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JOURNAL OF GERONTOLOGY AND GERIATRICS

Indexed in Embase, Excerpta Medica Database
and Scopus Elsevier Database

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Editorial

The Editorial Board and I are delighted to present this first issue of the *Journal of Gerontology and Geriatrics* (JGG), the new official journal of the Italian Society of Gerontology and Geriatrics (SIGG).

Over the past decades, significant changes have been reported in the growth of aged persons throughout the world, with a great impact on society. This growth is the result of both a general increase in the overall population size and a strong decline in leading causes of mortality. As a consequence, these demographic transformations are leading to an increase in medical care and social needs.

There are several journals devoted to aging topics already, having the word “geriatrics” in the title. So is there a need for yet another journal? The Editorial Board of the JGG certainly thinks so. This Journal is one of the new breed of online-only journals which are proving extremely successful. But it is not the magic word “internet” that makes the difference.

The JGG deals with topics as physiology, pathology, aetiology, pathogenesis, epidemiology, genetics and treatment of aging and age-related diseases. The JGG is published using an open access publication model, thus all readers are able to freely access the journal online, without the need for a subscription. SIGG will cover the costs of all activities related to the management and publication of the submitted manuscripts, giving Authors a great opportunity to disseminate the results of their basic research and clinical practices as well as their opinions and suggestions in an open debate among different professionals devoted to aging.

Open does not necessarily mean low quality. On the contrary, our strongly-committed Editorial Board includes well-known International Researchers, who are involved in selecting quality reviewers and ensuring the review process focuses on strong papers that report high-quality research. Authors of submitted papers will be receiving feedback that enables them to, sometimes significantly, improve their papers and respective research agendas.

One of the innovations of the JGG is to offer Authors the opportunity to publish different types of papers, namely: (1) original investigations, (2) short communications, (3) reviews, (4) clinical experiences and case reports, (5) clinical guidelines, (6) editorials and commentaries, and (7) hypothesis papers. Furthermore, the JGG aims to publish Special Issues on the hottest topics in geriatrics. These Special Issues will be freely available online with the maximum possible dissemination and recognition within the scientific community.

Thanks are due to many people who have helped in starting up this new journal. We are particularly grateful to the SIGG President (Nicola Ferrara) and the Section Editors (Marco Zoli and Patrizio Odetti), as well as the Associate Editors and the Editorial Board members who provided us with their support, and who will continue to represent the Journal in their geographical areas. We are sure that their International reputation and great expertise in the field will have a significant contribution in shaping up the Journal and making the JGG a prestigious first-class International Journal.

We are convinced that with this unreserved support from such a prominent and large team of researchers, the JGG will become one of the most prestigious journals in the field of ageing.

Finally, the Editor-in-Chief wishes to thank the authors who submitted papers to the first issue of JGG. We are grateful that they responded to our invitation.

We hope that the new JGG will serve the scientist community and this Journal will be the main vehicle of presenting ideas and research work in the prospective area. Any suggestion on how to improve our activity in order to deliver a better Journal to the Authors, readers and subscribers of this Journal will be always very much appreciated.

Gianluigi Vendemiale
Editor-in-Chief

Journal of Gerontology and Geriatrics

Mobility and handgrip strength but not aortic stiffness are associated with frailty in the elderly

L.M. Kannejieter, L. Tap, C. Oudshoorn, R.L. Van Bruchem-Visser, F.U.S. Mattace-Raso

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Background and aim. Frailty and several age-related conditions are associated with morbidity and mortality. This cross-sectional study is conducted to investigate the hypothesis whether frailty is associated with impaired mobility and handgrip strength, and aortic stiffness.

Methods. A total of 117 consecutive patients of the outpatient Geriatric Clinic, were included in this study. Frailty is measured using Fried's Frailty Index. Mobility was assessed with the Timed up And Go test and gait speed was measured with the 5 meter walk test. Handgrip strength was measured with a handheld dynamometer. Aortic stiffness was non-invasively measured by the Mobil-O-Graph and aortic Pulse Wave Velocity (aPWV) was calculated.

Results. 25% of the participants was classified as frail. Mean time for the TUG was 11,1 s (95% Confidence Interval, 9.4-12.8) for the non-frail participants, 13.5 s (12.4-14.7) for the pre-frail and 18.5 s (16.6-20.4) for the frail participants. Mean time for the 5MGS was 5.2 s (95% CI, 4.6-5.8) for the non-frail subjects, 5.8 s (5.4-6.2) for the pre-frail subjects and 9,2 s (8.5-9.9) for the frail subjects. Mean handgrip strength was 30.6 kg (95% CI, 28.3-32.9) for the non-frail, 24.8 kg (23.4-26.,3) for the pre-frail and 20.3 kg (18.1-22.5) for the frail participants. We did not find differences of aortic stiffness within groups.

Conclusion. Frail participants need significant more time to complete the Timed Up and Go test and the 5 Meter Gait Speed test, and have significant lower handgrip strength. Frail individuals do not have increased aortic stiffness.

Key words: Frailty, Timed up and Go test, 5 Meter Gait Speed test, Handgrip strength, Aortic stiffness

Introduction

Frailty is an age-related clinical syndrome characterized by decreased physiological reserves and a reduced ability to recover from acute stressors. Frailty is a strong predictor of many adverse health outcomes in the elderly¹; falls, worsening mobility or ADL disability, hospitalization and death. Frailty is also correlated to cardiovascular morbidity and mortality^{2,3}.

Several age-related conditions are associated with morbidity and mortality. The Timed Up and Go test⁴ and the 5 Meter Gait Speed test are easy measurements

of physical performance. A reduced physical status will result in more time needed to complete the tests. The walking tests are associated with morbidity and mortality in both a community-dwelling⁵ and an onco-geriatric population⁶. Muscle weakness is another age-related condition, that is frequently observed in the elderly. A reduced muscle strength is a risk factor for mortality in the elderly⁷. Previous studies found an association between aortic stiffness and the classical cardiovascular disease risk factors, such as aging^{8,9}, atherosclerosis¹⁰, higher blood pressure⁹ and diabetes mellitus¹¹. Aortic

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stiffness is an independent predictor of coronary heart disease and stroke in apparently healthy subjects¹². Pulse wave velocity (PWV) is a measure to evaluate aortic stiffness and PWV will increase in stiffer arteries. In the present study we have investigated whether these age-related conditions are associated with frailty. Patients and methods

PARTICIPANTS AND DESIGN

From April 2015 to August 2015, consecutive patients visiting the outpatient Geriatric Clinic of the Erasmus MC were recruited. Patients older than 60 years are asked to participate in this study. Data on frailty, mobility, handgrip strength, aortic stiffness and demographics were collected for this cross-sectional study. The Medical Ethics Committee of the Erasmus MC approved this study and written informed consent was obtained from all individual participants.

FRAILTY

Frailty was assessed using Fried's frailty index¹. This frailty model uses 5 items: exhaustion, unintentional weight loss, low daily physical activity, slow walking speed and weakness. Information is obtained during an interview. Two statements of the CES-D depression scale are asked to identify exhaustion¹³; "I felt that everything that I did last week was an effort" and "I could not get going." When a subject answers that this was the case 3 or more days in the past week, this person is indicated as positive for exhaustion. Weight loss is classified as > 5% loss in the past twelve months. To score low daily physical activity, subjects were asked if they perform daily activities like gardening, walking or light housework. For the classification of slow walking speed and weakness, see *mobility tests* and *handgrip strength*. Individuals are indicated as non-frail if they meet none of the criteria mentioned above, pre-frail when meeting one or two criteria and frail when meeting 3 or more criteria.

MOBILITY TESTS

Two mobility tests are used in this study. One measurement of the 5 Meter Gait speed test is used as a component of the frailty index. The second mobility test used, is the Timed Up And Go test⁴ (for cut-off points for slowness, see appendix).

HANDGRIP STRENGTH

Muscle weakness is determined by the handgrip strength, measured with a handheld dynamometer (Hand dynamometer 90 kg/0.1 kg EH101, Vetek, Sweden). The best of two measures is noted for the

dominant and the non-dominant hand. The measure of the dominant hand is used for analysis (for cut-off points for handgrip strength, see appendix).

AORTIC STIFFNESS

Aortic stiffness is measured non-invasively by the Mobil-O-Graph (Mobil-O-Graph 24h PWA Monitor, I.E.M. GmbH, Stolberg, Germany). This electronic blood pressure monitoring system uses a simple upper arm cuff and special software to calculate the pulse wave velocity. The reliability of this oscillometric method to determine aortic PWV (aPWV) was demonstrated in a previous study¹⁴. Measurements were conducted with subjects in sitting position and there were no restrictions in smoking, drinking coffee or tea and taking medications.

ADDITIONAL INFORMATION

During an interview, additional information is obtained. Katz index is used for scoring ADL (Activities of Daily Living)¹⁵ and the Lawton and Brody index is used for scoring iADL (instrumental Activities of Daily Living)¹⁶. (i)ADL dependency is defined as having ≥ 1 limited activity. Cohabitation status is classified as alone, with a partner or in a residential institute. Level of education can be primary education, lower secondary, upper secondary and tertiary education or higher based on the International Standard Classification of Education (ISCED). The number of different medications was asked and the number of different co-morbidities is noted (for subgroups of co-morbidity, see appendix).

STATISTICAL ANALYSIS

Continuous variables are expressed as median with range and categorical data were expressed as number and percentage. Differences in continuous variables for frail, pre-frail and non-frail individuals were assessed using an analysis for covariance (ANCOVA). Mean values the Timed up and Go test, the 5 Meter Gait Speed test and PWV were compared across levels of frailty. Analysis for the walk test and the handgrip strength are adjusted for age, sex and number of co-morbidities. Analysis for pulse wave velocity are adjusted for age, sex, heart rate, mean arterial pressure and number of co-morbidities. Statistical analysis was performed using SPSS statistical package 21.0 for Windows.

RESULTS

The study population consisted of 117 individuals, median age was 79 years (range 61-95) and 51.3% was male. Of all individuals, 52.1% lives with a partner, 67.5% is ADL independent and 29.1% is iADL independent. Baseline characteristics are shown in Table I.

Table I. Values are expressed as median with range for continuous variables, and dichotomous variables are expressed as number with percentage. Abbreviations used: ADL Activities of Daily Living, iADL instrumental Activities of Daily Living.

Baseline characteristics	
Age, years	79 (61-95)
Sex, number (%)	
Male	60 (51.3%)
Female	57 (48.7%)
Education, number (%)	
Primary	26 (22.2%)
Lower secondary	48 (41.0%)
Upper secondary	24 (20.5%)
Tertiary	19 (16.2%)
Cohabitation, number (%)	
Alone	56 (43.6%)
With partner	61 (56.4%)
ADL, n (%)	
Independent	79 (67.5%)
Dependent	38 (32.5%)
iADL, n (%)	
Independent	34 (29.1%)
Dependent	83 (70.9%)

In Table II, functional characteristics of the population are shown. 24.8% of the individuals can be indicated as frail, 52.1% as pre-frail and 23.1% as non-frail. Median time to complete the TUG was 13.0 seconds (range 5.7-49.0) and 5.7 seconds (range 3.6-17.2) for the 5MGS. Median handgrip strength is 23.6 kg (range 4.6-50.4) and median PWV is 12.2 m/s (8.5-16.7)

Age was found to be positively correlated with the Timed Up and Go test (Pearson's $r = 0.338$, $p < 0.001$), the 5 Meter Gait Speed test (Pearson's $r = 0.341$, $p < 0.001$) and pulse wave velocity (Pearson's $r = 0.880$, $p < 0.001$). There was a negative correlation between age and handgrip strength (Pearson's $r = -0.476$, $p < 0.001$). Results are shown in Figure 1.

Times for the TUG and the 5MGS were significantly higher for the frail participants, compared to the non-frail and pre-frail participants. Mean time for the TUG was 11.1 s (95% Confidence Interval, 9.4-12.8) for the non-frail participants, 13.5 s (12.4-14.7) for the pre-frail participants and 18.5 s (16.6-20.4) for the frail participants. Mean time for the 5MGS was 5.2 s (95% CI, 4.6-5.8) for the non-frail subjects, 5.8 s (5.4-6.2) for the pre-frail subjects and 9.2 s (8.5-9.9) for the frail subjects. Handgrip strength was significant lower for frail participants. Mean strength was 30.6 kg (95% CI, 28.3-32.9) for the non-frail participants, 24.8 kg (23.4-26.3) for the pre-frail participants and 20.3 kg (18.1-22.5) for the frail participants. Frailty is not associated

Table II. Values are expressed as median with range for continuous variables, and dichotomous variables are expressed as number with percentage. Abbreviations used: MMSE Minimal Mental State Examination, TUG Timed Up and Go test, 5MGS 5 Meter Gait Speed test, PWV Pulse Wave Velocity, pDBP peripheral Diastolic Blood Pressure, pSBP peripheral systolic blood pressure, BMI Body Mass Index.

Functional characteristics	
Fried, number (%)	
Nonfrail	27 (23.1%)
Pre-frail	61 (52.1%)
Frail	29 (24.8%)
MMSE, points	26 (8-30)
Co-morbidity, number	4 (0-8)
Medication, number	7.0 (0-23)
TUG, seconds	13.0 (5.7-49)
5MGS, seconds	5.7 (3.6-17.2)
Grip strength, kg	23.6 (4.6-50.4)
PWV, m/s	12.2 (8.5-16.7)
pDBP, mmHg	83.0 (59-142)
pSBP, mmHg	138.0 (86-235)
BMI, kg/m ²	25.2 (14.5-38.6)

with increasing PWV. Frail individuals have a mean PWV of 12.1 m/s (95% CI, 11.9-12.2), pre-frail a PWV of 12.1 m/s (12.0-12.2) and non-frail individuals have a PWV of 12.1 (11.9-12.3). Results are shown in Figure 2.

DISCUSSION AND CONCLUSION

In this present study we found that mobility and handgrip strength are impaired in frail elderly participants, aortic stiffness did not differ within frail and non-frail participants.

We found that frail participants need more time to complete the TUG and the 5MGS. These results are in agreement with the results of previous studies, which validated both tests for screening of frailty in the elderly population¹⁷⁻¹⁹. The Timed Up and Go test and the 5 Meter Gait Speed test are designed to test mobility, power and balance. Impaired mobility, power and balance will result in more time needed to perform the walk tests. These qualities can be trained with physical activity. Previous studies found that a long term structured physical activity program can reduce mobility disability and the presence of frailty^{20 21}. Therefore, the performance on the walk tests can be used as an indicator for attending a physical activity program, to modify the risk for frailty. Besides muscle weakness due to sedentary habits, muscle weakness is also the result of aging.

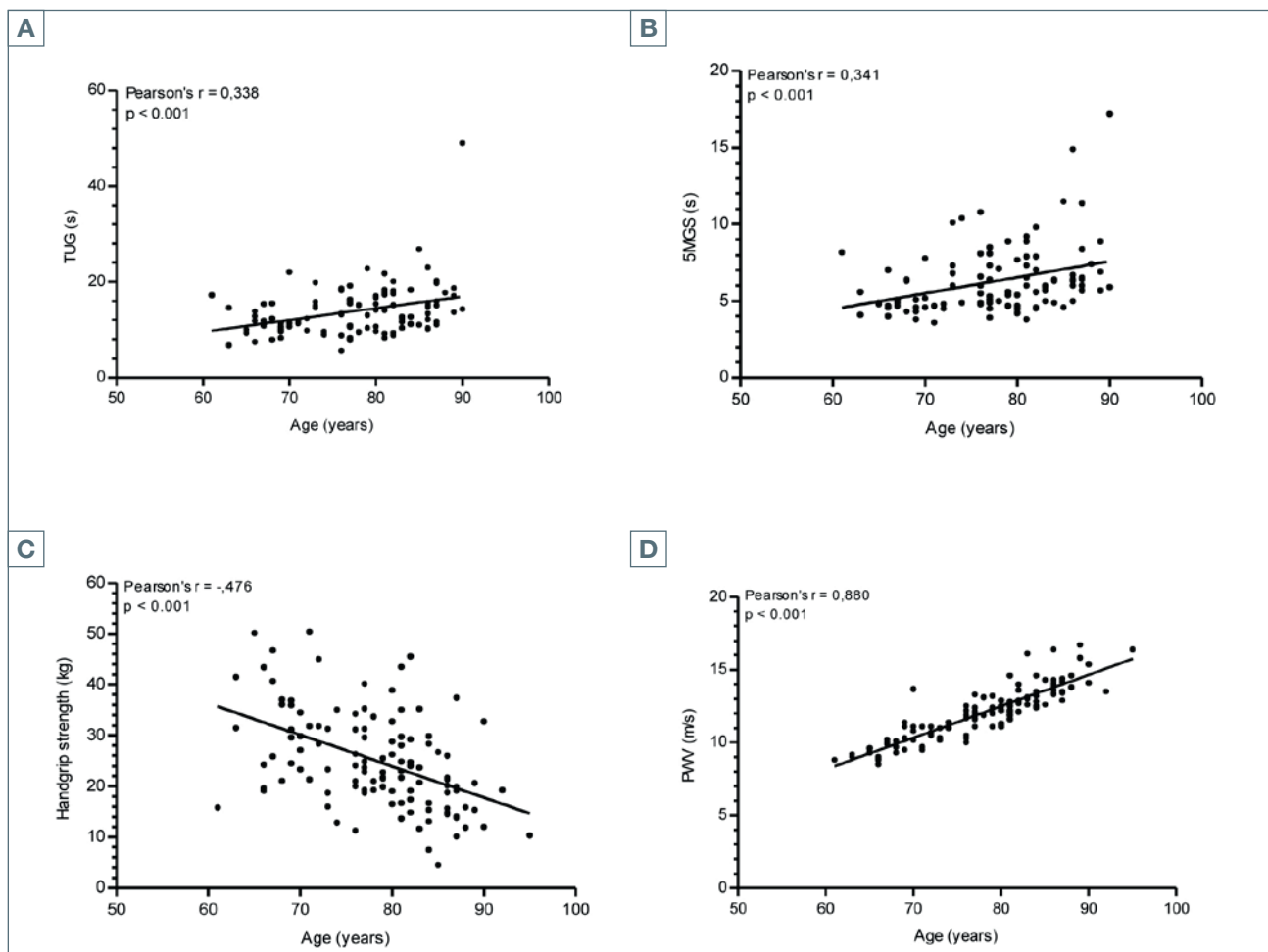


Figure 1. Correlation of age with different measures. **(A)** Timed Up and Go test, **(B)** 5 Meter Gait Speed, **(C)** Handgrip strength **(D)** Pulse wave velocity.

With aging, both muscle fiber size and number of fibers will decrease²². In this study, we found a strong correlation between the walk tests and age, and frailty too has a strong correlation with age¹. Therefore, age can partly explain the relationship between frailty and the walk tests. However, this relationship remains even after adjusting for age, sex and number of co-morbidities. The measurement of the handgrip strength is a direct measure of the muscle power. Like the walk tests, the handgrip strength is also of predictive value for mobility disability²³. The relationship between a reduced handgrip strength and frailty found in this study, is in agreement with a previous study²⁴. The different components of Fried's Phenotype have a relationship with muscle power. First, a reduced power can make a person feel exhausted. Second, involuntary weight loss can result in muscle weakness. Third, two components of Fried's Phenotype, namely handgrip strength and slowness, are direct measurements of power.

The relation between the walk test and handgrip strength, and frailty shows that these tests can be used as a proxy for frailty. The use of the walk tests in daily practice is easy, quick and does not require any special equipment. Additionally, the results of the walk tests and the handgrip strength are continuous measures and a cut-off point is not necessary. This is a main advantage over Fried's Phenotype, where 5 cut-off points are used to determine frailty in a range from 0 to 5. This frailty score again is divided into 3 groups: non-frail, pre-frail and frail. Using a continuous scoring system is more precise.

A previous study has investigated the possible role of a vascular measurement as a candidate biomarker for frailty. In contrast to our findings, a study by Avila-Funes et al.²⁵ found an association between age-related structural changes of the arteries such as the common carotid intima media thickness (IMT) and the diameter of the common carotid diameter, and frailty. Moreover,

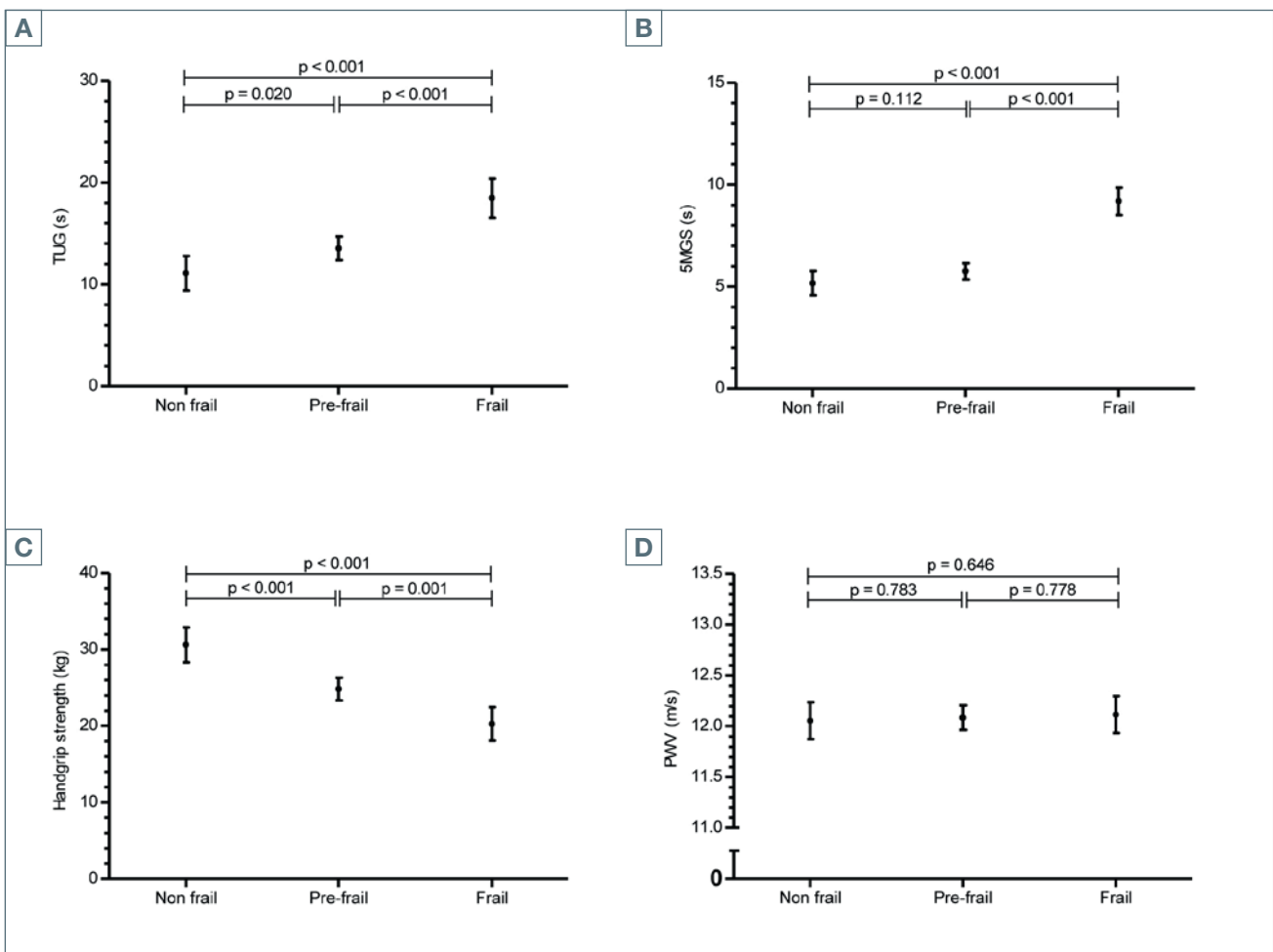


Figure 2. Mean values across levels of frailty for different measures. **(A)** the Timed Up and Go test, **(B)** the 5 Meter Gait Speed test, **(C)** Handgrip strength and **(D)** Pulse wave velocity. Dots represent mean values, lines represent 95% confidence intervals.

the carotid IMT and carotid diameter are measures other than PWV which reflect structural changes in central arterial structure. The measure of aortic PWV is a functional measure which gives information on the distensibility of the vessel walls.

In this study we measured a pre-clinical or a primary frailty, because the frailty is not directly associated a specific disease and there is limited disability among the participants. Additionally, the frailty is not associated with a known comorbidity or overt cardiovascular disease²⁶. This explains our findings that the screening tests for frailty, the walktests and the handgrip strength, are associated with frailty, but aortic stiffness is not. The association between aortic stiffness and frailty, measured by the aPWV, is more likely to present in a population with secondary frailty.

Previous studies have investigated the relationship between arterial stiffness and different components of frailty. A meta-analysis of 5 studies²⁷ with a total of

3687 participants showed that higher aortic stiffness significantly predicts cognitive decline, measured by the Minimal Mental State Examination (MMSE). The relationship between aortic stiffness and the development of dementia is not clear. Ochi et al.²⁸ found that arterial stiffness is associated with low thigh muscle mass in middle aged to elderly men, but not in women. They found a correlation between the mid-thigh muscle cross-sectional area corrected by body weight, and arterial stiffness measured by brachial-ankle PWV (baPWV) and carotid IMT. Sarcopenia results in weakness, one of the elements of frailty. Weakness in this study is measured in Fried's scale by the handgrip strength, and weakness is reflected in the Timed Up and Go test.

We found that 24.8% of the participant can be indicated as frail. This is a higher prevalence than in other studies, where prevalence is around the 10%^{17 19 25 29}. The population in these studies consisted of community-dwelling

elderly, while the population of our study consisted of patients from a geriatric outpatient clinic.

The present study has some limitations. First, due to the cross-sectional design it is impossible to determine the direction of the relationship. Second, there were no restrictions in smoking, drinking coffee or tea and taking medication on the day of the measurement. This may have influenced the measurements of the arterial stiffness. Third, a relatively small number of 117 participants was included in the study.

In conclusion, we found in this cross-sectional study that frail participants, need more time to complete the Timed Up and Go test and the 5 Meter Gait Speed test, have a lower handgrip strength, but do not have higher PWV-values.

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References

- Fried LP, Tangen CM, Walston J, et al. *Frailty in older adults: evidence for a phenotype*. J Gerontol A Biol Sci Med Sci 2001;56:M146-M57.
- Khan HKA, Georgiopoulou VV, Newman AB, et al. *Frailty and risk for heart failure in older adults: the health, aging and body composition study*. Am Heart J 2013;166:887-94.
- Cacciatore F, Abete P, Mazzella F, et al. *Frailty predicts long-term mortality in elderly subjects with chronic heart failure*. Eur J Clin Invest. 2005;35:723-30.
- Podsiadlo DRS. *The Timed "Up & Go": a test of basic functional mobility for frail elderly persons*. J Am Geriatr Soc 1991;39:142-8.
- Studenski S, Perera S, Patel K, et al. *Gait speed and survival in older adults*. JAMA 2011;305:50-8.
- Huisman MG, van Leeuwen BL, Ugolini G, et al. *"Timed Up & Go": a screening tool for predicting 30-day morbidity in onco-geriatric surgical patients? A multicenter cohort study*. PLoS ONE 2014;9:e86863.
- Alexandre Tda S DY, Santos JL, Wong R, et al. *Sarcopenia according to the European Working Group on Sarcopenia in Older people (EWGSOP) versus dynapenia as a risk for mortality in the elderly*. J Nutr Health Aging 2014;18:751-6.
- Laurent S CJ, Van Bortel L, Boutouyrie P, et al. *Expert consensus document on arterial stiffness: methodological issues and clinical applications*. Eur Heart J 2006;27:2588-605.
- Collaboration RVfAs. *Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: establishing normal and reference values*. Eur Heart J 2010;31:2338-50.
- Wada T, Kodaira K, Fujishiro K, et al. *Correlation of ultrasound-measured common carotid artery stiffness with pathological findings*. Arterioscler Thromb Vas 1994;14:479-82.
- Lehmann ED GR, Sönksen PH. *Arterial wall compliance in diabetes*. Diabet Med 1992;9:114-9.
- Mattace-Raso FUS, van der Cammen TJM, Hofman A, et al. *Arterial stiffness and risk of coronary heart disease and stroke: The Rotterdam Study*. Circulation 2006;113:657-63.
- Orme JG RJ, Herz EJ. *Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale*. J Clin Psychol 1986;42:28-33. doi:
- Hametner B WS, Kropf J, Mayer C, et al. *Oscillometric estimation of aortic pulse wave velocity: comparison with intra-aortic catheter measurements*. Blood Press Monit 2013;18:173-6.
- Katz S, Ford AB, Moskowitz RW, et al. *Studies of illness in the aged: The index of adl: a standardized measure of biological and psychosocial function*. JAMA 1963;185:914-9.
- Lawton MP BE. *Assessment of older people: self-maintaining and instrumental activities of daily living*. Gerontologist 1969;9:179-86.
- Castell M-V, Sanchez M, Julian R, et al. *Frailty prevalence and slow walking speed in persons age 65 and older: implications for primary care*. BMC Family Practice 2013;14:86.
- Clegg A, Rogers L, Young J. *Diagnostic test accuracy of simple instruments for identifying frailty in community-dwelling older people: a systematic review*. Age Ageing 2015;44:148-52.
- Sawa GM, Donoghue OA, Horgan F, et al. *Using timed up-and-go to identify frail members of the older population*. J Gerontol A Biol Sci Med Sci 2013;68:441-6.
- Pahor M, Guralnik JM, Ambrosius WT, et al. *Effect of structured physical activity on prevention of major mobility disability in older adults: the life study randomized clinical trial*. JAMA 2014;311:2387-96.
- Cesari M, Vellas B, Hsu F-C, et al. *A physical activity intervention to treat the frailty syndrome in older persons – results from the LIFE-P Study*. J Gerontol A Biol Sci Med Sci 2015;70:216-22. .
- Narici MV, Maffulli N. *Sarcopenia: characteristics, mechanisms and functional significance*. Brit Med Bull 2010;95:139-59. .
- Marsh AP, Rejeski WJ, Espeland MA, et al. *Muscle strength and BMI as predictors of major mobility disability in the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P)*. J Gerontol A Biol Sci Med Sci 2011;66A:1376-83.
- Auyeung TW LJ, Leung J, Kwok T, et al. *The selection of a screening test for frailty identification in community-dwelling older adults*. J Nutr Health Aging 2014;18:199-203.
- Avila-Funes JA, Meillon C, González-Colaço Harmand M, et al. *Association between frailty and carotid central structure changes: the three-city study*. J Am Geriatric Society 2014;62:1906-11.
- Strandberg TE, Pitkälä KH. *Frailty in elderly people*. Lancet 2007;369:1328-9.

- ²⁷ Pase MP, Herbert A, Grima NA, et al. *Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis*. *Internal Med J* 2012;42:808-15.
- ²⁸ Ochi M, Kohara K, Tabara Y, et al. *Arterial stiffness is associated with low thigh muscle mass in middle-aged to elderly men*. *Atherosclerosis* 2010;212:327-32.
- ²⁹ Santos-Eggimann B, Cuénoud P, Spagnoli J, et al. *Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries*. *J Gerontol A Biol Sci Med Sci* 2009;64A:675-81.

Appendix

Fried's Phenotype		
Weight loss	Unintentional weight loss > 5% in the previous year	1 point
Exhaustion	Two statements of the CES-D depression scale are read I felt that everything I did was an effort I could not get going Question is: 'How often in the last week did you feel this way?' If answering 3 or more days in the past week, a person is indicated as frail for exhaustion	1 point
Physical activity	Not performing daily leisure activities such as walking or gardening, or exercising at less than once a week	1 point
Slowness	Cutoff points are stratified by gender and height: Men: Height ≤ 173 cm ≥ 7.7 seconds Height > 173 cm ≥ 6.6 seconds Women: Height ≤ 173 cm ≥ 7.7 seconds Height > 173 cm ≥ 6.6 seconds	1 point
Handgrip strength	Cutoff points are stratified by gender and BMI: Men: BMI ≤ 24 ≤ 29 BMI 24.1 – 26 ≤ 30 BMI 26.1 – 28 ≤ 30 BMI > 28 ≤ 32 Women: BMI ≤ 23 ≤ 17 BMI 23.1 – 26 ≤ 17.3 BMI 26.1 – 29 ≤ 18 BMI > 29 ≤ 21	1 point
Co-morbidities		
Cardiac	<input type="radio"/> yes	<input type="radio"/> no
Hypertension	<input type="radio"/> yes	<input type="radio"/> no
Vascular	<input type="radio"/> yes	<input type="radio"/> no
Respiratory	<input type="radio"/> yes	<input type="radio"/> no
EENT	<input type="radio"/> yes	<input type="radio"/> no
Gastro-intestinal	<input type="radio"/> yes	<input type="radio"/> no
Hepatic	<input type="radio"/> yes	<input type="radio"/> no
Renal	<input type="radio"/> yes	<input type="radio"/> no
Urogenital	<input type="radio"/> yes	<input type="radio"/> no
Musculoskeletal	<input type="radio"/> yes	<input type="radio"/> no
Neurological	<input type="radio"/> yes	<input type="radio"/> no
Endocrine-metabolic	<input type="radio"/> yes	<input type="radio"/> no
Psychiatric	<input type="radio"/> yes	<input type="radio"/> no

Review

Management of oral drug therapy in elderly patients with dysphagia

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We aimed at summarizing current evidence on age-related changes in swallowing, the impact of selected medications on swallowing, and the management of oral drug therapy in older patients with dysphagia. The risk for oropharyngeal swallowing disorders increases with age. Though increasing age facilitates subtle physiologic changes in swallow function, age-related diseases are most significant factors in the onset and severity of dysphagia. In older people, dysphagia can also occur as a side effect of some medications. Drug-induced dysphagia can appear as a drug side effect or as a complication of the therapeutic action of the drug, mainly through induction of xerostomia, impaired swallowing muscle function or esophageal injury. Whatever the mechanism leading to dysphagia, the administration of drugs to dysphagic patients is a really challenging issue. Manipulations of solid oral drugs frequently occur in geriatric settings, leading to potential medication errors and changes in drug performance. The implementation of guidelines for management of oral drug therapy in dysphagic patients may contribute to improve the quality of care provided to this very frail population.

Key words: Swallowing disorders, Dysphagia, Elderly, Functional status, Polypharmacy, Medication-induced dysphagia

INTRODUCTION

Dysphagia refers to the loss of swallowing function ¹, and is a growing health concern in aging populations. Its incidence in acute care settings has been reported as high as 33%, and affects up to 68% of elderly nursing home residents ², resulting in a high incidence of respiratory complications ³.

Age-related changes in swallowing functions place older adults at risk for dysphagia for two major reasons. First, healthy aging takes its toll on head and neck anatomy, as well as physiologic and neural mechanisms underpinning swallowing function. Such mechanisms of naturally diminishing functional reserve

contribute to swallowing alterations in healthy older adults which are known as *presbyphagia*. Second, age-related diseases, including neurological (e.g. stroke, Parkinson's and Alzheimer's disease) and non-neurological diseases (e.g. gastro-oesophageal reflux disease) ^{4 5} may be associated with swallowing disorders. Finally, older patients with multiple chronic diseases are often treated with complex polypharmacy regimens, and selected medications may contribute to the onset of swallowing disorders by several different mechanisms.

The clinical implications of dysphagia are complex and potentially dangerous. Indeed, besides increasing the risk of aspiration pneumonia, swallowing disorders

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could compromise medication adherence and therapeutic outcomes. Big size and poor quality of tablet coatings are among reasons to withdraw oral medications⁶, and older age is associated with increasing prevalence of oral drug administration problems⁷. Despite this bulk of evidence, swallowing problems often remain concealed in older adults, leading to dehydration/malnutrition⁸ and pneumonia^{9,10}. Therefore, the aim of this review is to summarize current evidence on age-related changes in swallowing, the impact of selected medications on swallowing, and the management of oral drug therapy in older patients with dysphagia.

AGING AND PRESBYPHAGIA

The physiologic process of swallowing requires a complex series of psychological, sensory, and motor

functions, that are both voluntary and involuntary. Swallowing process is divided in three stages: 1) *Oral stage* (voluntary); 2) *Pharyngeal stage*; 3) *Esophageal stage* as reported in figure 1.

During the oral stage, the food is manipulated (masticated if a solid) into a cohesive unit (referred to as bolus) in preparation for the remaining phases of the swallowing process. Food is chewed and mixed with saliva to form a bolus and it is positioned on the tongue for transport. Once the bolus is prepared, the tongue begins the anterior to posterior propulsion of the bolus for passage to the pharynx. Sensory receptors in the oropharynx and tongue itself are stimulated and pharyngeal swallow is triggered. The food enters the upper throat area, the soft palate elevates and the epiglottis closes off the trachea, as the tongue moves backwards and the pharyngeal wall moves forward. These actions help force the food downward to the esophagus. Finally, the food bolus enters the esophagus and it is moved

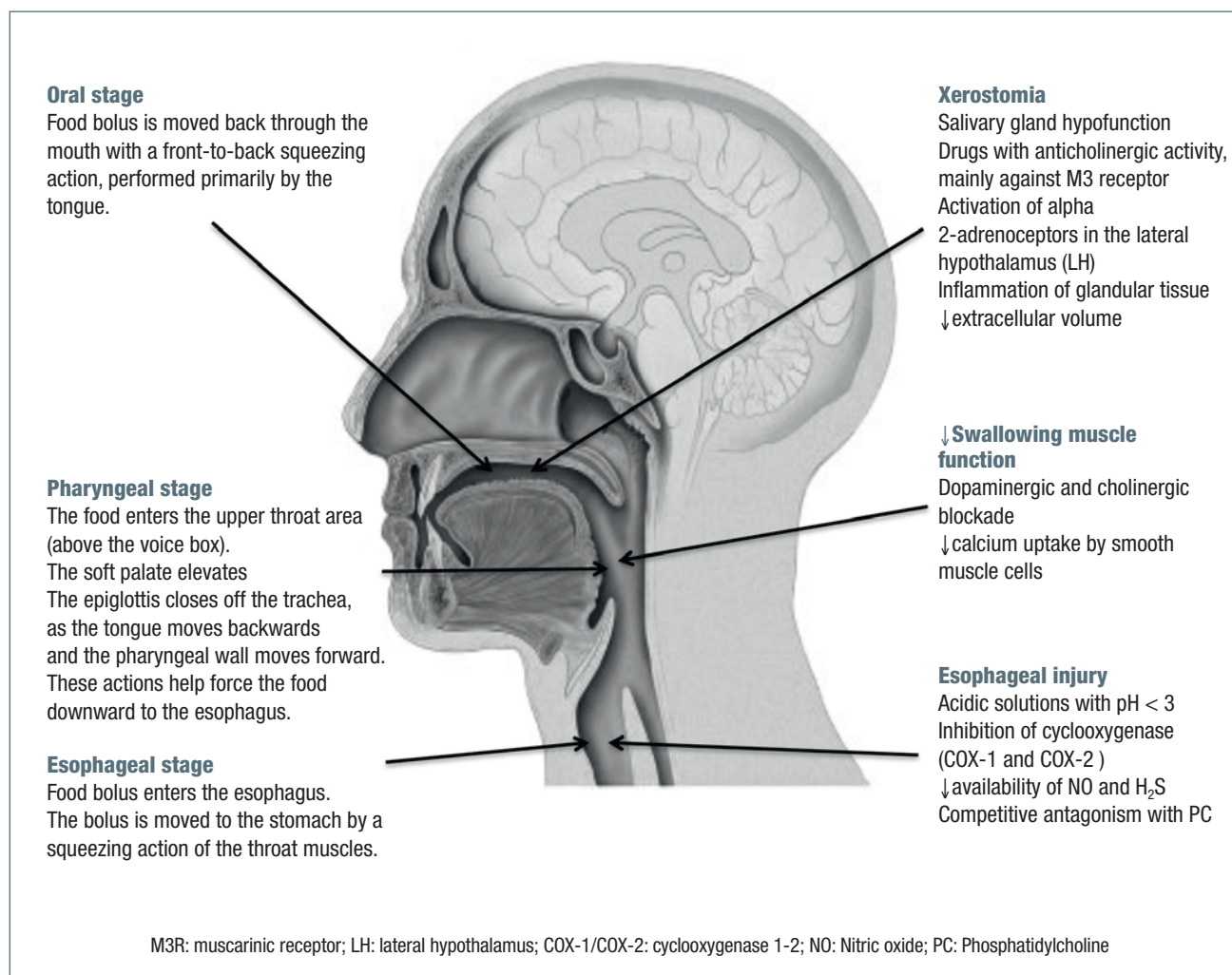


Figure 1. The main stages in the swallowing process, (left) and the main mechanism of drug induced dysphagia (right).

to the stomach by a peristaltic action of the throat muscles (esophageal stage). Bolus transport in the thoracic esophagus is quite different from that in the pharynx, because it is driven by true peristalsis regulated by the autonomic nervous system. Once the food bolus enters the esophagus passing the upper esophageal sphincter (UES), a peristalsis wave carries the bolus down to stomach through the lower esophageal sphincter (LES). Gravity assists peristalsis in upright position.

Aging is characterized by changes occurring in the structure, motility, coordination, and sensitivity of the swallowing process¹¹, and it has been estimated that 35–68% of people aged 65 or more have some degree of swallowing dysfunction^{12–13}. Declining muscle strength, receptor density and sensory receptor responsiveness are associated with a reduced lingual pressure leading to slow bolus velocity¹⁴. Periventricular white matter lesions and cerebral atrophy are usually associated with longer duration of swallowing and prolonged swallowing response time¹⁵. A desynchronization of the swallowing response of glossopalatal junction, velopharyngeal junction, laryngeal vestibule and UES¹⁶ can lead to intra-esophageal stasis (bolus retention) and reflux from the lower pharyngo-UES¹⁷. Effortful swallowing has shown to impact the swallowing response in young and older adults. While effortful swallowing can increase the oral pressure and the swallow response durations at various levels in both age groups, there were significant differences between young and older volunteers whereby the older achieved a lower maximum pressure and higher residues in the pyriform sinuses upon effortful swallowing¹⁸. Swallowing might also be affected by a decline of saliva production, which in turn impairs

bolus formation. Even if the saliva secretion, which is triggered by cholinergic stimulation of the muscarinic receptors within the saliva glands, remains stable over the life span, the decreasing number of saliva-producing acinar cells might decrease the salivary reserve. Additionally, the composition of saliva also changes with age. The saliva is composed of water, mucin, and various bactericidal components like proteolytic enzymes, antibodies, amylases and lipases. Density and viscosity of saliva increases with aging, also contributing to impaired swallowing function among older people¹⁹. Finally, sarcopenia, defined as the loss of skeletal muscle mass and strength with increased risk of adverse outcomes²⁰, contributes to presbyphagia. Indeed, it affects the muscles of the upper aero-digestive tract involved in the swallowing process, thus reducing the strength and function of the swallowing response¹⁹.

CAUSES AND CONSEQUENCES OF DYSPHAGIA

Stages of swallowing (i.e. oropharyngeal and esophageal) may be differentially affected by several diseases (Tab. I). Among these, neurologic disorders are the most frequent cause of swallowing impairment in elderly patients. Dysphagia occurs commonly after stroke, with prevalence estimates ranging between 40%–60% in the acute phase of stroke^{21–22}, mainly due to the interruption of voluntary control of the oral phase²³. Dysphagia is often observed among patients with Parkinson's disease (PD), where swallowing problems affect over 80% of diseased population, reflecting the underlying motor impairments and the extent of

Table I. Causes of dysphagia.

A. Causes of oropharyngeal dysphagia ^{106–107}	
Neurologic	Stroke, Dementia, Traumatic brain injury, Cerebral palsy Guillain-Barré syndrome, Poliomyelitis Myopathy, Coma
Myopathic	Connective tissue disease, Dermatomyositis, Myasthenia gravis, Myotonic dystrophy, Oculopharyngeal dystrophy, Sarcoidosis, Paraneoplastic syndromes
Neoplastic	Any tumor involving the aerodigestive tract
Geriatric	Age-related changes
Iatrogenic	Drugs (chemotherapy, neuroleptics etc.), Radiation therapy
Infective	Diphtheria, botulism, Lyme disease, Syphilis, Mucositis (herpes, cytomegalovirus, Candida etc.)
Metabolic	Amyloidosis, Cushing's syndrome, Thyrotoxicosis, Wilson's Disease
Dysfunctional	Gastroesophageal Reflux Disease
B. Causes of esophageal dysphagia ^{106–107}	
Mechanical (intrinsic and extrinsic)	Pyloric stenosis, Tumors, Thoracic aorta aneurysm, Muscleskeletal problems
Neuromuscular (primary and secondary)	Achalasia, Diffuse esophageal spasm, Scleroderma, Collagen diseases
Anatomical	Cricopharyngeal Barra, Zenker's diverticulum, Osteophytes, Congenital malformations, Cervical scars

the disease's progression²⁴. The swallowing disorders most frequently observed in PD patients are related to the oral and pharyngeal phase, resulting in abnormal bolus formation, delayed swallowing response, and prolonged pharyngeal transit time, with repetitive swallows to clear the throat. Dementia is frequently associated with dysphagia, and it has been estimated that up to 45% of institutionalized patients with dementia have some degree of swallowing difficulty²⁵. These difficulties may relate to cognitive impairment, motor deficits such as weakness or apraxia, loss of appetite, and/or food avoidance. As a result, patients with dementia may experience weight loss and increased dependency for feeding.

Moreover, swallowing disorders can be caused by combinations of several underlying conditions or comorbidities whose impact on risk of dysphagia is not always as obvious as for neurological diseases. Gastroesophageal reflux disease may lead to esophageal motility disturbances due to the reflux of acidic gastric contents into the esophagus and symptomatic chronic irritation or injury to the esophageal mucosa²⁶. The gastrointestinal complications of diabetes mellitus are the outward forms of the diabetic visceral neuropathy, which can affect tonus and motility of the esophagus, especially in late stages of diabetes²⁷. Recently, the association between chronic obstructive pulmonary disease (COPD) and swallowing disorders has been investigated²⁸. Limited laryngeal elevation, decreased tongue strength and movements, and delayed swallowing response are the most frequent alterations of swallowing in COPD patients²⁹. Preiksaitis et al. suggested that patients with COPD may be prone to disrupted breathing/swallowing pattern because of the combined effects of deglutition apnea and reduced ventilatory capacity³⁰. Dysphagia of cardiac origin is yet rarely diagnosed symptom³¹. The position of the esophagus relative to the spine seems to be an important factor in determining whether or not an enlarged left atrium can cause compression of the esophagus. If the oesophagus is displaced to the left, its lateral movement is limited by the descending aorta and it can then be compressed against the spine by the enlarged heart³². Finally, esophagus motor dysfunction has been reported in patients with chronic renal failure (CKD) in uremic stage. Though uremic neuropathy and/or myopathy are likely involved in esophageal motor dysfunction³³, the pathogenesis of CKD-related dysphagia is still unclear³⁴.

As for consequences of dysphagia, swallowing difficulties may contribute to malnutrition and dehydration. Up to 30% of neurological patients and up to 55% of frail older patients with dysphagia present or are at risk of malnutrition with a strong relationship between

severity of dysphagia and incidence of malnutrition^{35,36}. In a recent study in older patients with dysphagia the prevalence of malnutrition (36.8%) and risk of malnutrition (55.3%) was significantly higher compared older patients without dysphagia³⁷. A recent resolution of the Council of Europe on food and nutritional care in hospitals identified functional oropharyngeal dysphagia as a major contributor to malnutrition and its consequences, including prolonged hospital stay, impaired quality of life, and unnecessary health care costs³⁸. Dehydration also is an important concern among dysphagic patients³⁹. About 75% of individuals in long-term care have been reported to be dehydrated when relying on thickened liquids for oral hydration⁴⁰. Moreover, dehydration increases the risk of falls, kidney failure, constipation, urinary tract infections, delirium, respiratory infections, loss of muscle strength and pressure sores among bedridden patients⁴¹. Thus, nutritional and hydration status should be carefully scrutinized among older people with swallowing disorders.

Aspiration pneumonia is among leading causes of mortality after stroke, accounting for nearly 35% of post-stroke deaths⁴². Additionally, aspiration pneumonia is associated with worsening nutritional status during hospitalization³⁷, increased costs due to longer hospital stay⁴³, and more severe disability after stroke³⁷. Swallowing problems increase the risk of aspiration (inhaling fluid or stomach contents into the lungs) and pneumonia¹⁹. Altered mental status, esophageal motility disorders and vomiting, oropharyngeal colonization, and enteral feeding also represent important risk factors which need to be taken into account when assessing a dysphagic patient⁴⁴. Oral care, and among patients with tube feeding, postpyloric feeds may reduce the risk of aspiration pneumonia^{45,46}.

Finally, another important consequence of dysphagia is the difficulty in the administration of oral medications. Indeed, difficulty swallowing pills is often the first sign of dysphagia among older patients, and select medications themselves can cause swallowing problems³¹. Current evidence about these important issues will be summarized in the following sections.

MEDICATION-INDUCED DYSPHAGIA

Adverse drug reactions might cause swallowing dysfunction, mainly through induction of xerostomia, impaired swallowing muscle function or esophageal injury (Tab. II).

Xerostomia (dry mouth), is often observed among users of selected medications¹⁰, especially in patients treated with complex polypharmacy regimens⁴⁷. More than 400 pharmaceutical products have been

Table II. Drugs that may contribute to swallowing disorders (from Stegemann et al., 2012¹⁰, mod.).

Drugs that may contribute to esophageal injury	Drugs that may contribute to xerostomia	Drugs that may contribute to dysphagia
Antibiotics <ul style="list-style-type: none"> • Tetracycline • Macrolids • Penicilline NSAID <ul style="list-style-type: none"> • Acetilsalicylic Acid • Piroxicam • Indometacin Bisphosphonate <ul style="list-style-type: none"> • Alendronate 	<ul style="list-style-type: none"> • Antipsychotics • Antidepressants • Antiemetics • Anxiolytics • Antihistamines • Diuretics • Anticholinergics • Antihypertensive • Bronchodilators 	Antipsychotics <ul style="list-style-type: none"> • Haloperidol • Olanzapine • Clozapine • Paliperidone • Risperidone Anticholinergics <ul style="list-style-type: none"> • Nitrazepam • Clonazepam Chemotherapy <ul style="list-style-type: none"> • Vincristine

considered to have adverse effects on the mechanisms responsible for salivary output, although experimental support for this evidence is available only for some medications⁴⁸. Probably the most common mechanism of medication-induced salivary gland hypofunction (SGH) is an impairment of the signaling pathway in salivary tissue reducing the saliva production or release from the salivary glands. Drugs with anticholinergic activity, mainly against the muscarinic receptor (M3R) are the most reported cause of reduced salivation. The M3R mediate parasympathetic cholinergic neurotransmission to salivary (and lacrimal) glands. Tricyclic antidepressants present anticholinergic effects in a variety of degrees⁴⁹. They block the effects of acetylcholine on the muscarinic receptors, resulting in a decreased salivary flow rate. Therefore, sympathetic stimulation predominates, which leads to more viscous saliva production⁵⁰. Anticholinergic bronchodilators, including the most recent glycopyrronium⁵¹ and acridinium bromide⁵², also diminish salivary production and secretion, with a reduction in flow rates of whole and parotid saliva⁵³. Select antihypertensive agents that act on central alpha 2-adrenergic receptors, such as clonidine, usually cause dry mouth. The study of Takakura et al.⁵⁴ demonstrated that activation of alpha 2-adrenoceptors in the lateral hypothalamus (LH) inhibits salivation, suggesting that LH is one of the possible central sites involved in anti-salivatory effects. Selected chemotherapy treatments also causes transient xerostomia: cyclophosphamide, epirubicin or methotrexate, and 5-fluorouracil appear to affect the function of acinar and ductal cells, by inducing dilation of the excretory duct⁵⁵, acinar degeneration and inflammation of glandular tissue⁵⁶, with recovery of salivary function after the end of treatment cycles.

Finally, some medications may cause xerostomia without affecting salivary flow. Diuretics cause an overall decrease extracellular volume or electrolyte loss secondary

to the increased urine output. As a consequence, there is a decrease on the salivary flow rate^{57 58}.

Selected drugs may affect swallowing by impairment of muscle function. Psychotropic medications may depress bulbar centres and result into inhibition of the cough, gag and swallow reflex. The well known extrapyramidal effects of antipsychotics and neuroleptics may lead to dysphagia by reducing the tonus of the pharyngeal muscles⁵⁹. Psychotropic drugs may also produce dopaminergic and cholinergic blockade producing peripheral and central effects on swallowing and potential impairment of oesophagus motility and the gag reflex⁶⁰. A number of drugs act directly on the smooth muscle of the lower oesophageal sphincter to reduce resting sphincter pressure. Several experience has been reported with isosorbide dinitrate and the calcium antagonists, particularly nifedipine⁶¹. The sublingual use of isosorbide dinitrate before meals has been shown to decrease mean resting lower oesophageal sphincter pressures, with relaxation usually lasting at least 90 minutes⁶². Calcium antagonists interfere with calcium uptake by smooth muscle cells, producing relaxation of the lower oesophageal sphincter as well as reducing the amplitude of peristaltic contractions in the body of the oesophagus.

Medication-induced esophageal injury has been reported with many medications. In some cases, it is a class effect and can be caused by a direct dose-dependent erosive effect on the esophageal mucosa or an indirect effect mediated by changes in the esophageal pH. Patients may experience a sudden onset of burning and retro-sternal pain aggravated upon swallowing⁶³. These injuries, including esophageal ulceration, perforation, strictures, and esophagitis, often present as a perception that food or a pill is stuck in the throat⁶⁴. The majority of cases are attributed to anti-microbial medications, including penicillines, macrolides and tetracyclines (doxycycline generates strongly acidic solutions with

pH < 3)⁶⁵. Other drug classes prone to induce esophageal disorders are nonsteroidal anti-inflammatory drugs (NSAID), such as acetylsalicylic acid, indomethacin and piroxicam. NSAIDs cause gastroduodenal damage by 2 main mechanisms: a physicochemical disruption of the gastric mucosal barrier and systemic inhibition of gastric mucosal protection, through inhibition of cyclooxygenase (COX) and prostaglandin-endoperoxide synthase 2 (PG G/H synthase) activity of the gastrointestinal mucosa⁶⁶. A reduced synthesis of mucus and bicarbonate, an impairment of mucosal blood flow, and an increase in acid secretion are the main consequences of NSAID-induced PG deficiency⁶⁷. There is mounting evidence to suggest that gastric damage induced by ns-NSAIDs does not occur because of COX-1 inhibition; dual suppression of COX-1 and COX-2 is necessary for damage. However, against a background of COX inhibition by antiinflammatory doses of NSAIDs, their physicochemical properties, in particular their acidity, underlie the topical effect, leading to short-term damage⁶⁸. Additional mechanisms may contribute to damage, including uncoupling of oxidative phosphorylation leading to ATP depletion, reduced mucosal cell proliferation and DNA synthesis, as well as neutrophil activation. Evidence suggests that NSAIDs may also induce GI damage by interference with mucosal synthesis and availability of Nitric oxide (NO)⁶⁹ and hydrogen sulfide (H₂S)⁷⁰. These mediators are endogenously generated gaseous mediators, important in maintaining gastric mucosal integrity, which share many biologic effects with PGs.

Even bisphosphonates may cause mucosal injury. Bisphosphonates act as topical irritants to the GI lining resulting in chemical esophagitis. It is hypothesized that bisphosphonates compromise the protective, hydrophobic mucosal barrier of the GI tract allowing gastric acid to agitate the epithelial lining. The chronic irritation and inflammation leads to erosions and/or ulcerations. Phosphatidylcholine (PC) is one of the phospholipids responsible for the hydrophobic properties of the bilayer⁷¹. Phosphatidylcholine has demonstrated an ability to create a protective environment on both inert and biological surfaces and protect GI cells from irritating agents. Both bisphosphonates and PC are similar in size and molecular structures – with a negatively charged phosphate group and a positively charged nitrogen group connected by a 2-carbon chain. The comparable molecular composition of bisphosphonates and phospholipids creates competitive binding on the mucosal layer. When bisphosphonates bind, this prevents PC or other protective phospholipids from binding and producing the hydrophobic barrier that protects the epithelial lining from gastric acid⁷¹. Gastrointestinal toxicity seems to be less relevant with risedronate⁷². In many

cases of upper gastrointestinal ulcers caused by bisphosphonates, patients failed to take their medications correctly. In these cases, alendronate in the stomach was likely refluxed back into the esophagus, causing esophageal ulcers, erosive esophagitis, odynophagia, dysphagia, esophageal hemorrhage, and esophageal stricture⁷³. Finally, mucoadhesive substances able to adhere to mucosal wall, e.g. gelatine in capsule pharmaceutical formulations⁷⁴, can cause oesophageal injury, which can be severe if the medicinal agent has corrosive properties⁷⁵. Whatever is the mechanism by which a given drug adversely affect the gastrointestinal system, these adverse effects are clinically important even when are not severe. Indeed, prolonged gastrointestinal symptoms can ultimately cause medication non-adherence and its inherent negative outcomes.

In conclusion, drugs may affect swallowing through several different mechanisms. Drug-induced swallowing disorders are usually reversible and might be resolved by changing the medication regimen^{47,59}. Thus, healthcare professionals can play an important role in reducing the burden of drug-induced swallowing disorders by alerting patients and caregivers to early warning signs and providing education to help patients prevent these effects.

MEDICATION ADHERENCE

The oral route of administration of medications is the most preferred one, but swallowing oral medications in the form of pills, tablets, or capsules also represents a really challenging task for many individuals with dysphagia. Indeed, medication non-adherence is among the most relevant clinical issues among patients with swallowing disorders.

Medication adherence is directly affected by dysphagia, as it increases the risk for omissions in general practice population⁶ as well as in nursing home residents⁷⁶. For example, 15% of all residents in long-term care facilities reported difficulty swallowing tablets and capsules. Of them, 5% regularly expectorated, while 27% did not even attempt to swallow the medication⁷⁶. Consequences of non-adherence may be more serious, and less easily detected and resolved in older compared to younger patients⁷⁷. Patients with dysphagia who fail to comply with prescribed medications are likely to encounter increased morbidity and mortality. In addition to worse medical treatment outcomes, medication non-adherence leads to higher hospitalization rates and healthcare costs⁷⁸⁻⁸⁰.

Thus, awareness of dysphagia-related non-adherence is of paramount importance for correct management of pharmacological therapy.

MANAGEMENT OF ORAL MEDICATIONS IN DYSPHAGIC PATIENTS

Problems related to enteral feeding and drug administration to patients with swallowing issues is a growing concern for physicians, pharmacists and nurses⁸¹, and this issue is even more complex when patients are treated at home with or without the assistance of a caregiver.

RISK OF TABLET CRUSHING

Crushing tablets and opening capsules are the main alterations of dosage forms in patients with swallowing difficulty and account for up to one third of oral drug administrations in nursing homes⁸². This practice may alter the rate and extent to which the active ingredient is absorbed^{83,84}, leading to overdosing or underdosing. Overdosing is particularly dangerous when the drug has a narrow therapeutic index, because a small difference in plasma concentration can cause serious adverse effects⁸⁵. This evidence should be applied for products containing carbamazepine, digoxin, lithium, theophylline, phenytoin, phenobarbital, and others. For example, crushing tablets of digoxin exposes patients to the risk of clinically relevant arrhythmias⁸⁶. Opening a capsule of the oral anticoagulant dabigatran increases the drug's bioavailability by about 75%, thus exposing patients to the risk of haemorrhage⁸⁷. Thus, these medications should never be chewed or opened.

As regards the risk of underdosing, gastro-resistant (or enteric-coated) tablets and capsules containing gastro-resistant granules are designed to release the active ingredient beyond the stomach. The purpose is usually to protect the active ingredient from gastric acid. When a gastro-resistant layer is destroyed by crushing, underdosing is very likely, as for example with gastro-resistant tablets of sulfasalazine or proton pump inhibitors⁸⁸.

Besides causing overdosing or under dosing, tablet crushing raise several other issues. For example, crushing products with carcinogenic or teratogenic potential may expose carers or healthcare professionals to health risks through powder aerosolisation. Similarly, preparations containing hormones (oral contraceptives, hormonal replacement therapy), corticosteroids (such as dexamethasone) and some other drugs (finasteride, mycophenolate) should not be crushed due to the risks associated with powder aerosolisation⁸⁹. In addition several drug substances may also cause irritation if the powder is aerosolised and inhaled or contact with eyes, skin, or other mucosal membranes (e.g. alendronate, piroxicam, ganciclovir, hydroxycarbamide)⁹⁰. Finally, for drugs which have a particularly bitter taste, a coating (sugar/film) is often used to help mask the taste of the

active substance. A sugar coating provides a thick hard coat to a tablet and is traditionally used to mask the taste of particularly unpleasant tasting drugs such as ibuprofen or quinine. Crushing tablets containing bitter or unpleasant tasting drug substances may produce a preparation which is unpleasant to taste and which a patient may refuse to take unless the taste can be masked using a suitable food or liquid⁹¹.

DRUG THERAPY WITH ENTERAL TUBES

Crushing of tablets and opening of capsules were used by 85.5% of the nurses to convert them into an applicable form for enteral tubing⁹². However, several issues must be considered with concurrent administration of oral medications and enteral formulas, especially during continuous tube feeding, because incorrect administration methods may result in clogged feeding tubes, decreased drug effectiveness, increased risk adverse effects or drug-enteral formula incompatibilities⁹³.

Liquid formulations should be preferred because they are readily absorbed and are less likely to cause tube occlusions. Since syrups are more likely to cause clumping when exposed to enteral nutrition, elixirs or suspensions should be favored⁹⁴. However, also oral liquid medications may potentially cause adverse effects. Many liquid preparations are extremely hyperosmolar or contain large amounts of sorbitol, increasing the risk of GI intolerance. This is particularly troublesome when a large volume of drug is dispensed per dose. Hypertonic medications may not be well tolerated when delivered into the small intestine. Additionally, when hypertonic medications are rapidly administered into the stomach, they may easily reach the small bowel resulting in osmotic diarrhea⁹⁵. In this case, it may be necessary to change the medication with a therapeutically equivalent agent not containing sorbitol or carrying lower osmolarity. Switching the administrative route may also be helpful. Changing the medication formulation (e.g., from a liquid to a crushed tablet or opened capsule when it can be safely done) may be another option.

The addition of medication directly to the enteral formula should be avoided. Although it may be convenient to mix drugs with enteral feedings, this practice can result in physical incompatibilities, decreased drug absorption, increased risk of tube occlusions, and potential microbial contamination⁹⁶. Various medications may cause drug-formula incompatibilities and result in tube occlusions. For example, mixing certain acidic syrups and elixirs with enteral formulas may produce clumping or thickening because the acidic liquid preparations cause protein denaturation in the enteral formula. Formulas containing intact proteins are more affected than those that contain free amino acids or hydrolyzed protein. To avoid these potential interactions

and incompatibilities, medications should be given as a bolus and separated from enteral nutrition, and feeding tubes should be flushed with 15-30 mL of water before and after medication administration ⁹⁷.

While it should be reminded that product licence of each clearly states the conditions for which the medication may be suitably administered, the above issues raised the need for algorithms for medication management to be applied in different settings in order to improve medication adherence and reduce drugs manipulation in patients with dysphagia.

Recently, guidelines for the management of oral therapy in patients with swallowing problems have been developed in order to ensure that the most appropriate formulation is prescribed for each patient ⁸⁸. Guidelines strategies are summarized in Table III.

LEGAL IMPLICATIONS OF CRUSHING TABLETS

Besides the pharmacological aspects of crushing tablets, there are also legal implications ⁹⁸. Indeed, the administration of medications outside their product licence, as well as mixing medication inappropriately with food or drink before administration takes on a degree of liability for any adverse effects and this practice can be judged as unlawful according to the civil law.

In Italy, the Italian Medicines Agency (AIFA) grant the Marketing Authorisation to the pharmaceutical companies based on some declared parameters that include product characteristics related to: i) therapeutic indications; ii) contraindications and adverse reactions; iii) dosage, pharmaceutical form, route for drug administration. The pharmacological activity of an oral medication depends on its molecular structure, ionization, lipid

solubility and binding to plasma protein and tissue ⁹⁹, and inappropriate manipulations can lead to mucosal damage and to significant changes in efficacy and safety profile of the drug ^{100 101}. Liability can be minimized through an improved communication and proper assessment of the swallowing difficulty and a clear documentation of the reason for drug manipulations. In this context, following guidelines and recommendations reported in the summaries of product will improve the quality of pharmacological treatment provided to dysphagic patients.

CONCLUSIONS

Swallowing disorders are multifactorial in nature and affects a significant number of older patients. Age-related changes in swallowing functions are attributed to physiological, anatomical, motor and sensory alterations. Swallowing disorders are highly prevalent among older patients with neurological diseases, but less obvious non-neurological causes should not be ignored. Some medications may increase the risk of dysphagia. People with swallowing disorders tend to refrain from food and beverages which leads to increased risk of malnutrition and dehydration. Manipulation of drug products is a significant source for medication errors and harmful outcomes, as well as it might have some legal implications ¹⁰². Oral drug prescription to patients with dysphagia should be limited to medications that can be administered without manipulation or for which the manipulation is clearly described in the summary of product. Medication adherence is directly affected by

Table III. Summary of guidelines strategies and practice suggestions for the management of oral medications in dysphagic patients.

Guideline strategy	Suggestions
Switching to liquid or dispersible oral formulations	<ul style="list-style-type: none"> • Check dose equivalence • Evaluate efficacy and side effects frequently
Alternative routes of administration	<ul style="list-style-type: none"> • Transdermal • Parenteral/injectable • Buccal • Rectal • Intranasal • Sublingual
Altering a solid-dose oral medication	<ul style="list-style-type: none"> • Consider how stable the product is once opened to the environment • Drug manipulation may impact efficacy and the potential for side effects (e.g. phenytoin, digoxin, carbamazepine) – Check summary of product for informations.
Administering medications via enteral tube	<ul style="list-style-type: none"> • Ensure that there is a functional and accessible gastrointestinal tract • Check for risk of tube blockage and drug-tube interactions • Check for drug-enteral feed interactions • Flush the tube before and after giving medications (with ≥ 30 ml water) • If more than one drug is required, give drugs separately and flush between administrations (with ≥ 10 ml water)

difficulties of swallowing or administration of solid oral dosage forms to the patient as it increases the risk for drug omissions¹⁰³.

Dysphagia management should be considered a 'team event', in which many professionals may contribute¹⁰⁴. Furthermore, no single strategy is appropriate for all elderly patients with dysphagia. Guidelines for the management of oral therapy in patients with swallowing problems provide some useful information to be implemented into clinical practice. Additionally, in many countries long-term care continues to shift from institutional care to an array of home- and community-based options. Thus, informal or family caregivers that are being expected to share increasingly complex care for dependent elderly persons, should be adequately trained before being involved in the management of dysphagia¹⁰⁵. Finally, healthcare professionals involved in treating patients with swallowing disorders should also consider to alert the industry to provide suitable dosage forms where they do not exist yet.

References

- Malagelada JR. *World Gastroenterology Organisation Practice Guidelines: Dysphagia*, 2007.
- Sura L, Madhavan A, Carnaby G, et al. *Dysphagia in the elderly: management and nutritional considerations*. *Clin Interv Aging* 2012;7:287-98.
- Morris H. *Dysphagia in the elderly – a management challenge for nurses*. *Br J Nurs* 2006;15:558-62.
- Perry L, Love CP. *Screening for dysphagia and aspiration in acute stroke: a systematic review*. *Dysphagia* 2001;16:7-18.
- Calabrese C, Fabbri A, Di Febo G. *Long-term management of GERD in the elderly with pantoprazole*. *Clin Interv Aging* 2007;2:85-92.
- Schiele JT, Quinzler R, Klimm HD, et al. *Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms*. *Eur J Clin Pharmacol* 2013;69:937-48.
- Payot V, Cordonier AC, Marquis J, et al. *Prevalence of patients' difficulties in swallowing solid SODF*. *Int J Clin Pharmacol* 2011;33:402.
- Altman KW, Yu GP, Schaefer SD. *Consequence of dysphagia in the hospitalized patient: impact on prognosis and hospital resources*. *Arch Otolaryngol Head Neck Surg* 2010;136:784-9.
- Masiero S, Pierobon R, Previato C, et al. *Pneumonia in stroke patients with oropharyngeal dysphagia: a six-month follow-up study*. *Neurol Sci* 2008;29:139-45.
- Stegemann S, Gosch M, Breikreutz J. *Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy*. *Int J Pharm* 2012;430:197-206.
- Nilsson H, Ekberg O, Olsson R, et al. *Quantitative aspects of swallowing in an elderly nondysphagic population*. *Dysphagia* 1996;11:180-4.
- Lindgren S, Janzon L. *Prevalence of swallowing complaints and clinical findings among 50-79-year-old men and women in an urban population*. *Dysphagia* 1991;6:187-92.
- Carnaby-Mann G, Crary M. *Pill swallowing by adults with dysphagia*. *Arch Otolaryngol Head Neck Surg* 2005;131:970-5.
- Robbins J, Levine R, Wood J, et al. *Age effects on lingual pressure generation as a risk factor for dysphagia*. *J Gerontol A Biol Sci Med Sci* 1995;50:M257-62.
- Nagaya M, Sumi Y. *Reaction time in the submental muscles of normal older people*. *J Am Geriatr Soc* 2002;50:975-6.
- Clave P, Arreola V, Romea M, et al. *Accuracy of the volume-viscosity swallow test for clinical screening of oropharyngeal dysphagia and aspiration*. *Clin Nutr* 2008;27:806-15.
- Jou J, Radowsky J, Gangnon R, et al. *Esophageal clearance patterns in normal older adults as documented with videofluoroscopic esophagram*. *Gastroenterol Res Pract* 2009;2009:965062.
- Hind JA, Nicosia MA, Roecker EB, et al. *Comparison of effortful and noneffortful swallows in healthy middle-aged and older adults*. *Arch Phys Med Rehabil* 2001;82:1661-5.
- Ney DM, Weiss JM, Kind AJ, et al. *Senescent swallowing: impact, strategies, and interventions*. *Nutr Clin Pract* 2009;24:395-413.
- Shiozu H, Higashijima M, Koga T. *Association of sarcopenia with swallowing problems, related to nutrition and activities of daily living of elderly individuals*. *J Phys Ther Sci* 2015;27:393-6.
- Mann G, Hankey GJ, Cameron D. *Swallowing function after stroke: prognosis and prognostic factors at 6 months*. *Stroke* 1999;30:744-8.
- Singh S, Hamdy S. *Dysphagia in stroke patients*. *Postgrad Med J* 2006;82:383-91.
- Poorjavad M, Jalaie S. *Systemic review on highly qualified screening tests for swallowing disorders following stroke: validity and reliability issues*. *J Res Med Sci* 2014;19:776-85.
- Potulska A, Friedman A, Krolicki L, et al. *Swallowing disorders in Parkinson's disease*. *Parkinsonism Relat Disord* 2003;9:349-53.
- Kyle G. *Managing dysphagia in older people with dementia*. *Br J Community Nurs* 2011;16:6-10.
- Diener U, Patti MG, Molena D, et al. *Esophageal dysmotility and gastroesophageal reflux disease*. *J Gastrointest Surg* 2001;5:260-5.
- Bril V, England J, Franklin GM, et al. *Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation*. *Neurology* 2011;76:1758-65.
- Cassiani RA, Santos CM, Baddini-Martinez J, et al. *Oral and pharyngeal bolus transit in patients with chronic obstructive pulmonary disease*. *Int J Chron Obstruct Pulmon Dis* 2015;10:489-96.
- Kobayashi S, Kubo H, Yanai M. *Impairment of swallowing in COPD*. *Am J Respir Crit Care Med* 2009;180:481.

- 30 Preiksaitis HG, Mayrand S, Robins K, et al. *Coordination of respiration and swallowing: effect of bolus volume in normal adults*. *Am J Physiol* 1992;263:R624-30.
- 31 Kress S, Martin WR, Benz C, et al. *Dysphagia secondary to left atrial dilatation*. *Z Gastroenterol* 1997;35:1007-11.
- 32 Whitney B, Croxon R. *Dysphagia caused by cardiac enlargement*. *Clin Radiol* 1972;23:147-52.
- 33 Kayatas M, Ustundag Y, Okudan B, et al. *Evaluation of esophageal [correction of oesophageal] motor function in chronic renal failure and the role of hemodialysis treatment*. *Nephron* 2002;91:534.
- 34 Dogan I, Unal S, Sindel S, et al. *Esophageal motor dysfunction in chronic renal failure*. *Nephron* 1996;72:346-7.
- 35 Clave P, Verdaguer A, Arreola V. *Oral-pharyngeal dysphagia in the elderly*. *Med Clin (Barc)* 2005;124:742-8.
- 36 Clave P, de Kraa M, Arreola V, et al. *The effect of bolus viscosity on swallowing function in neurogenic dysphagia*. *Aliment Pharmacol Ther* 2006;24:1385-94.
- 37 Cabre M, Serra-Prat M, Palomera E, et al. *Prevalence and prognostic implications of dysphagia in elderly patients with pneumonia*. *Age Ageing* 2010;39:39-45.
- 38 Volkert D, Berner YN, Berry E, et al. *ESPEN Guidelines on Enteral Nutrition: Geriatrics*. *Clin Nutr* 2006;25:330-60.
- 39 Finestone HM, Foley NC, Woodbury MG, et al. *Quantifying fluid intake in dysphagic stroke patients: a preliminary comparison of oral and nonoral strategies*. *Arch Phys Med Rehabil* 2001;82:1744-6.
- 40 Leibovitz A, Baumoehl Y, Lubart E, et al. *Dehydration among long-term care elderly patients with oropharyngeal dysphagia*. *Gerontology* 2007;53:179-83.
- 41 Wotton K, Crannitch K, Munt R. *Prevalence, risk factors and strategies to prevent dehydration in older adults*. *Contemp Nurse* 2008;31:44-56.
- 42 Sellars C, Bowie L, Bagg J, et al. *Risk factors for chest infection in acute stroke: a prospective cohort study*. *Stroke* 2007;38:2284-91.
- 43 Smithard DG, O'Neill PA, Parks C, et al. *Complications and outcome after acute stroke. Does dysphagia matter?* *Stroke* 1996;27:1200-4.
- 44 DiBardino DM, Wunderink RG. *Aspiration pneumonia: a review of modern trends*. *J Crit Care* 2015;30:40-8.
- 45 Metheny NA, Schallom ME, Edwards SJ. *Effect of gastrointestinal motility and feeding tube site on aspiration risk in critically ill patients: a review*. *Heart Lung* 2004;33:131-45.
- 46 Sirvent JM, Torres A, El-Ebiary M, et al. *Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma*. *Am J Respir Crit Care Med* 1997;155:1729-34.
- 47 Dzewas R, Warnecke T, Schnabel M, et al. *Neuroleptic-induced dysphagia: case report and literature review*. *Dysphagia* 2007;22:63-7.
- 48 Narhi TO, Meurman JH, Ainamo A. *Xerostomia and hyposalivation: causes, consequences and treatment in the elderly*. *Drugs Aging* 1999;15:103-16.
- 49 Kumar NN, Panchaksharappa MG, Annigeri RG. *Modified schirmer test – a screening tool for xerostomia among subjects on antidepressants*. *Arch Oral Biol* 2014;59:829-34.
- 50 de Almeida Pdel V, Gregio AM, Brancher JA, et al. *Effects of antidepressants and benzodiazepines on stimulated salivary flow rate and biochemistry composition of the saliva*. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;106:58-65.
- 51 Rennard S, Fogarty C, Reisner C, et al. *Randomized study of the safety, pharmacokinetics, and bronchodilatory efficacy of a proprietary glycopyrronium metered-dose inhaler in study patients with chronic obstructive pulmonary disease*. *BMC Pulm Med* 2014;14:118.
- 52 Beier J, Kirsten AM, Mroz R, et al. *Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study*. *COPD* 2013;10:511-22.
- 53 Levin JA, Glick M. *Dental management of patients with asthma*. *Compend Contin Educ Dent* 1996;17:284, 7-8, 90 *passim*.
- 54 Takakura AC, Moreira TS, Colombari DS, et al. *Activation of alpha(2)-adrenoceptors in the lateral hypothalamus reduces pilocarpine-induced salivation in rats*. *Neurosci Lett* 2009;450:225-8.
- 55 Jensen SB, Pedersen AM, Reibel J, et al. *Xerostomia and hypofunction of the salivary glands in cancer therapy*. *Support Care Cancer* 2003;11:207-25.
- 56 Peterson DE. *Research advances in oral mucositis*. *Curr Opin Oncol* 1999;11:261-6.
- 57 Nederfors T, Nauntofte B, Twetman S. *Effects of furosemide and bendroflumethiazide on saliva flow rate and composition*. *Arch Oral Biol* 2004;49:507-13.
- 58 Smidt D, Torpet LA, Nauntofte B, et al. *Associations between oral and ocular dryness, labial and whole salivary flow rates, systemic diseases and medications in a sample of older people*. *Community Dent Oral Epidemiol* 2011;39:276-88.
- 59 Mendhekar DN, Agarwal A. *Paliperidone-induced dystonic Dysphagia*. *J Neuropsychiatry Clin Neurosci* 2010;22:451-v e37-e37.
- 60 Kohen I, Lester P. *Quetiapine-associated dysphagia*. *World J Biol Psychiatry* 2009;10:623-5.
- 61 Gelfond M, Rozen P, Gilat T. *Isosorbide dinitrate and nifedipine treatment of achalasia: a clinical, manometric and radionuclide evaluation*. *Gastroenterology* 1982;83:963-9.
- 62 Gelfond M, Rozen P, Keren S, et al. *Effect of nitrates on LOS pressure in achalasia: a potential therapeutic aid*. *Gut* 1981;22:312-8.
- 63 Soto-Solis R. *Pill-induced esophagitis*. *Rev Gastroenterol Mex* 2015;80:160.
- 64 Kikendall JW. *Pill esophagitis*. *J Clin Gastroenterol* 1999;28:298-305.
- 65 Pinos T, Figueras C, Mas R. *Doxycycline-induced esophagitis: treatment with liquid sucralphate*. *Am J Gastroenterol* 1990;85:902-3.
- 66 Scarpignato C, Hunt RH. *Nonsteroidal antiinflammatory*

- drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis, and prevention. *Gastroenterol Clin North Am* 2010;39:433-64.
- 67 Wallace JL. Pathogenesis of NSAID-induced gastroduodenal mucosal injury. *Best Pract Res Clin Gastroenterol* 2001;15:691-703.
- 68 Bjarnason I, Scarpignato C, Takeuchi K, et al. Determinants of the short-term gastric damage caused by NSAIDs in man. *Aliment Pharmacol Ther* 2007;26:95-106.
- 69 Wallace JL, Miller MJ. Nitric oxide in mucosal defense: a little goes a long way. *Gastroenterology* 2000;119:512-20.
- 70 Wallace JL. Physiological and pathophysiological roles of hydrogen sulfide in the gastrointestinal tract. *Antioxid Redox Signal* 2010;12:1125-33.
- 71 Lichtenberger LM, Romero JJ, Gibson GW, et al. Effect of bisphosphonates on surface hydrophobicity and phosphatidylcholine concentration of rodent gastric mucosa. *Dig Dis Sci* 2000;45:1792-801.
- 72 Taggart H, Bolognese MA, Lindsay R, et al. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clin Proc* 2002;77:262-70.
- 73 de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. *N Engl J Med* 1996;335:1016-21.
- 74 Channer KS, Virjee JP. The effect of formulation on oesophageal transit. *J Pharm Pharmacol* 1985;37:126-9.
- 75 Pemberton J. Oesophageal obstruction and ulceration caused by oral potassium therapy. *Br Heart J* 1970;32:267-8.
- 76 Wright D. Medication administration in nursing homes. *Nurs Stand* 2002;16:33-8.
- 77 Morisky DE, Ang A, Krousel-Wood M, et al. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich)* 2008;10:348-54.
- 78 Wroth TH, Pathman DE. Primary medication adherence in a rural population: the role of the patient-physician relationship and satisfaction with care. *J Am Board Fam Med* 2006;19:478-86.
- 79 DiMatteo MR, Giordani PJ, Lepper HS, et al. Patient adherence and medical treatment outcomes: a meta-analysis. *Med Care* 2002;40:794-811.
- 80 Sokol MC, McGuigan KA, Verbrugge RR, et al. Impact of medication adherence on hospitalization risk and health-care cost. *Med Care* 2005;43:521-30.
- 81 Kelly J, D'Cruz G, Wright D. Patients with dysphagia: experiences of taking medication. *J Adv Nurs* 2010;66:82-91.
- 82 Kirkevold O, Engedal K. What is the matter with crushing pills and opening capsules? *Int J Nurs Pract* 2010;16:81-5.
- 83 Kelly J, Wright D. Administering medication to adult patients with dysphagia. *Nurs Stand* 2009;23:62-8.
- 84 Mitchell J. Dosage forms that should not be crushed or chewed. *Hosp Pharm* 2002;37:213-4.
- 85 Morris H. Administering drugs to patients with swallowing difficulties. *Nurs Times* 2005 27;101:28-30.
- 86 Kelly J, Wright D, Wood J. Medication errors in patients with dysphagia. *Nurs Times* 2012;108:12-4.
- 87 Dabigatran: life-threatening bleeding. *Prescrire Int* 2013;22:41-3.
- 88 Wright D, Chapman N, Foundling-Miah M, et al. *Consensus guidelines on the medication management of adults with swallowing difficulties*. Berkhamsted: Medenium Group Publishing Ltd. 2006.
- 89 Simpson C. *Crushed medications: an emerging guideline*. *Aust Nurs J* 2005;13:21-3.
- 90 Layne BA, Seibert DJ. Should medications be crushed? *Pa Med* 1998;101:16.
- 91 *Crushing tablets or opening capsules: many uncertainties, some established dangers*. *Prescrire Int* 2014;23:209-11, 13-4.
- 92 Phillips NM, Endacott R. Medication administration via enteral tubes: a survey of nurses' practices. *J Adv Nurs* 2011;67:2586-92.
- 93 Beckwith MC, Feddema SS, Barton GR, et al. *A guide to drug therapy in patient with enteral feeding tube: Dosage form selection and administration methods*. *Hosp Pharm* 2004;39:225-37.
- 94 Magnuson BL, Clifford TM, Hoskins LA, et al. Enteral nutrition and drug administration, interactions, and complications. *Nutr Clin Pract* 2005;20:618-24.
- 95 Morgan LM, Dickerson RN, Alexander KH, et al. Factors causing interrupted delivery of enteral nutrition in trauma intensive care unit patients. *Nutr Clin Pract* 2004;19:511-7.
- 96 Gora ML, Tschampel MM, Visconti JA. Considerations of drug therapy in patients receiving enteral nutrition. *Nutr Clin Pract* 1989;4:105-10.
- 97 Nyffeler MS, Frankel E, Hayes E, et al. Drug-nutrient interactions. In: Merritt R, DeLegge MH, Holcombe B, et al. (Eds.). *The ASPEN nutrition support practice manual*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition 2005, pp. 118-36.
- 98 Wright D. *Swallowing difficulties protocol: medication administration*. *Nurs Stand* 2002;17:43-5.
- 99 Breikreutz J, Boos J. *Paediatric and geriatric drug delivery*. *Expert Opin Drug Deliv* 2007;4:37-45.
- 100 *Diagnosis and treatment of swallowing disorders (dysphagia) in acute-care stroke patients*. *Evid Rep Technol Assess (Summ)*. 1999;Mar 8:1-6.
- 101 Jordan S, Griffiths H, Griffith R. *Administration of medicines. Part 2: Pharmacology*. *Nurs Stand* 2003;18:45-54; quiz 5-6.
- 102 Griffith R, Griffiths H, Jordan S. *Administration of medicines. Part 1: The law and nursing*. *Nurs Stand* 2003;18:47-53; quiz 4, 6.
- 103 Kelly J, D'Cruz G, Wright D. *A qualitative study of the problems surrounding medicine administration to patients with dysphagia*. *Dysphagia* 2009;24:49-56.
- 104 Robbins J, Kays S, McCallum S. *Team management of dysphagia in the institutional setting*. *J Nutr Elder* 2007;26:59-104.
- 105 Legare F, Briere N, Stacey D, et al. *Improving Decision making On Location of Care with the frail Elderly and their caregivers (the DOLCE study): study protocol for a cluster randomized controlled trial*. *Trials* 2015;16:567.

¹⁰⁶ [Http://www.usl3.toscana.it/allegati/disfagiacorretta_100526010818.pdf](http://www.usl3.toscana.it/allegati/disfagiacorretta_100526010818.pdf)

¹⁰⁷ Farneti D. *Disordini della deglutizione nella pratica*

medica ambulatoriale. www.progettoasco.it/riviste/rivista_simg/2004/03_2004/6.pdf

Acute monoparesis onset in recent aortic valve replacement: a case report

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Vertebral metastases are frequent in patients with cancer. They are much more frequent in higher age groups (> 50 years); the lesions can be asymptomatic despite a setting of widespread metastatic disease and may become symptomatic due to bone pain, pathological compression fractures, or extension into spinal canal with cord compression ensuing neurological symptoms.

We report the case of a patient, without known history of malignancy, in which shoulder pain was attributed for few months to sequela of recent cardiac surgery for ascending aortic aneurysm. She was admitted to our ward because of acute onset of lower limb monoparesis which evolved in several days in paraparesis. Only a dorsal magnetic resonance study revealed the presence of a bulky vertebral lesion at D1-D2 level involving the peri-dural space. Neuro-surgical decompression was performed obtaining specimens for histological analysis, which suggested the presence of metastatic adenocarcinomatous lesions of gastrointestinal origin. A computed tomography study partially supported this hypothesis showing only a thickening of rectal wall, even if endoscopic exploration did not show macroscopic mucosal abnormalities. Surgical and medical therapies did not improve the patient's clinical course and she died few months later.

Key words: Spinal metastasis, Rectal cancer, Paraparesis, Spinal cord compression

CASE REPORT

A 72 year old female presented to Emergency Room referring acute onset of left leg weakness started two days before; she could not walk. She first underwent a neurological evaluation (left leg monoparesis) and brain CT scan (negative); then, the patient came to our ward for clinical observation.

Her medical history revealed arterial hypertension in good pharmacological control and a previous surgical correction of cystocele. Moreover, six months before she had undergone surgical correction of ascending aortic aneurysm associated with aortic valve insufficiency with reconstruction by composite valve graft. Post-operative period was characterized by pain to

left upper extremity and shoulder; the symptom was considered a normal surgical sequela and was treated with analgesics. She was currently treated with anti-platelet therapy, anti-hypertensive drugs, minor opiates, acetaminophen, pregabalin and paroxetine to control chronic pain.

At admission to hospital, the patient was cooperative and orientation in time and space were good. Neurologic examination revealed left leg paresis with associated tactile hypoesthesia below the knee, but normal deep tendon reflexes. In the first hours after admission the patient referred inability to voluntarily pass urine, with evidence of urinary retention. Her vital signs were stable, with only asymptomatic bradycardia attributable to beta-blockade therapy; pulmonary and

cardiovascular examination were normal. Initial laboratory tests showed no abnormalities in haematological parameters, coagulation, renal and hepatic function.

In order to investigate the monoparesis we asked for carotid ultrasound examination (negative), brain scan at 48 h from admission (negative) and electromyography (altered central motor conduction at lower limbs, in particular at the left side).

Because of the persistence of left shoulder and upper extremity pain, we speculated on aortic dissection related to the recent surgical correction, involving medullar vessels and asked for chest and abdominal CT scan; no aortic aneurysms or dissections were found, while at D1 it is observed a collapse of the vertebral body with extended replacement of bone by new tissue; also multiple lymphonodes in mediastinic and peritoneal space were described, together with thickening of rectal wall. In suspicion of a malignancy, additional laboratory tests were performed and rectal endoscopic studies were performed. A significant elevation of Ca 19.9 (798 U/ml, n.v. 27) was observed; colonoscopy was negative while sigmoidoscopy revealed normal mucosal pattern; thus, the endoscopist decided not to obtain bioptic specimens.

In addition the patient underwent cervical and dorsal MRI study. A bulky vertebral lesion was revealed at D1-D2 level involving the peri-dural space. The medullary cord on T2 weighted sequences appeared hyperintense, suggesting a parenchymal suffering from C7 to D2 (Fig. 1).

The lesion also involved the left conjugation foramen, reached the spinous process and, in part, the soft paravertebral tissue. In the meanwhile we noticed an evolution of neurological picture, with appearance of hypostenia at right lower limb and global anesthesia below D4 dermatome.

After a high dose steroid course of 4-5 days and discontinuance of antiplatelet therapy, D1-D2 laminectomy was performed. Pathologic examination showed neoplastic cells with CDX2 +/- CK7 +/- CK20 + phenotype, suggesting a gastrointestinal-pancreatic origin. Further molecular analysis documented the presence of *KRAS* mutation in exon 2 with G12V substitution.

The patient was taken in charge by oncologists. A first line therapy was made but during the hospitalization patient's condition quickly impaired because of the onset of flaccid paraparesis, thus she was assigned to an Oncology Palliative Care Unit where she died four months later.

DISCUSSION

Spinal metastasis is common in patients with cancer, constituting the third metastatic site, following the lung and the liver^{1,2}. Approximately 5-30%³ of patients with systemic cancer will have spinal metastasis. Generally, only 10% of patients are symptomatic⁴, and the majority of them present with epidural and/or vertebral involvement. Back pain is the most common presenting

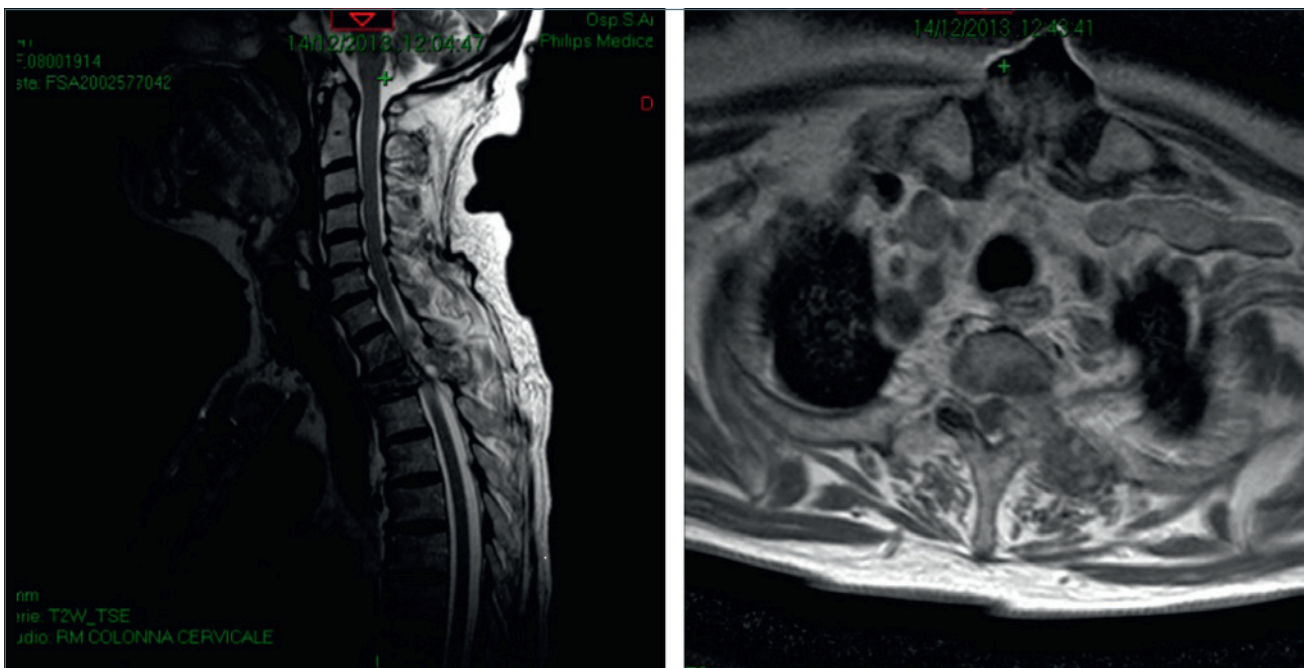


Figure 1. Cervical dorsal spine RMN shows vertebral (D1) involvement and spinal cord compression.

symptom and can precede the development of neurologic symptoms by weeks or months. Intradural extramedullary and intramedullary seeding of systemic cancer is unusual; this condition accounts for 5-6% and 0.5-1% of spinal metastases, respectively. Bone marrow metastases are an uncommon mode of onset of malignant disease (10%). Furthermore in only about 7% of symptomatic patients, the primary tumour remains occult⁵. The most common primary neoplasm involving vertebrae include breast, lung, prostate cancer, lymphoma, melanoma, and renal cell carcinoma.

In our case the diagnosis was difficult, due to two aspects: 1) the recent heart surgery was misleading for the understanding of the pain reported by the patient, thereby causing only a symptomatic therapy for few months; 2) the absence of symptoms suggesting a specific organ involvement, particularly change in bowel habit, intestinal bleeding, and weight loss made it difficult to identify the primary tumour.

Based on the instrumental relief of thickening of the rectal walls, and the phenotype of the cytological metastatic tissue, we hypothesize the presence of a rectal cancer. Isolated bone metastases from colon-rectal cancer are unusual, but some cases have been reported in literature⁶⁻⁸, although bone involvement is rarely described as a manifestation of colon-rectal cancer onset⁹⁻¹¹. Skeletal metastases generally appear when the disease is in an advanced stage; in this context the bone involvement is mostly multifocal and typically liver and lung metastases coexist¹². The lack of involvement of liver and lung may be explained by the existence of the venous plexus of Batson¹³. This is a system extended from sacrum to cranium that forms a large capacitance venous system and communicates with the other venous systems through segmental vessels; it is widely anatomised with the spinal venous system, the azygos vein, the dorsal and the intercostal veins. The plexus has not valves; thus, each increase in the pressure in the system of vena cava might result in an increased flow level of the plexus. In our patient, the heart failure secondary to aortic valve insufficiency may have played a pathophysiological role.

We also speculated that the rapid course of disease is well explained by *KRAS* mutation and above all by G12V substitution; *KRAS* phenotype is known to be associated with poorer prognosis in gastrointestinal tumor, increased risk of recurrence and death¹⁴. Especially the presence of a valine in codon 12 adversely affected overall survival¹⁴ and it has recently been analyzed in a murine experimental model¹⁵: increased metastatic propensity and a higher growth rate in lymph node metastases was observed in this oncogene mutation in agreement with clinical higher aggressiveness observed in patients with CRC.

CONCLUSIONS

Our case draws attention to several key-points. First, the presence of a persisting musculoskeletal pain, even if a plausible aetiology is identified, requires a careful diagnostic work-up to rule out a neoplastic involvement. Second, the absence of liver and lung metastases in a patient with suspected colorectal cancer must not represent an exclusion criteria, since other ways of spread can by-pass these organs (i.e. Batson's plexus). Of consequence, colon-rectal cancer should be included in the differential diagnosis of a solitary bone metastasis.

References

- 1 Boland PJ, Lane JM, Sundaresan N. *Metastatic disease of the spine*. Clin Orthop Relat Res 1982;169:95-102.
- 2 Hosono N, Yonenobu K, Fuji T, et al. *Orthopaedic management of spinal metastase*. Clin Orthop Relat Res 1995;312:148-59.
- 3 Mundy GR. *Metastasis to bone: causes, consequences and therapeutic opportunities*. Nat Rev Cancer 2002;2:584-93.
- 4 Harrington KD. *Orthopedic surgical management of skeletal complications of malignancy*. Cancer 1997;80:1614-27.
- 5 Levack P, Graham J, Collie D, et al. *Don't wait for a sensory level – listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression*. Clin Oncol (R Coll Radiol) 2002;14:472-80.
- 6 Padhi P, Mackey C. *Spine and scapular pain: an unusual presentation of colon adenocarcinoma*. BMJ Case Rep 2013;Jul 16.
- 7 Yamazaki K, Katsumura N, Ozawa N, et al. *A case of mucinous adenocarcinoma of the sigmoid colon with disseminated carcinomatosis of the bone marrow successfully treated with FOLFOX4/bevacizumab*. Gan To Kagaku Ryoho 2013;40:1105-9.
- 8 Isozaki Y, Yamanishi M, Utsunomiya S, et al. *A case of disseminated carcinomatosis of bone marrow with disseminated intravascularcoagulation caused by advanced colon cancer treated by mFOLFOX6*. Gan To Kagaku Ryoho 2011;38:1705-8.
- 9 Kose F, Sakalli H, Sezer A, et al. *Colon adenocarcinoma and solitary tibia metastasis: Rare entity*. J Gastrointest Cancer 2008;39:146-8.
- 10 Anoop TM, George S, Divya KP, et al. *Metastatic phalangeal osteolysis as an initial presentation of carcinoma colon*. Am J Surg 2010;200:e61-3.
- 11 Mason AC, Azari KK, Farkas LM, et al. *Metastatic adenocarcinoma of the colon presenting as a mass in the mandible*. Head Neck 2005;27:729-32.
- 12 Santoro GA. *Rectal cancer – a multidisciplinary approach to management*. InTech 2011. doi: 10.5772/1293
- 13 Geldof AA. *Models for cancer skeletal metastasis: a reappraisal of Batson's plexus*. Anticancer Res 1997;17:1535-9.

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- ¹⁴ Jervoise H, Andreyev N, Norman AR, et al. *Kirsten ras Mutations in Patients With Colorectal Cancer: the Multicenter "RASCAL" Study*. *J Natl Cancer Inst* 1998;90:675-84.
- ¹⁵ Alamo P, Gallardo A, Di Nicolantonio F, et al. *Higher metastatic efficiency of KRas G12V than KRas G13D in a colorectal cancer model*. *FASEB J* 2015;29:464-76.

Depression or prodromal fronto-temporal dementia?

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Introduction. Frontotemporal dementia (FTD) is a rare neurodegenerative disease, occasionally late onset, whose prevalence is underestimated especially in the geriatric population. The initial symptoms can be confused with some psychiatric disorders, such as depression, so the differential diagnosis may require careful investigations. Here we report the case of a 75 years old patient presenting with severe anxiety symptoms, initial social withdrawal and mild cognitive impairment.

Materials and methods. Longitudinal observational clinical study of 3 years. The patient underwent three successive cognitive assessments that included the Mini Mental State Examination (MMSE) and a battery of neuropsychological tests, imaging studies of the brain with a computer tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) and genetic analysis of a few possible mutations involved in FTD (C9ORF72, progranulin).

Results. The results after the first visit showed a picture of non amnesic single cognitive domain (dysexecutive) Mild Cognitive Impairment (MCI) associated with anxious-depressive symptomatology. The initial neuroimaging demonstrated fronto-temporal cortical atrophy with mild enlargement of the frontal horns of the lateral ventricles, and moderate glucose hypometabolism of bilateral prefrontal cortex. Genetic tests were instead negative. These data were suggestive of a diagnosis of prodromal FTD. However, in the three years follow-up, following a treatment with paroxetine the patient completely resolved her depressive symptoms, and in parallel she did not worsen her cognitive status nor developed behavioural disorders. Therefore we concluded for a depressive disorder and we diminished our suspects for a prodromal dementia.

Key words: Fronto-temporal dementia, Depression, Elderly

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INTRODUCTION

Frontotemporal dementia (FTD) is a rare neurodegenerative disease, with a typical pre-senile onset (on average at 58 years old)¹, rarely after 75 years old².

FTD can be classified into 3 main clinical phenotypes: the behavioural FTD, the most common one, characterized by changes in personality; the progressive non-fluent aphasia, in which the language deficit is the most prominent feature; the semantic dementia, dominated by semantic language disorders and semantic memory deficits. Overlapping syndromes, in which the FTD occurs associated with a motor neuron disease (amyotrophic lateral sclerosis) or atypical parkinsonism (corticobasal degeneration or progressive supranuclear paralysis)³ also exist.

Because of diagnostic difficulties, especially in the elderly, the prevalence of this disease is underestimated². Despite a strong hereditary component has been demonstrated⁴ and genetic mutations (most frequently C9ORF72, progranulin and MAPT) have been identified in familial cases, sporadic cases are reported in literature, in which the mutations occur *de novo*, or the clinical phenotype is not associated to known gene defects⁵. Especially in those forms not associated with a known genetic substrate, the diagnosis is particularly challenging because it relies on clinical symptoms and imaging techniques to rule out other diseases that may present similar manifestations. The differential diagnosis between a late onset sporadic FTD and depression might be particularly difficult. Depression is indeed a very common disorder in the elderly, and it can be developed for the first time in the old age, or become manifest with aging in subjects who have been suffering from sub-threshold mood disorders⁶. Both FTD and depression can be characterized by positive symptoms, such as excessive emotionality, distractibility and impulsiveness, or negative ones, such as apathy, social withdrawal, feelings of sadness, mental rigidity, loss of spontaneity and empathy. The two diseases differ in the type of management required, and in the impact they can have not only on the quality but also on the quantity of life. Indeed, some forms of FTD can lead to the patient exitus in only 4 years⁷.

Our work aim is to show the difficulties encountered in practice in the differential diagnosis between depression and a prodromal geriatric onset of FTD, through the presentation of a clinical case.

CLINICAL CASE

We report the case of a 75-year old patient, who, during her first geriatric visit, in December 2012, complained of

anxious symptoms, progressive loss of interests, social withdrawal, and initial fears related to unknown situations. Moreover, she reported difficulties in finding words and recent episodic memory loss (i.e. she lost objects at home). The symptoms had begun insidiously a year before, without apparent triggers. Her general practitioner had prescribed bromazepam without any benefit.

The patient's familiar anamnesis was positive for unspecified late onset dementia. Her father's cognitive disorder started when he was 80 years old and he died 5 years later for a stroke; whereas in her 79 year-old brother the first symptoms of cognitive impairment appeared insidiously, when he was 77 years old.

The patient's anamnesis was positive for hypertension, osteoporosis, chronic gastritis and gastro-oesophageal reflux disease. She had undergone a right mastectomy for breast cancer in 1978; subsequent follow-up had always been negative. When she was 30 years old, she had presented an episode of depression deemed as reactive to her father's death.

Functional assessment scales showed a complete preservation of autonomy in performing basic and instrumental activities of daily living (Activity of Daily Living - Index Katz - (ADL) = 6/6; Instrumental Activity of Daily Living - Home Lawton - (IADL) = 8/8). The screening cognitive tests, despite the reported memory loss, were normal: Mini Mental State Examination (MMSE) = 30/30; Clock Drawing Test (CDT) = 4/5. The assessment of the affective state, as reported by the patient, confirmed the presence of deflected mood (Geriatric Depression Scale (GDS) = 14/30).

To rule out any organic cause, blood tests were carried out and they excluded thyroid dysfunction or vitamin deficiencies. Complete blood count, coagulation, liver and kidney function indexes, electrolytes, glycaemia, glycated haemoglobin, lipid profile, serum uric acid concentration, reactive C protein, creatine phosphokinase and albumin were all normal.

The patient was investigated with brain computed tomography (CT) scan, which demonstrated a mild vasculopathy and a slight enlargement of the frontal horns of the lateral ventricles (Fig. 1A). A carotid Doppler ultrasound detected only a diffuse myointimal thickness.

Despite the normality of the cognitive screening, considering the relatively young age of the patient, the presence of psychiatric symptoms characterized predominantly by apathy and anxiety, the abrupt onset of the symptoms without any apparent trigger, and the enlargement of the frontal horns of the lateral ventricles detected by CT scan, we prudently decided to consider the hypothesis of a possible neurodegenerative disease, like FTD, in a prodromal phase.

Therefore we further evaluated the patient's cognitive state with neuropsychological tests, which showed a

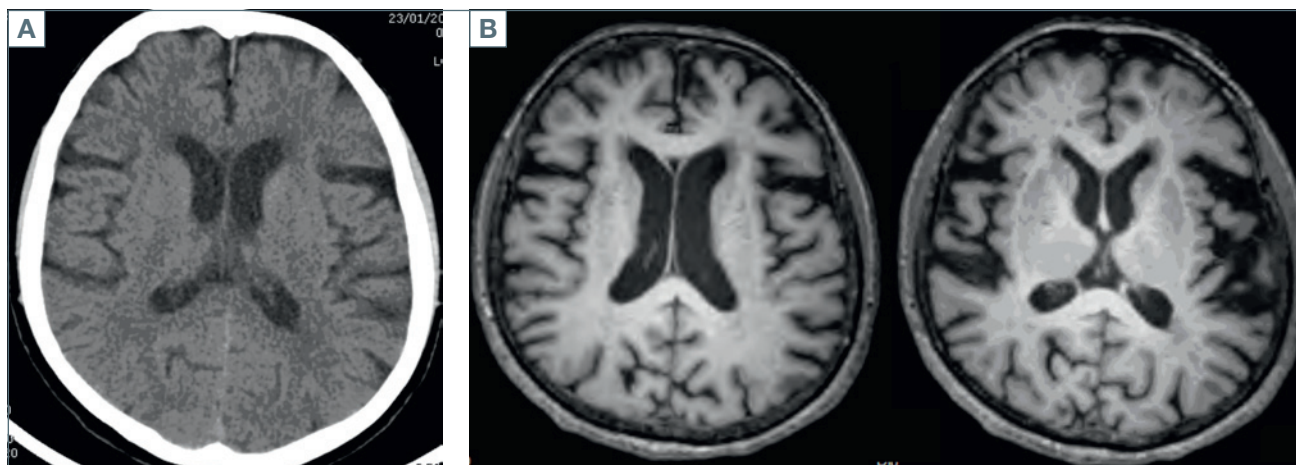


Figure 1. A. Brain CT showing off the slight enlargement of bilateral frontal horns of the lateral ventricles. **B.** Brain MRI: the frontal and temporal atrophy.

focal pre-frontal executive dysfunction (phonological fluency, bizarre cognitive estimates) associated with bradyphrenia, adynamic behavioural traits (characterized by a reduction of spontaneity and variability of emotional responses) and confirmed the anxious symptoms. The assessment was therefore conclusive for a non-amnesic (dysexecutive) single domain Mild Cognitive Impairment (MCI).

The result of the cognitive evaluation, although not specific and common to other aetiologies too (i.e. vascular disorders), could be compatible with the hypothesis of prodromal FTD.

Therefore we proceeded to a more sensitive neuroimaging study with brain magnetic resonance imaging (MRI), and with brain positron emission tomography (PET) to early detect hypo-functioning cerebral areas. The MRI confirmed the mild vasculopathy and the modest expansion of the anterior horns of the lateral ventricles already seen with CT, and demonstrated an initial cortical atrophy of the frontal and temporal cortex (Fig. 1B). The PET detected a moderate glucose hypometabolism in the bilateral prefrontal cortex (Fig. 2).

Considering the neuroimaging results, which seemed to support the hypothesis of prodromal FTD, and the family history of cognitive disorders we performed genetic analyses. We checked the presence of esanucleotidic expansion of the C9ORF72 gene and dosed plasmatic progranulin, which, if reduced, is suggestive of the presence of a genetic mutation causing gene haploinsufficiency. However we found no expansion of the C9ORF72 gene and normal plasmatic progranulin levels (75 ng/ml [normal values > 61.5 ng/ml]). Additionally, in the hypothesis of a frontal variant of Alzheimer's disease (AD)⁸, apolipoprotein E (ApoE) was genotyped and resulted homozygous for epsilon 3.

In the meanwhile, we modified the psychopharmacological therapy to cope with the patient's symptoms. We tried with sertraline, later substituted due to inefficacy, with escitalopram, levosulpiride and alprazolam, but we achieved only modest results. Finally, in January 2014, the patient was evaluated by a neurologist who, because of the high degree of anticipatory anxiety, avoidance behaviours and irritability presented by the patient, replaced escitalopram and levosulpiride with paroxetine. Subsequently the patient's depressive and anxious symptoms gradually improved with practically a complete resolution in June 2015 (Tab. I).

During the three year follow-up, from 2012 to 2015, the cognitive state of the patient remained substantially stable. Table II shows the results of longitudinal neuropsychological assessments; the neuropsychological phenotype remained unchanged: non amnesic (dysexecutive) single domain MCI.

DISCUSSION

A clinically overt dementia can be preceded by an early stage, now formally called Mild Cognitive Impairment (MCI), in which the activities of everyday life are not compromised, but deficits in one or more cognitive domains are already detectable through neuropsychological tests⁹. This phase may be also characterized by mild personality changes and behavioural symptoms.

The diagnosis of MCI-FTD is mainly clinical and is very complicated, because, the initial symptoms (behaviour or mood changes) are often similar to those found in psychiatric disorders. Moreover, depression in the elderly may be one of the first manifestations of dementia, either as an initial behavioural disorder, or as an emo-

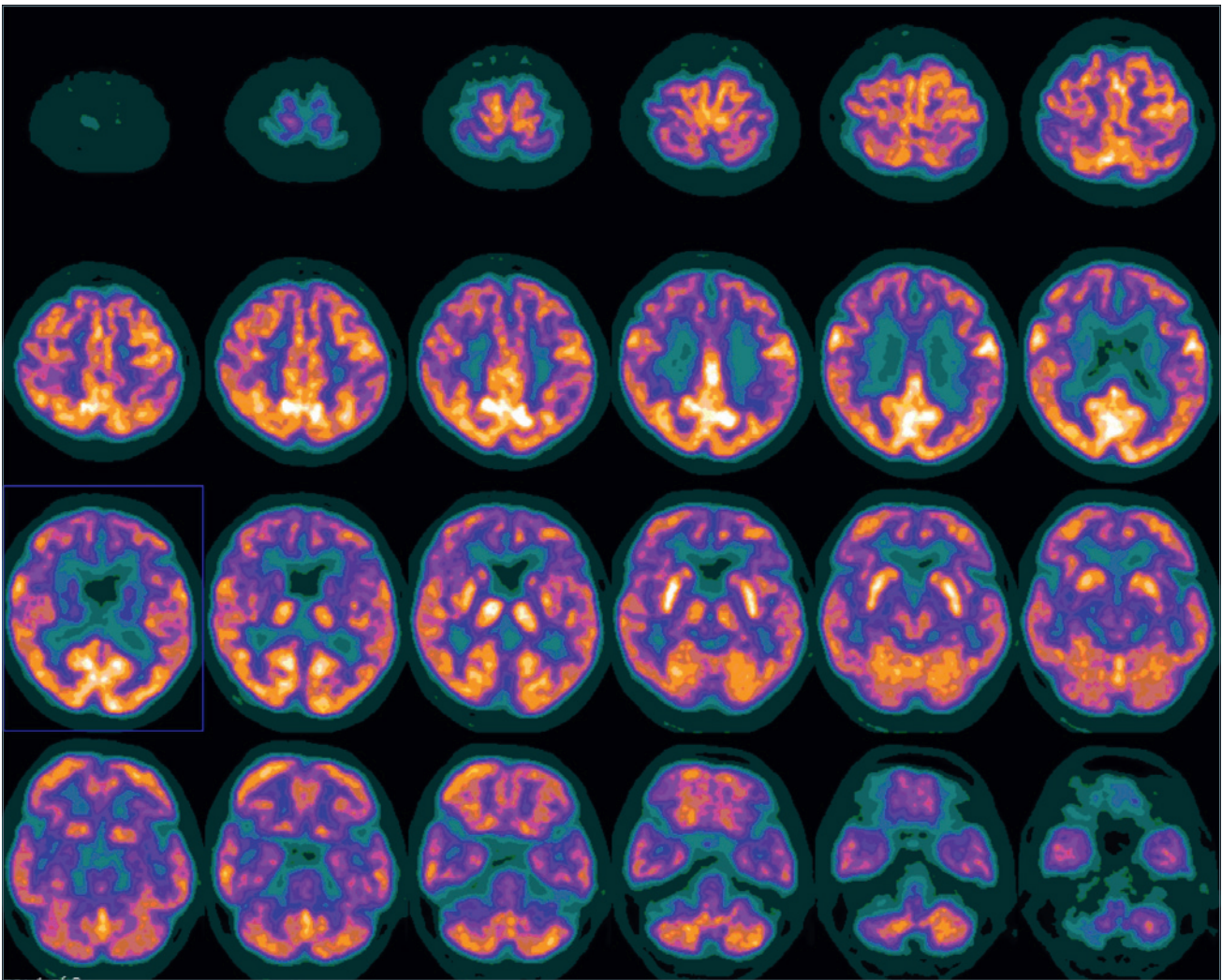


Figure 2. Brain PET showing a moderate bilateral prefrontal glucose hypo-metabolism.

Table 1. Evolution of anxious-depressive symptoms over time and parallel changes in psychopharmacological therapy.

	Feb. '13	Nov. '13	Mar. '14	Sept. '14	Dec. '14	Jun. '15
Symptoms	Insecurity, tension, agitation, anticipatory anxiety overall for activities outside the daily routine; deflected mood; insomnia	Deflected mood; anxiety and apathy	Improvement of the mood and the anxious state since it was introduced paroxetine (January 2014). Social withdrawal persist	Fair compensation of mood, no more anxiety	Improvement of anxiety symptoms and mood; no more social withdrawal	Neither deflected mood nor anxiety
Treatment	Sertraline (25 mg x 2) Alprazolam (0.25 mg)	Escitalopram (8 mg) Alprazolam (0.25 mg) Levosulpiride (25 mg x 2)	Paroxetine (20 mg) Alprazolam (0.25 mg)	Paroxetine (10 mg) Alprazolam (0.25 mg)	Unchanged	Unchanged
GDS (0-30)	14	15				3

Table II. Neuropsychological assessment.

Test	March 2013		December 2013		February 2015		Maximum score
	Raw score	Equivalent score or qualitative	Raw score	Equivalent score or qualitative	Raw score	Equivalent score or qualitative	
Global							
MMSE	30	+	26	+	28	+	/30
Attention							
Matrices test (visual search)	53	4	49	4	52	4	/60
Bells test	34	+	32	+	34	+	/35
Psychomotor speed							
Trail Making Test A	64	3	48	4	46	4	-
Memory							
Prose memory	11.3	2	11.8	2	12.5	3	/16
Rey-Osterrieth Figure (recall)	14.5	4	11.5	4	12	4	/36
Digit span forward	5	3	5	3	5	3	-
Prefrontal functions							
Digit span backward	3	+	3	+	3	+	-
Trail Making Test B	122	4	96	4	126	4	-
Raven test (coloured)	29	4	30	4	27	3	/36
Phonological fluency	16	0**	17	1*	22	1*	-
Short Stroop test (times)	25.5	4	34.5	3	21.5	4	-
Short Stroop test (errors)	0	4	3	2	2.5	3	/0
Cognitive Estimates CET (tot)	14	+	18	+	17	+	/0
CET (bizarre errors)	6	Deficit**	2	+	6	Deficit**	/0
Weigl's Sorting test					12	4	/15
Language							
Picture naming	73	+	70	+	69	+	/80
Praxis							
De Renzi's test (right)	69	+	67	+	69	+	/72
De Renzi's test (left)	65	+	70	+	65	+	/72
Visuospatial functions							
Copy of geometrical drawings	12	3	13	4	13	4	/14
Copy of Rey-Osterrieth Figure	30	3	31	4	29	2	/36

** impaired scores (< 5th percentile); scores in the lower normal range (< 20th percentile).

tional reaction to the awareness of one's own cognitive deficits. Depression is also known to be an independent risk factor for the development of dementia¹⁰. Alzheimer's dementia (AD) should also be contemplated among the possible diagnoses since its frontal variant could appear clinically indistinguishable from a behavioural FTD, especially in its early stages. The ApoE genotype (more frequently homo- or heterozygous for the allele epsilon 4 in AD cases) and the neuroimaging (showing a different distribution of the areas of brain atrophy) can help¹¹.

A comprehensive neuropsychological assessment can detect an early deficit in executive functions, such as the ability to plan, initiate and complete tasks, typically compromised in the FTD and less easily identifiable through the standard interview with the patients and/or caregiver compared with amnesic deficits. Nevertheless, even depression, especially if associated with a cerebrovascular disease may be associated with executive dysfunctions.

Neuroimaging studies can help to exclude organic diseases (e.g. tumors or infarction in the frontal lobes etc),

and support the diagnosis of behavioural FTD if there is evidence of focal atrophy of the frontal/anterior temporal lobes and/or a dilation of the frontal horns of the lateral ventricles. However, in the early stages of the disease, atrophy may not be detectable. At these stages functional studies, such as PET, can show a glucose hypometabolism in the fronto-temporal lobes when the brain parenchyma is still volumetrically intact.

Genetic tests are used to identify the mutations that cause familial forms of FTD but if negative do not rule out sporadic variants.

Unfortunately, often, only the disease course can help in the differential diagnosis. A condition of MCI can, in some cases, remain clinically stable for long periods. This is less likely if it is the manifestation of a prodromal FTD because this dementia type has usually a rapid course towards death (4-8 years). During the three-year follow-up, our patient did not reveal either psychotic symptoms or language disorders, which are instead typical during the progression of FTD. Finally, the response of our patient to the therapy with paroxetine, an antidepressant of the class of selective serotonin reuptake inhibitors (SSRIs), was impressive. Serotonin neurotransmission is involved in social control (basal orbitofrontal circuit), attention and planning (dorsolateral circuit), and in motivation and selective thinking (frontomedial circuit). It is known that in FTD serotonin concentration is reduced in the frontal subcortical circuits and that SSRIs, and in particular paroxetine, can improve non-cognitive symptoms and reduce the use of antipsychotic drugs¹². However, it is unlikely that these molecules can lead to a complete resolution of behavioural symptoms in a neurodegenerative disorder¹³, as much as when they are used for the treatment of depression¹⁴.

Finally, the presence of a chronic cerebrovascular disease should be taken into consideration. Cerebrovascular diseases increase the vulnerability of the elderly to the development of depression through various neurobiological mechanisms, such as damage to the frontal subcortical circuits important in emotional control¹⁵. In our patient it is possible that the cerebrovascular disease detected at the neuroimaging, although mild, could have played a role in the development of both depressive symptoms and executive dysfunction.

CONCLUSIONS

The early recognition of prodromal forms of FTD in the elderly remains a difficult challenge of fundamental importance for the geriatrician. It is of particular importance the differential diagnosis with the forms of depression in the elderly, which are often difficult to detect, and

which, if not properly treated, can amplify the disability of patients, reducing their quality of life, increase the mortality rate and increase the economic burden of the healthcare system. Unlike the FTD, whose prognosis is necessarily unfavourable, depression can be treated effectively, especially if therapy is started early, so it is of fundamental importance to make a proper early diagnosis which allows a therapeutic approach able to improve the life quality both of patients and family members.

References

- 1 Johnson JK, Diehl J, Mendez MF, et al. *Frontotemporal lobar degeneration: demographic characteristics of 353 patients*. Arch Neurol 2005;62:925.
- 2 Suzee E, Miller BL. *Frontotemporal dementia: Epidemiology, pathology, and pathogenesis*. www.uptodate.com
- 3 Landqvist Waldö M. *The frontotemporal dementias*. Psychiatr Clin N Am 2015;38:193-209.
- 4 Ratnavalli E, Brayne C, Dawson K, et al. *The prevalence of frontotemporal dementia*. Neurology 2002;58:1615.
- 5 Irwin DJ. *Frontotemporal lobar degeneration: defining phenotypic diversity through personalized medicine*. Acta Neuropathol 2015;129:469-91.
- 6 Kessler RC, Ormel J, Petukhova M, et al. *Development of lifetime comorbidity in the World Health Organization World Mental Health Surveys*. Arch Gen Psychiatry 2011;68:90.
- 7 Roberson ED, Hesse J, Rose K, et al. *Frontotemporal dementia progresses to death faster than Alzheimer disease*. Neurology 2005;65:719.
- 8 Ossenkoppele R, Pijnenburg YA, Perry DC, et al. *The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features*. Brain 2015;138:2732-49.
- 9 American Psychiatric Association. *Diagnostic Statistical Manual of Mental disorders IV edizione*. Washington DC: American Psychiatric Association 1994.
- 10 Espinoza RT, Unützer J. *Diagnosis and management of late-life unipolar depression*. www.uptodate.com
- 11 Hernandez I, Mauleón A, Rosense-Roca M, et al. *Identification of misdiagnosed fronto-temporal dementia using apoE genotype and phenotype-genotype correlation analyses*. Curr Alzheimer Res 2014;11:182-91.
- 12 Moretti R, Torre P, Antonello RM, et al. *FDT: paroxetine as a possible treatment of behavior symptoms*. Eur Neurol 2003;49:13-9.
- 13 Mocellin R, Scholes A, Walterfang M, et al. *Clinical update in frontotemporal dementia: diagnosis and treatment*. Australas Psychiatry 2015;23:481-7.
- 14 Newhouse PA. *Use of serotonin selective reuptake inhibitors in geriatric depression*. J Clin Psychiatry 1996;57(Suppl 5):12-22.
- 15 Kales HC, Maixner DF, Mellow AM. *Cerebrovascular disease and late-life depression*. Am J Geriatr Psychiatry 2005;13:88.

Pain management in dementia: so far, not so good

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Pain is highly prevalent in the aging population. Individuals with neurological disorders such as dementia are susceptible patient groups in which pain is frequently under-recognised, underestimated, and under-treated. The inability to successfully communicate pain in moderate-severe dementia is a major barrier to effective treatment and several observational studies indicate that pain is under-treated among cognitively impaired elderly people.

Pain has been related to neuropsychiatric symptoms in dementia, such as agitation, aggression, mood syndrome and sleep problems. Adequate pain management has been demonstrated as possibly effective in mediating or alleviating those symptoms.

Recent guidelines (American Geriatric Society 2009, British Geriatric Society 2013) recommend a comprehensive, disease-specific assessment to determine appropriate treatment for each individual. Whereas in old patients data on pain management are becoming more consistent, we still lack clinical evidence in those affected by dementia.

In this narrative review, we summarize the best-available evidence regarding the aetiology, assessment and treatment of pain in people with dementia. Further large-scale trials of treatment approaches in people with dementia are needed to improve clinical guidance for the diagnosis and treatment of pain in these fragile individuals.

Key words: Pain, Dementia, Alzheimer disease, Elderly, Opioids

INTRODUCTION: CRITICAL ISSUES ABOUT PAIN IN DEMENTIA

Dementia is a “clinical syndrome due to disease of a progressive nature, which leads to disturbances multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment”¹. Dementia affects approximately 44 million people worldwide, and this is expected to double every 20 years as the population

ages (Fig. 1). One-third of people with dementia reside in nursing homes².

Ample evidence shows that aging is associated with a high rate of painful conditions, irrespective of cognitive status. Chronic pain is common in older people, affecting about 60% of people aged more than 65 years and functionally impairing 45%-80% of older people in nursing homes³. The most common types of pain are musculoskeletal, such as arthritis, or neuropathic pain as result of diabetes or stroke⁴.

The number of patients with dementia who will

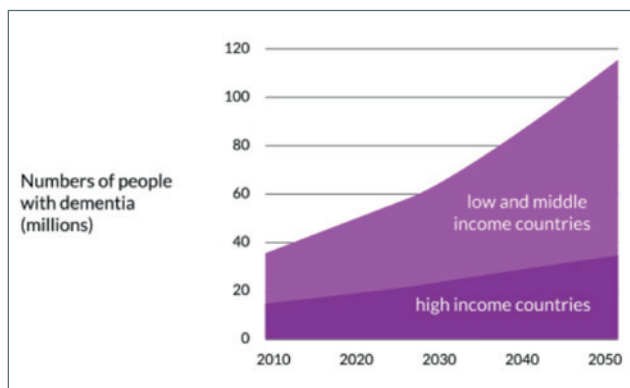


Figure 1. Expected growth of people affected by dementia in 2050.

Modified from Ferri et al. The Lancet 2005. Alzheimer's Disease International (2009), World Alzheimer's Report.

experience painful conditions is therefore likely to increase and the majority of them experience persistent pain lasting 6 months or longer⁵. Despite the high prevalence of pain in affected individuals, the assessment and management of their perceived pain is difficult due to the frequent loss of cognitive and communicative abilities. This begs the question of exactly how patients with dementia and other chronic cognitive neurodegenerative disorders perceive pain⁶.

Little is known about the relationship between dementia and the neurophysiology of pain. Dementia is associated with central nervous system changes such as the destruction of cortical neuronal cells and depletion of cortical chemical neurotransmitters. Nociceptor response and transmission of pain sensation, however, are not thought to be affected by these physiological changes. In particular, the somatosensory cortex, crucial to the central modulation of pain, is largely unaffected by dementia⁷ (Tab. I).

Patients with dementia may express their pain in ways that are quite different from those of elderly people

without dementia. Particularly in the more severe stages of dementia, the complexity and consequent inadequacy of pain assessment leads to the under-treatment of pain itself⁸.

Several observational studies indicate that pain is under-treated among cognitively impaired elderly people^{9,10}. A major problem associated with the under-treatment of pain in the elderly who are cognitively impaired is the challenging nature of pain assessment¹¹. The under-treatment of pain therefore has been associated with withdrawal, sleep disturbance, increased disability, and depression¹². In addition, failure to adequately treat pain could compromise the effectiveness of rehabilitation therapies and may irreversibly alter the patient's ability to remain in their homes.

It has been reported that fewer analgesics are prescribed for the oldest category of cancer patients (over 75 years) than for younger patients, and low cognitive performance was one of the independent predictors of this finding¹³. In addition, it has been shown that among patients with history of hip fractures, those in advanced stages of dementia receive significantly less opioid analgesics than cognitively intact patients do¹⁴. All these observations stress the importance of increasing our knowledge of pain pathways, recognition and management in this specific, fragile population.

PAIN PERCEPTION IN ALZHEIMER DISEASE

Alzheimer's Disease (AD) is primarily a disorder of the neocortex, while the somatosensory cortex is relatively unaffected by the histological changes that are the hallmark of this disorder. Furthermore, although some senile plaques have been identified in the diencephalon it is unlikely that thalamic nuclei are significantly affected in AD. Consequently the sensory/discriminative quality of pain perception might be expected to be preserved in cases of AD, although distortions of sensation associated with parietal dysfunction may occur^{15,16}. On the

Table I. Characteristics of dementia subtypes (modified from International AsD. World Alzheimer Report 2009. London: Alzheimer's Disease International, 2009).

Dementia subtypes	Early characteristics symptoms	Neuro-pathology	Proportion of dementia cases
Alzheimer's Disease (AD)*	Impaired memory, apathy and depression, gradual onset	Cortical amyloid plaques and neurofibrillary tangles	50-75%
Vascular Dementia (VaD)*	Similar to AD, but memory less affected, and mood fluctuations more prominent Physical frailty Stepwise onset	Cerebrovascular disease Single infarcts in critical regions, or more diffuse multi-infarct disease	20-30%
Frontotemporal dementia	Personality changes Mood changes Disinhibition Language difficulties	No single pathology – damage limited to frontal and temporal lobes	5-10%

* Post mortem studies suggest that many people with dementia have mixed Alzheimer's disease and vascular dementia pathology, and that this 'mixed dementia' is underdiagnosed.

contrary, intralaminar thalamic nuclei, which represent a strategic pathway of the non-discriminative medial pain system, are early and progressively affected by the AD-related cellular changes¹⁷. As a consequence, emotional and affective function may be altered, and this is related to conspicuous neuronal and synaptic loss in prefrontal and limbic regions¹⁸.

A detailed study on patterns of brain structural deficits across the cortex in AD suggested a spatially complex model of different atrophic patterns as AD progresses. Three main features were observed: 1) the overall deficit pattern spreads through the brain in a temporal-frontal-sensorimotor sequence, with a time lag in the right hemisphere; 2) the left hemisphere degenerates faster than the right; this asymmetric loss rate increases the existing asymmetry in cortical gray matter found in healthy elderly subjects; 3) some phylogenetically older brain systems are spared late in the disease (e.g., sensory-motor cortices)¹⁹. With regard to pain perception, all brain regions related to medial system are affected during AD. Those pathways related to lateral pain pathways, such as the primary somatosensory cortex, are also preserved in late stages of AD²⁰.

Several studies observed a dissociation between sensory/discriminative pain perception, usually elaborated through the lateral pathway, and affective/emotional pathways, generally mediated by the medial system. A detailed and systematic study by Benedetti et al. showed a dissociation of pain perception in AD patients. By comparing AD patients with normal subjects of the same age, no differences in stimulus detection and pain thresholds were found, whereas a clearcut increase in pain tolerance was present in AD patients. They found pain thresholds to be unchanged, whereas pain tolerance increased according to the severity of the disease. A correlation between pain tolerance and the severity of AD, measured by means of neuropsychological (MMSE) and neurophysiological tests (spectral EEG), was also performed. There was a straightforward correlation between MMSE scores and pain tolerance demonstrating that the more severe the cognitive impairment the higher the tolerance to pain. What emerged from this analysis was that pain tolerance can be estimated by the degree of impairment of both MMSE and EEG. As a generalisation, MMSE scores ranging from 10-19 tend to follow the rule of thumb: 'the more severe the MMSE and EEG changes, the higher the tolerance to pain' as pain tolerance tends to co-vary in both MMSE's and EEG's. These findings show that, whereas the sensory-discriminative component of pain is maintained in AD patients, pain tolerance is altered and depends on cognitive and affective factors²¹.

Pain perception and autonomic responses to pain are known to be altered in dementia. As a proof of that,

neither stimulus detection nor pain threshold was correlated to cognitive status and a decline in brain activity²². In contrast, there is a correlation between autonomic responses and the deterioration of both cognitive functions and brain electrical activity. In particular, the heart rate increase after pain stimulation was correlated to the presence of slowed brain electrical activity (delta and theta frequencies). This correlation was also found for the anticipatory heart rate increase just before pain stimulation. These results indicate that pain anticipation and reactivity depend on both the cognitive status and the frequency bands of the electroencephalogram. On the contrary, both stimulus detection and pain threshold are not affected by the progression of AD. These findings clearly show that, whereas the sensory-discriminative components of pain are preserved even in advanced stages of AD, the cognitive and affective functions, which are related to both anticipation and autonomic reactivity, are severely affected. This sensory-affective dissociation is well correlated with the neuropathological findings in AD, mentioned above²³.

The degree of progression of AD could deeply influence the functioning of the medial and lateral pain systems. Cole and colleagues studied pain responses and compared them with cognitive function evaluations through f-MRI after mechanical stimulation in patients early stage dementia. They observed that medial and lateral systems were preserved in AD patients and controls had similar results²⁴.

It has been observed therefore that in early stages of AD both networks – medial and lateral – work correctly. The next step, clinically, is to understand the influence of severe cognitive loss on pain perception in this patient population.

PAIN PERCEPTION IN VASCULAR DEMENTIA

In comparison to AD, where brain lesions are topographically constant, vascular dementia (VaD) is a heterogeneous disorder. In fact, vascular lesions could affect different brain regions and consequently determine different effects on pain perception. As a consequence it is not possible to predict how a vascular dementia patient feels pain.

However it's known that VaD is mainly determined by white substance lesions. These lesions becomes clinically relevant when they block afferent fibres, for example thalamus-cortex projections, and cause a deafferentation syndrome and consequently hyperalgesia²⁵. Scherder and colleagues observed that patients with VaD showed an increase affectivity in pain perception due to several conditions such as osteoarthritis, fractures and diabetic neuropathy²⁶. Another study showed

that periventricular hyper-density is correlated to an increase of pain perception's affectivity²⁷. Therefore it is reasonable to observe that patients with VaD could feel pain differently, showing a more affective/emotional component.

PAIN PERCEPTION IN FRONTO-TEMPORAL DEMENTIA

In fronto-temporal dementia (FTD) a degeneration of frontal and temporal lobes occurs. As frontal lobes have a central role in pain elaboration, pain experience is altered. Some studies described loss of pain consciousness as one of remarkable behavioural symptoms of FTD, useful for differential diagnosis with other sub-type dementias.

Therefore, it can be hypothesized that stricter neuroanatomical criteria may play a central role in demonstrating an increase in pain tolerance as well as improved detection of neuroanatomical changes. Such measures may improve the identification of patients with compromised medial pain system areas. In particular, areas such as the anterior cingulate cortex, the insula, and the prefrontal cortex show signs of atrophy in FTD.

The observed changes in pain processing in FTD patients depend on how the diagnosis of FTD is performed. The clinical diagnosis alone, mainly based on neuropsychological testing, may fail to isolate the specific frontal and temporal impairment. Conversely, neuroimaging techniques may reveal specific frontal and temporal anatomical changes that are more specifically related to some aspects of pain processing²⁸.

These findings differ in part from those described in AD. In fact, while a selective loss of the affective components of pain have been reported in AD patients with conserved aspects of the sensory-discriminative component, herein, studies also found elevated pain thresholds in FTD patients²⁹. Pain threshold is a sensory-discriminative aspect of pain sensation, which is

mediated by the lateral pain system, while pain tolerance represents an affective aspect that is mediated by the medial pain system (Tab. II).

CHALLENGING PAIN ASSESSMENT IN DEMENTIA

In clinical practice, pain in elderly verbal patients – with or without mild cognitive impairment – is usually assessed by means of self-reports. Self-reporting is considered as the 'gold standard' in pain assessment. A broad range of self-report scales is currently available to assess pain in the elderly. The great majority of these have been developed and tested in very different settings before being applied to elderly people with dementia. The most frequently assessed component of pain is pain intensity³⁰.

Commonly used measures of pain intensity include Visual Analogue Scales, Verbal Rating Scales, Numeric Rating Scales and Facial Pain Scales. It is generally worth noting that elderly people find it difficult to use self-report scales correctly and no single self-report scale seems appropriate for all elderly people, especially with dementia. For instance these scales typically assess only sensorial-discriminative characteristics of pain instead of emotional and affective ones. Approaching pain in non-verbal patients by using self-reports scales is inadequate, as dementia patients feel pain differently depending on the sub-type of dementia and individual communication deficits⁴.

The progression of dementia severely compromises the ability to communicate, and verbal reports of pain tend to become less reliable. Other approaches, such as observational and surrogate reporting, are necessary in patients with moderate and advanced dementia. Over the past decade a number of observational tools for use with nonverbal older adults with dementia have been developed. These tools focus on the assessment of non verbal behaviours such as facial expressions, paralinguistic vocalizations, guarding, bracing, changes in

Table II. Relation between neuropathology and results of experimental and clinical studies in subtypes of dementia on motivational-affective aspects and presence or intensity of pain (modified from Scherder et al., 2005).

Condition	Motivational-affective aspects of pain (medial system)			Presence or intensity of pain (lateral system)
	Neuropathological involvement	Experimental and clinical results	Neuropathological involvement	Experimental and clinical results
Alzheimer's disease	Degeneration of thalamic intralaminar nuclei	↓ Decreased	Unaffected	Unaffected
Vascular dementia	De-afferentation	↑ Increased	Not examined	Not examined
Fronto-temporal dementia	Degeneration of prefrontal cortex	↓ Decreased	Not examined	Not examined

social behaviour, changes in sleeping patterns, aggressive behaviour, changes in psychomotor activity, and others^{31 32}. While the validity of several of these tools has been supported, many of the behaviours assessed by pain assessment tools also represent manifestations frequently present in psychogeriatric disorders, such as delirium, depression or Parkinson disease³³.

Another weakness of this approach is the considerable inter-individual variability between patients with dementia in their expression of pain via behavioural demonstration. This consideration is immensely important, given the presence of atypical behaviour in different types of dementia and the frequently associated concomitant neuropsychiatric disorders^{34 35}.

In non verbal patients the autonomic responses do not seem to be useful in pain assessment, as these reactions do not directly represent pain intensity. As previously described, AD patients show reduced autonomic responses, but they can discriminate between a tactile or pain experience¹⁸.

Clinical guidelines for older adults have been published by the American Geriatric Society (AGS) panel from 1998, with regular updates in 2002 and 2009. The latest version also includes recommendations for accurate pain assessment in patients with dementia³⁶ (Tab. III).

Although a standardized assessment tool is not yet available for widespread use, a comprehensive approach to pain assessment is recommended in non-verbal older adults with dementia.

PAIN MANAGEMENT IN DEMENTIA. PRACTICAL AND CLINICAL ISSUES

The issue of pain treatment in literature is lacking in some key areas but the evidence does provide consistent support for specific approaches to address pain. Randomized controlled trials (RCTs) and systematic reviews show a high level of agreement around the value of treatment with acetaminophen as a first-line approach, aligning with the recent and current guidelines from both the AGS and British Geriatric Society (BGS)^{36 37}. The value of stepped treatment approaches to address pain is greatly enhanced in the literature, starting with a comprehensive medical and personalized non-drug 'comfort' approaches before escalating to pharmacological treatment^{38 39}.

Despite this, non steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for pain in the elderly, and those drugs must be used with caution in older people. This is due to the high risk of potentially serious and life-threatening side effects, as prostaglandins have a pivotal role in the normal human physiological functions of the GI tract, renal and cardiovascular systems,

Table III. Common pain behaviours in elderly patients with dementia according to AGS Panel on persistent pain in older persons.

1. Facial expressions	<ul style="list-style-type: none"> • Slight frown; sad, frightened face • Grimacing, wrinkled forehead • Closed or tightened eyes • Any distorted expression • Rapid blinking
2. Verbalizations, vocalizations	<ul style="list-style-type: none"> • Sighing, moaning, groaning • Grunting, chanting, calling out • Noisy breathing • Asking for help • Verbally abusive
3. Body movements	<ul style="list-style-type: none"> • Rigid, tense body posture, guarding • Fidgeting • Increased pacing, rocking • Restricted movement • Gait or mobility changes
4. Changes in interpersonal interactions	<ul style="list-style-type: none"> • Aggressive, combative, resisting care • Decreased social interactions • Socially inappropriate, disruptive • Withdrawn
5. Changes in activity patterns or routines	<ul style="list-style-type: none"> • Refusing food, appetite change • Increase in rest periods • Sleep, rest pattern changes • Sudden cessation of common routines • Increased wandering
6. Mental status changes	<ul style="list-style-type: none"> • Crying or tears • Increased confusion • Irritability or distress

as well as others. Of note, data about hospital admission due to adverse drug reactions is shocking in its scope (23.5% in the elderly population)³⁷.

Opioid use in older people may be associated with less risk than that of NSAIDs, particularly in those older people who are at particular risk of NSAID-related events. As there is marked inter-patient variability in efficacy and tolerability of individual opioids, if there is no analgesic response or significant adverse events with one opioid, switching or rotation may be considered. Opioid analgesics should be considered an effective alternative therapy for older patients with moderate-to-severe pain or for pain that impairs functioning and quality of life, instead of NSAIDs. Additionally, they should be administered as part of a comprehensive pain management strategy. Although older people tend to require lower doses than younger individuals, opioid effects do not appear to vary with age and careful dose titration based on individual response is required⁴⁰.

Many side effects, such as sedation, nausea and vomiting, may be worse during opioid initiation or dose

escalation, and may resolve after 2 or 3 days⁴¹. On the other hand, constipation does not readily improve and may be managed with laxative therapy or a peripheral opioid antagonist (such as oral prolonged-release naloxone). In this regard, a recent open-label prospective study of our group has demonstrated that low-dose of oxycodone/naloxone is effective and well tolerated for treatment of moderate-to-severe chronic pain in geriatric population. In particular, this opioid agonist-antagonist combination reduced the impact of pain on daily activities with significant improvement in daily functioning; of note, no changes were observed in cognitive status and bowel function. Besides its effectiveness, these data indicate that low-dose opioids may be reasonably considered a safe analgesic option in fragile patients^{42,43}.

Of note, some adjuvant drugs treating associated conditions such as tricyclic antidepressants and some anti-epileptic medicines have been shown to have a significant beneficial effect on the attenuation of neuropathic pain⁴¹.

Therefore a recent research by Dublin and colleagues has revealed that people with the heaviest opioid or NSAID use had slightly higher dementia risk than people with little or no use. These results may reflect an effect of chronic pain on cognition. Although opioids have other risks, little evidence of long-term cognitive harm specific to opioids was found⁴⁴.

Despite this data and the high prevalence of pain in dementia, the quality of pain management is currently lacking in clinical practice.

Recent interventions in pain management have been effective in reducing both pain and behavioural symptoms in dementia⁴⁵. Manfredi and colleagues investigated effect of opioid analgesics on pain intensity and behavioural disturbances in these specific subpopulations. They evaluated 25 patients with agitation assessed by Cohen-Mansfield Agitation Inventory. Of the 25 subjects, 13 showed significant reduction of agitation after 4 weeks⁴⁶.

In a placebo-controlled crossover trial with 25 patients, Chibnall et al investigated the efficacy of acetaminophen on emotional well-being and behaviour and they reported significant improvement in activities but found no effect on agitation⁴⁷.

Another RCT in 114 patients with behavioural disturbances were assigned randomly to either a serial trial intervention (STI) of stepped assessment and treatment or usual care; results indicate that the STI approach improved behavioural symptoms significantly, although the effect of analgesics was not reported⁴⁸.

A clear limitation in the existing literature is the lack of large RCT studies with pain intensity as the main outcome. To date, no large-scale pain intervention studies

have focused upon improvement of pain intensity as a key outcome.

Interestingly, a recent study on 352 patients with dementia showed that a stepwise protocol on pain intensity in nursing homes significantly reduced pain intensity as assessed through observational scales (Mobilization-Observation-Behaviour-Intensity-Dementia-2 Pain Scale). Remarkably it was also observed that administration of acetaminophen also improved ADL function⁴⁹.

Moreover in a prospective observational study on 53 elderly patients with cognitive impairment Petrò and colleagues proved oxycodone/naloxone to be effective in improving control of pain and behavioral symptoms associated to dementia, with a favorable safety and tolerability profile and no bowel interference⁵⁰.

Indeed, further large-scale trials of treatment approaches in people with dementia are needed to improve clinical guidance.

PAIN AND ITS RELATION WITH BEHAVIOURAL PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

In addition to cognitive decline, dementia is commonly accompanied by neuropsychiatric symptoms, which largely overlap with the term “behavioural and psychological symptoms of dementia” (BPSD). The aetiology of the neuropsychiatric symptoms is poorly understood. It is suggested that the cause is multifactorial, based on chemical, anatomical and transmitter changes in the brain. Other hypotheses speculate that it’s related to physical diseases, or to unmet needs such as boredom, fear or pain. There is an association between pain and neuropsychiatric symptoms in patients with dementia. A considerable number of items in current pain tools for patients with dementia overlap with those in neuropsychiatric inventories.

Some of these BPSDs appear to be dictated by the severity of pain, with more severe pain resulting in reduced wandering and pacing but increased aggressive responses. Importantly, these symptoms may also respond to analgesic treatment in clinical trials, with the largest RCT reporting improvement in agitation and aggression following stepped treatment of pain. As a matter of fact, verbally agitated behaviours such as complaining, negativism, repetitious sentences and questions, constant requests for attention, cursing or verbal aggression have been found to respond to pain treatment⁴⁹.

However the literature on whether pain is associated with agitation in people with dementia is inconsistent. Volicer et al.⁵¹ found in a longitudinal study of 2032 Dutch nursing home residents that pain was not highly

related to agitation and pain scores did not change in proportion to agitation scores. Other studies have found an association between agitation and pain in hospital-dwelling people with dementia⁵².

In a recent prospective study, pain was found to predict the development of aggression⁵³. Further investigations have suggested that pain can manifest as agitation or aggression in people with dementia and that pain treatment may ameliorate these symptoms⁵⁴.

A recent study confirmed the efficacy of pain treatment in ameliorating mood symptoms. Those patients received individual daily pain treatment with acetaminophen, extended release morphine, buprenorphine transdermal patch or pregabalin for 8 weeks. Mood symptoms, including depression, were found to significantly improve with pain treatment, emphasizing the importance of more rigorous treatment of pain in agitated people with dementia⁵⁵.

Current literature shows no improvement in psychotic symptoms such as deliria and hallucinations with the treatment of pain in these populations. This defines a clear and typical impact of pain on behaviour of Dementia patients.

The impact of pain on BPSD is of particular importance since these symptoms are commonly treated with antipsychotic medications. Antipsychotic drugs are associated with considerable and severe side effects, including worsening of cognitive decline, Parkinsonism, stroke and death. Despite recent reductions in the use of these drugs, prescription levels remain high, and are often outside their licensed use⁵⁶.

Another similar concern is raised on the treatment of sleep disorders. Several studies have suggested that the use of sedative drugs masks the underlying causative pain⁵⁷. This issue highlights the concern about inappropriate drug prescription in the elderly and the consequent risk of polypharmacy, which might be avoided by an accurate assessment and treatment of the underlying pain.

However, in patients with dementia, if the presence of pain is uncertain, an analgesic intervention may be warranted to evaluate the presence of pain. If the interventions appear to provide pain relief, pain may be assumed as the likely cause and the length of intervention protracted.

DISCUSSION AND FUTURE PERSPECTIVES

When considering pain management in dementia, clinicians are frequently faced with situations that question the very nature of suffering. The inability of individuals to accurately convey their feelings complicates our efforts to identify and measure the nature of their discomfort.

The diminished capacity of individuals with dementia to advocate for themselves, however, increases the duty of care of those who are charged with this responsibility. There is a high risk for under-treatment of pain in dementia, particularly in non-communicative patients with white matter lesions, but also in dementia patients who report less prevalent and intense pain. Older adults with dementia receive less pain medication than those who are able to communicate, even though they are just as likely to experience painful illnesses⁹.

In fact, findings from clinical and experimental pain studies do not suggest that pain is less frequent and intense even if it's no longer reported. On the contrary, the impact of dementia on pain processing varies in patterns and quality, depending on the type of pain, neuropathology and stage of dementia.

The most important finding is that according to type of dementia, patient could experience different pain perception related to specific brain damage¹⁶⁻¹⁸. It's reasonable to conclude that consequently for each type and stage of dementia, there is a specific pattern of pain thresholds and detection. Critically, treating physicians should consider the unique pattern of cognitive degeneration in managing the pain in each and every patient with dementia.

Assessment of pain in non-verbal older adults with dementia remains a challenge for clinicians and researchers. Future pain assessment in this vulnerable population may reveal opportunities for recognizing pain through enhanced brain imaging techniques and monitoring of pain-related chemical substances currently under study. However, for the immediate future our focus must be on strategies to assist clinicians recognize pain with readily available methods and resources. A great priority is to raise awareness of pain presence and potential indicators to screen for potential pain.

Critically, very poor literature is present on pain treatment in older persons with dementia at this time. Adequate pain control in patients with dementia depends on good pain evaluation and may express itself in an improvement in behaviour and activities of daily life, since verbal communication about pain is not reliable.

It is essential that implementation and continuous education and training programs be developed, implemented, and evaluated to ensure the effective use of any new tool. These are prerogative steps for better management. There is a great need to provide support and clear guidance for clinicians and other health professionals.

"Start slow and go slow" is the key word in pain therapy in geriatrics, but the benefit-risk ratio of any analgesic treatment must also be kept in mind. Further studies in older persons with dementia with regard to the therapeutic approach and the link between pain and

behavioural symptoms would be of great importance in order to clarify these issues.

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References

- 1 The ICD-10 Classification of Mental and Behavioural Disorders. World Health Organization, Geneva, 1992.
- 2 Hoffmann F, Kaduszkiewicz H, Glaeske G, et al. Prevalence of dementia in nursing home and community-dwelling older adults in Germany. *Aging Clin Exp Res* 2014;26:555-9.
- 3 Davis MP, Srivastava M. Demographics, assessment and management of pain in the elderly. *Drugs Aging* 2003;20:23-57.
- 4 Scherder EJ, Plooij B. Assessment and management of pain, with particular emphasis on central neuropathic pain, in moderate and severe dementia. *Drugs Aging* 2012;29:701-6.
- 5 Pickering G, Jourdan D, Dubray C. Acute versus chronic pain treatment in Alzheimer's disease. *Eur J Pain* 2006;10:379-84.
- 6 Horgas AL, Elliott AF. Pain assessment and management in persons with dementia. *Nurs Clin North Am* 2004;39:593-606.
- 7 Wells N, Kaas M, Feldt K. Managing pain in the institutionalized elderly: the nursing role. In: Mostofsky DI, Lomranz J, eds. *Handbook of pain and aging*. New York: Plenum Press 1997, pp.129-151.
- 8 Herr K, Decker S. Assessment of pain in older adults with severe cognitive impairment. *Ann Long Term Care* 2004;12:46-52.
- 9 Horgas AL, Tsai PF. Analgesic drug prescription and use in cognitively impaired nursing home residents. *Nursing Research* 1998;47:235-42.
- 10 Loeb JL. Pain management in long-term care. *Am J Nurs* 1999;99:48-52.
- 11 Zwakhalen SMG, Hamers JPH, Abu-Saad HH, et al. Pain in elderly people with severe dementia: a systematic review of behavioural pain assessment tools. *BMC Geriatrics* 2006;6:3.
- 12 Ferrell BA, Ferrell BR, Rivera L. Pain in cognitively impaired nursing home patients. *J Pain Symptom Manage* 1995;10:591-8.
- 13 Bernabei R, Gambassi G, Lapane K, et al. Management of pain in elderly patients with cancer. *JAMA* 1998;279:1877-82.
- 14 Morrison RS, Siu AL. A comparison of pain and its treatment in advanced dementia and cognitively intact patients with a hip fracture. *J Pain Symptom Manage* 2000;19:240-8.
- 15 Farrell MJ, Katz B, Helme RD. The impact of dementia on pain experience. *Pain* 1996;67:7-15.
- 16 Rudelli RD, Ambler MW, Wisniewski HM. Morphology and distribution of Alzheimer neuritic (senile) and amyloid plaques in striatum and diencephalon. *Acta Neuropathologica* 1984;64:273-81.
- 17 Rub U, Del Tredici K, Del Turco D, et al. The intralaminar nuclei assigned to the medial pain system and other components of this system are early and progressively affected by the Alzheimer's disease-related cytoskeletal pathology. *J Chem Neuroanat* 2002;23:279-90.
- 18 Scheff SW, Price DA. Alzheimer's disease related synapse loss in the cingulate cortex. *J Alzheimers Dis* 2001;3:495-505.
- 19 Thompson PM, Hayashi KM, De Zubicaray G, et al. Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci* 2003;23:994-1005.
- 20 Scherder EJ, Sergeant JA, Swaab DF. Pain processing in dementia and its relation to neuropathology. *Lancet Neurology* 2003;2:677-86.
- 21 Benedetti F, Vighetti S, Ricco C, et al. Pain threshold and tolerance in Alzheimer's disease. *Pain* 1999;80:377-82.
- 22 Raniero I, Vighetti S, Bergamasco B, et al. Autonomic responses and pain perception in Alzheimer's disease. *Eur J Pain* 2000;4:267-74.
- 23 Benedetti F, Arduino C, Vighetti S, et al. Pain reactivity in Alzheimer patients with different degrees of cognitive impairment and brain electrical activity deterioration. *Pain* 2004;111:22-9.
- 24 Cole LJ, Farrell MJ, Duff EP, et al. Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease. *Brain* 2006;129:2957-65.
- 25 O'Brien JT, Erkinjuntti T, Reisberg, et al. Vascular cognitive impairment. *Lancet Neurol* 2003;2:89-98.
- 26 Scherder EJ, Slaets J, Deijen JB, et al. Pain assessment in patients with possible vascular dementia. *Psychiatry* 2003;66:133-45.
- 27 Oosterman JM, van Harten B, Weinstein HC, et al. Pain intensity and pain affect in relation to white matter changes. *Pain* 2006;125:74-81.
- 28 Carlino E, Benedetti F, Rainiero I, et al. Pain perception and tolerance in patients with frontotemporal dementia. *Pain* 2010;151:783-9.
- 29 Rosen HJ, Gorno-Tempini ML, Goldman WP, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology* 2002;58:198-208.
- 30 Herr KA, Spratt K, Mobily PR, et al. Pain intensity assessment in older adults: use of experimental pain to compare psychometric properties and usability of selected pain scales with younger adults. *Clin J Pain* 2004;20:207-19.
- 31 Lichtner V, Dowding D, Esterhuizen P, et al. Pain assessment for people with dementia: a systematic review of systematic reviews of pain assessment tools. *BMC Geriatr* 2014;17:14-138.
- 32 Zwakhalen SM, Hamers JP, Abu-Saad HH, et al. Pain in elderly people with severe dementia: a systematic review of behavioural pain assessment tools. *BMC Geriatr* 2006;6:3.
- 33 Kovach CR, Weissman DE, Griffie J, et al. Assessment and treatment of discomfort for people with late-stage dementia. *J Pain Symptom Manage* 1999;18:412-9.

- ³⁴ Caligiuri MP, Peavy G, Galasko DR. *Extrapyramidal signs and cognitive abilities in Alzheimer's disease*. *Int J Geriatr Psychiatry* 2001;16:907-11.
- ³⁵ Van der Steen JT, Sampson EL, Van den Block L, et al. *Tools to assess pain or lack of comfort in dementia: a content analysis*. *J Pain Symptom Manage*. 2015;S0885-3924(15)00335-8.
- ³⁶ American Geriatric Society. *Pharmacological management of persistent pain in older persons*. *J Am Geriatr Soc* 2009;57:1331-46.
- ³⁷ British Geriatric Society. *Guidance on the management of pain in older people*. *Age Ageing* 2013;42(suppl 1):i1-i57.
- ³⁸ Husebo BS, Ballard C, Sandvik R, et al. *Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial*. *BMJ* 2011;343:d4065.
- ³⁹ Corbett A, Husebo BS, Malcangio M, et al. *Assessment and treatment of pain in people with dementia*. *Nat Rev Neurol* 2012;8:264-74.
- ⁴⁰ Mercadante S, Ferrera P, Villari P, et al. *Opioid escalation in patients with cancer pain: the effect of age*. *J Pain Sympt Manage* 2006;32:413-9.
- ⁴¹ Podichetty VK, Mazanec DJ, Biscup RS. *Chronic non-malignant musculoskeletal pain in older adults: clinical issues and opioid intervention*. *Postgrad Med J* 2003;79:627-33.
- ⁴² Guerriero F, Sgarlata C, Marcassa C, et al. *Efficacy and tolerability of low-dose oral prolonged-release oxycodone/naloxone for chronic non-oncological pain in older patients*. *Clin Interv Aging* 2014;10:1-11.
- ⁴³ Guerriero F, Maurizi N, Francis M, et al. *Is oxycodone/naloxone effective and safe in managing chronic pain of a fragile elderly patient with multiple skin ulcers of the lower limbs? A case report*. *Clin Interv Aging* 2015;10:1283-7.
- ⁴⁴ Dublin S, Walker RL, Gray SL, et al. *Prescription opioids and risk of dementia or cognitive decline: a prospective cohort study*. *J Am Geriatr Soc* 2015;63:1519-26.
- ⁴⁵ Achterberg W, Pieper M, van Dalen-Kok AH, et al. *Pain management in patients with dementia*. *Clin Interv Aging* 2013; 8:1471-82.
- ⁴⁶ Manfredi PL, Breuer B, Wallenstein S, et al. *Opioid treatment for agitation in patients with advanced dementia*. *Int J Geriatr Psychiatry* 2003;18:700-5.
- ⁴⁷ Chibnall JT, Tait RC, Harman B, et al. *Effect of acetaminophen on behavior, well-being, and psychotropic medication use in nursing home residents with moderate-to-severe dementia*. *J Am Geriatr Soc* 2005;53:1921-9.
- ⁴⁸ Husebo BS, Ballard C, Sandvik R, et al. *Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial*. *BMJ* 2011;343:d4065.
- ⁴⁹ Husebo BS, Ballard C, Cohen-Mansfield J, et al. *The response of agitated behavior to pain management in persons with dementia*. *Am J Geriatr Psychiatry* 2014;22:708-17.
- ⁵⁰ Petrò E, Ruffina E, Cappuccio M, et al. *Low-dose oral prolonged-release oxycodone/naloxone for chronic pain in elderly patients with cognitive impairment: an efficacy-tolerability pilot study*. *Neuropsychiatric Disease and Treatment* 2016;12:559-69.
- ⁵¹ Volicer L, Frijters DH, van der Steen JT. *Relationship between symptoms of depression and agitation in nursing home residents with dementia*. *Int J Geriatr Psychiatry* 2012;27:749-54.
- ⁵² Sampson EL, White N, Lord K, et al. *Pain, agitation, and behavioural problems in people with dementia admitted to general hospital wards: a longitudinal cohort study*. *Pain* 2015;156:675-83.
- ⁵³ Morgan RO, Sail KR, Snow AL, et al. *Modeling causes of aggressive behavior in patients with dementia*. *Gerontologist* 2013;53:738-47.
- ⁵⁴ Husebo BS, Ballard C, Aarsland D. *Pain treatment of agitation in patients with dementia: a systematic review*. *Int J Geriatr Psychiatry* 2011;26:1012-8.
- ⁵⁵ Husebo BS, Ballard C, Fritze F, et al. *Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial*. *Int J Geriatr Psychiatry* 2014;29:828-36.
- ⁵⁶ Gallini A, Andrieu S, Donohue JM, et al. *Trends in use of antipsychotics in elderly patients with dementia: impact of national safety warnings*. *Eur Neuropsychopharmacol* 2014;24:95-104.
- ⁵⁷ Giron MS, Forsell Y, Bernsten C, et al. *Sleep problems in a very old population: drug use and clinical correlates*. *J Gerontol A Biol Sci Med Sci* 2002;57:M236-40.