300	12.16 ± 3.79	January	0.033
Urinary tract infection, site not specified (code 599.0)	3808	21.85 ± 8.68	January	0.091
Escherichia coli infections (code 041.4)	988	6.25 ± 2.92	January	0.156
Volume depletion (code 276.5)	995	4.20 ± 2.66	April/May	0.335
Alzheimer's disease and senile degeneration of brain (codes 331.0–331.2)	2652	12.65 ± 5.71	December	0.143
Cerebral atherosclerosis and other generalised ischemic cerebrovascular diseases (codes 430–437.1)	15 219	53.10 ± 25.8	April and October/November	0.025
Congestive heart failure, unspecified and heart failure, unspecified (codes 428.0–428.9)	3704	3.32 ± 11.97	January	0.962
Injury and trauma (codes 800–959)	3274	9.89 ± 8.37	December	0.523

Amplitude: one-half the difference between the absolute maximum and minimum of the fitted curve, expressed in degrees; acrophase (peak): the absolute maximum value during the observed period, expressed in months (see text for details).

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equally distributed during the entire year and not in certain seasons only, and it is unlikely that this may interfere with the results. Moreover, a choice was made to limit the study to the patients admitted to medical units only, which represent our peculiar professional expertise also in the view of ICD-9 codification. This represents a strength of our study, but at the same time a significant limitation, because the findings cannot be generalised to general population nor to the overall population admitted to a general hospital. Further studies are needed to investigate the role and temporal seasonal influence of possible favouring or triggering factors, to try to better understand this syndrome and to improve prevention strategies.

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References

1. McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. Arch Intern Med 2002;**162**:457–463.
2. Lundström M, Edlund A, Karlsson S, Bränström B, Bucht G, Gustafson Y. A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. J Am Geriatr Soc 2005;**53**:622–628.
3. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing 2006;**35**:350–364.
4. Yang FM, Marcantonio ER, Inouye SK et al. Phenomenological subtypes of delirium in older persons: patterns, prevalence, and prognosis. Psychosomatics 2009;**50**:248–254.
5. Saxena S, Lawley D. Delirium in the elderly: a clinical review. Postgrad Med J 2009;**85**:405–413.
6. Mittal V, Muralee S, Williamson D et al. Review: delirium in the elderly: a comprehensive review. Am J Alzheimers Dis Other Demen 2011;**26**:97–109.
7. Balan S, Leibovitz A, Freedman L et al. Seasonal variation in the incidence of delirium among the patients of a geriatric hospital. Arch Gerontol Geriatr 2001;**33**:287–293.
8. Mojòn A, Fernàndez JR, Hermida RC. Chronolab: an interactive software package for chronobiologic time series analysis written for the Macintosh computer. Chronobiol Int 1992;**9**:403–412.
9. Bachman D, Rabins P. "Sundowning" and other temporally associated agitation states in dementia patients. Annu Rev Med 2006;**57**:499–511.
10. Dodek PM, Norena M, Keenan SP, Teja A, Wong H. Intensive care unit admissions for community-acquired pneumonia are seasonal but are not associated with weather or reports of influenza-like illness in the community. J Crit Care 2011;**26**:228–233.
11. Donaldson GC, Goldring JJ, Wedzicha JA. Influence of season on exarcebation characteristics in patients with COPD. Chest 2012;**141**:94–100.
12. Manfredini R, Manfredini F, Boari B et al. Seasonal and weekly patterns of hospital admissions for nonfatal and fatal myocardial infarction. Am J Emerg Med 2009;**27**:1097–1103.
13. Barnett AG, de Looper M, Fraser JF. The seasonality in heart failure deaths and total cardiovascular deaths. Aust N Z J Public Health 2008;**32**:408–413.
14. Gallerani M, Boari B, Manfredini F, Manfredini R. Seasonal variation in heart failure hospitalization. Clin Cardiol 2011;**34**:389–394.
15. Gallerani M, Boari B, Smolensky MH et al. Seasonal variation in occurrence of pulmonary embolism: analysis of the database of the Emilia-Romagna region, Italy. Chronobiol Int 2007;**24**:143–160.
16. Manfredini R, Manfredini F, Boari B et al. Temporal patterns of hospital admissions for transient ischemic attack. A retrospective population-based study in the Emilia-Romagna region of Italy. Clin Appl Thromb Hemost 2010;**16**:153–160.
17. Gallerani M, Manfredini R, Ricci L et al. Chronobiological aspects of acute cerebrovascular diseases. Acta Neurol Scand 1993;**87**:482–487.
18. Spencer FA, Goldberg RJ, Becker RC, Gore JM. Seasonal distribution of acute myocardial infarction in the second National Registry of Myocardial Infarction. J Am Coll Cardiol 1998;**31**:1226–1233.
19. Boulay F, Berthier F, Sisteron O, Gendreike Y, Gibelin P. Seasonal variation in chronic heart failure hospitalizations and mortality in France. Circulation 1999;**100**:280–286.
20. Dentali F, Ageno W, Rancan E et al. Seasonal and monthly variability in the incidence of venous thromboembolism: a systematic review and a meta-analysis of the literature. Thromb Haemost 2011;**106**:439–447.
21. Anderson JE. Seasonality of symptomatic bacterial urinary infections in women. J Epidemiol Community Health 1983;**37**:286–290.
22. Freeman JT, Anderson DJ, Sexton DJ. Seasonal peaks in *Escherichia coli* infections: possible explanations and implications. Clin Microbiol Infect 2009;**15**:951–953.
23. Chazan B, Colodner R, Edelstein H, Raz R. Seasonal variation in *Escherichia coli* blood stream infections in northern Israel. Clin Microbiol Infect 2011;**17**:851–854.
24. Inouye SK. Delirium in older persons. N Engl J Med 2006;**354**:1157–1165.
25. Lin RY, Heacock LC, Bhargave GA, Fogel JF. Clinical associations of delirium in hospitalized adult patients and the role of on admission presentation. Int J Geriatr Psychiatry 2010;**25**:1022–1029.

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