



Official Journal of
the Italian Society of Gerontology
and Geriatrics

03
2019
vol. LXVII

JGGG

JOURNAL OF GERONTOLOGY AND GERIATRICS

Indexed in Embase, Excerpta Medica Database, Scopus Elsevier Database and Emerging Sources Citation Index (ESCI), a new edition of Web of Science

Regular Issue

Original Investigations

- A cross-sectional study to investigate dominant leg balance performance in healthy elderly individuals
- Effects of endurance, resistance and neuromuscular electrical stimulation trainings to the anthropometric and functional mobility domains in elderly
- The caregivers' iceberg: qualitative narratives of Italian caregivers' roles and challenges

Reviews

- Differential diagnosis of nontraumatic purpura in the elderly – Have you considered acquired hemophilia?
- Gait Speed test in physically frailty patients with ST-segment elevation myocardial infarction

Clinical Observations in Geriatrics

- A very unusual case of atlantoaxial dislocation
- How the systematic detection of delirium may help physicians avoid a misdiagnosis of acute myocardial infarction: two case reports

PACINI
EDITORE
MEDICINA

www.jgerontology-geriatrics.com



Official Journal of
the Italian Society of Gerontology
and Geriatrics

JGG
JOURNAL OF
GERONTOLOGY
AND GERIATRICS

Indexed in Embase, Excerpta Medica Database,
Scopus Elsevier Database and Emerging
Sources Citation Index (ESCI), a new edition of
Web of Science

03 **2019**
vol. LXVII

Editorial Board

Editor-In-Chief

Gianluigi Vendemiale – *Università di Foggia, Italy*

Former Editor

Mario Barbagallo – *Università di Palermo, Italy*

Deputy Editor

Gaetano Serviddio – *Università di Foggia, Italy*

Managing Editor

Francesco Bellanti – *Università di Foggia, Italy*

Honorary Editors

Pier Ugo Carbonin – *Università Cattolica del Sacro Cuore, Roma, Italy*

Gaetano Crepaldi – *Consiglio Nazionale delle Ricerche, Italy*

Giulio Masotti – *Azienda Ospedaliera Careggi, Firenze, Italy*

Franco Rengo – *Scientific Direction, Genova, Italy*

Gianfranco Salvioli – *Università di Modena e Reggio Emilia, Italy*

Umberto Senin – *Università di Perugia, Italy*

Senior Editors

Roberto Bernabei – *Università Cattolica del Sacro Cuore, Roma, Italy*

Sergio Della Sala – *University of Edinburgh, UK*

Paul Edison – *Imperial College, London, UK*

Nicola Ferrara – *Università di Napoli "Federico II", Italy*

Luigi Ferrucci – *National Institute of Aging, Bethesda, USA*

Paul T. Francis – *King's College, London, UK*

Laura Fratiglioni – *Stiftelsen Stockholm Läns Aldrecenter, Sweden*

Walter J. Koch – *Temple University, Philadelphia, USA*

Niccolò Marchionni – *Azienda Ospedaliera Careggi, Firenze, Italy*

Jean-Pierre Michel – *Geneva University, Switzerland*

Giuseppe Paolisso – *Università della Campania "Luigi Vanvitelli", Napoli, Italy*

Nicola Pavese – *Newcastle University, UK*

Munir Pirmohamed – *University of Liverpool, UK*

Giuseppe Poli – *Università di Torino, Italy*

Michele Tagliati – *Cedars-Sinai Medical Center, Los Angeles, USA*

Marco Trabucchi – *Italian Psychogeriatric Association, Brescia, Italy*

José Vina Ribes – *Universidad de Valencia, Spain*

Associate Editors

Biogerontology

Ettore Bergamini – *Università Campus Bio-Medico, Roma, Italy*

Tommaso Cassano – *Università di Foggia, Italy*

Graziamaria Corbi – *Università del Molise, Campobasso, Italy*

Mauro Di Bari – *Università di Firenze, Italy*

Claudio Franceschi – *Istituto delle Scienze Neurologiche, Bologna, Italy*

Anna Maria Giudetti – *Università del Salento, Lecce, Italy*

Fabrizia Lattanzio – *Istituto Nazionale Riposo e Cura Anziani, Ancona, Italy*

Dario Leosco – *Università di Napoli "Federico II", Italy*

Patrizio Odetti – *Università di Genova, Italy*

Maria Cristina Polidori – *Uniklinik Köln, Germany*

Clinical Geriatrics

Angela Marie Abbatecola – *Alzheimer's Disease Clinic Department, Frosinone, Italy*

Pasquale Abete – *Università di Napoli "Federico II", Italy*

Giorgio Annoni – *Università di Milano "Bicocca", Italy*

Raffaele Antonelli Incalzi – *Università Campus Bio-Medico, Roma, Italy*

Lodovico Balducci – *Moffitt Cancer Center, Tampa, USA*

Michelangelo Barbieri – *Università della Campania "Luigi Vanvitelli", Napoli, Italy*

Mario Belvedere – *Università di Palermo, Italy*

Bruno Bernardini – *Consiglio Nazionale delle Ricerche, Italy*

Marco Bertolotti – *Università di Modena e Reggio Emilia, Italy*

Angelo Bianchetti – *Istituto Clinico Sant'Anna, Brescia, Italy*

Massimo Calabrò – *Ospedale Ca' Foncello, Treviso, Italy*

Vincenzo Canonico – *Università di Napoli "Federico II", Italy*

Cristiano Capurso – *Università di Foggia, Italy*

Giovanna Elisiana Carpagnano – *Università di Foggia, Italy*

Michele Cassano – *Università di Foggia, Italy*

Giampaolo Ceda – *Università di Parma, Italy*

Alberto Cester – *Ospedale Civile di Dolo, Venezia, Italy*

Antonio Cherubini – *Istituto Nazionale Riposo e Cura Anziani, Ancona, Italy*

Francesco Corica – *Università di Messina, Italy*

Andrea Corsonello – *Istituto Nazionale Riposo e Cura Anziani, Ancona, Italy*

Domenico Cucinotta – *Università di Messina, Italy*

Walter De Alfieri – *Ospedale di Castel del Piano, Grosseto, Italy*

Ligia Juliana Dominguez Rodriguez – *Università di Palermo, Italy*

Lorenzo Maria Donini – *Università di Roma "La Sapienza", Italy*

Paolo Falaschi – *Azienda Ospedaliera Sant'Andrea, Roma, Italy*

Giovanni Gambassi – *Università Cattolica del Sacro Cuore, Roma, Italy*

Antonio Guaita – *Golgi Cenci Foundation, Milano, Italy*

Giancarlo Isaia – *Università di Torino, Italy*

Francesco Landi – *Università Cattolica del Sacro Cuore, Roma, Italy*

Maria Lia Lunardelli – *Consiglio Nazionale delle Ricerche, Italy*

Marcello Giuseppe Maggio – *Università di Parma, Italy*

Enzo Manzato – *Università di Padova, Italy*

Daniela Mari – *Università di Milano, Italy*

Francesco Mattace Raso – *Erasmus University Medical Center, Rotterdam, The Netherlands*

Domenico Maugeri – *Università di Catania, Italy*

Riccardo Memeo – *Università di Bari, Italy*

Chiara Mussi – *Università di Modena e Reggio Emilia, Italy*

Claire Nicholl – *Addenbrooke's Hospital, Cambridge, UK*

Gabriele Noro – *Ospedale Santa Chiara, Trento, Italy*

Emanuela Orsi – *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy*

PACINI
EDITORE
MEDICINA

Ernesto Palummeri – *Ospedali Galliera, Genova, Italy*
Giuseppe Rengo – *Università di Napoli "Federico II", Italy*
Giovanni Ricevuti – *Università di Pavia, Italy*
Maria Rosaria Rizzo – *Università della Campania "Luigi Vanvitelli", Napoli, Italy*
Giuseppe Romanelli – *Università di Brescia, Italy*
Antonino Davide Romano – *Università di Foggia, Italy*
Renzo Rozzini – *Fondazione Poliambulanza, Brescia, Italy*
Afro Salsi – *Università di Bologna, Italy*
Giuseppe Sergi – *Università di Padova, Italy*
Sebastiano Bruno Solerte – *Università di Pavia, Italy*
Vincenzo Solfrizzi – *Università di Bari, Italy*
Gabriele Toigo – *Azienda Sanitaria Universitaria Integrata, Trieste, Italy*
Mariateresa Ventura – *Università di Bari, Italy*

Stefano Volpato – *Università di Ferrara, Italy*
Giuseppe Zuccalà – *Università Cattolica del Sacro Cuore, Roma, Italy*
Giovanni Zuliani – *Università di Ferrara, Italy*

Geriatric Nursing

Nicoletta Nicoletti – *Dipartimento Salute Anziani, Torino, Italy*
Ermellina Zanetti – *Azienda Ospedaliera San Gerardo, Monza, Italy*

Psychosocial Gerontology

Luisa Bartorelli – *Fondazione Roma Sanità, Roma, Italy*
Orazio Zanetti – *IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy*

Statistical Analysis and Trials

Corrado Crocetta – *Università di Foggia, Italy*
Eliano Pio Navarese – *University of Alberta, Edmonton, Canada*

Scientific secretariat

Valentina Barberi
Journal of Gerontology and Geriatrics
Pacini Editore Srl
Via Gherardesca - 56121 Pisa, Italy
Tel. +39 050 3130376 - Fax +39 050 3130300
secretary@jgerontology-geriatrics.com

Società Italiana di Gerontologia e Geriatria

Via G.C. Vanini 5, 50129 Firenze, Italy
Tel. +39 055 474330 - Fax +39 055 461217
E-mail: sigg@sigg.it - www.sigg.it

© Copyright by

Società Italiana di Gerontologia e Geriatria

Managing Director

Raffaele Antonelli Incalzi

Publisher

Pacini Editore Srl
Via Gherardesca - 56121 Pisa, Italy
Tel. +39 050 313011 - Fax +39 050 3130300
info@pacinieditore.it

Published online by Pacini Editore Srl,
Pisa, September 2019
online: www.jgerontology-geriatrics.com

Authors Informations

www.jgerontology-geriatrics.com/category/authorsinformation/

Submission online

submission.jgerontology-geriatrics.com

Journal registered at "Registro pubblico degli Operatori della Comunicazione" (Pacini Editore srl registration n. 6269 - 29/8/2001).

The Publisher remains at the complete disposal of those with rights whom it was impossible to contact, and for any omissions.

Subscriber data are treated according to Italian law in DLgs, 30 June 2003, n. 196 as updated with the UE General Data Protection Regulation 2016 - by means of computers operated by specifically responsible personnel. These data are used by the Publisher to mail this publication. In accordance with Art. 7 of the above mentioned DLgs, 30 June 2003, n. 196, subscribers can, at any time, view, change or delete their personal data or withdraw their use by writing to Pacini Editore S.r.L. - Via A. Gherardesca 1, 56121 Ospedaletto (Pisa), Italy. For further information refer to the website: <http://www.jgerontology-geriatrics.com/informativa-privacy-privacy-policy/>

Photocopies, for personal use, are permitted within the limits of 15% of each publication by following payment to SIAE of the charge due, article 68, paragraphs 4 and 5 of the Law April 22, 1941, No 633. Reproductions for professional or commercial use or for any other other purpose other than personal use can be made following a written request and specific authorization in writing from AIDRO, Corso di Porta Romana, 108, 20122 Milan, Italy (segreteria@aidro.org - www.aidro.org).

CONTENTS

Journal of Gerontology and Geriatrics



Official Journal of
the Italian Society of Gerontology
and Geriatrics

03 2019
vol. LXVII

Regular Issue

Original Investigations

- A cross-sectional study to investigate dominant leg balance performance in healthy elderly individuals
B. Zeynalzadeh Ghoochani, S.A. Derakhshanrad, S.A. Hosseini..... 141
- Effects of endurance, resistance and neuro-muscular electrical stimulation trainings to the anthropometric and functional mobility domains in elderly
T. Pietrangelo, C. Doria, D. Bondi, E. Kinel, G. Renda, G. Neri, G. Fanò-Illic, V. Verratti 148
- The caregivers' iceberg:
qualitative narratives of Italian caregivers' roles and challenges
R. Papa, G. Lamura..... 156

Reviews

- Differential diagnosis of nontraumatic purpura in the elderly –
Have you considered acquired hemophilia?
M.A. Escobar, CB Dyer..... 168
- Gait Speed test in physically frailty patients
with ST-segment elevation myocardial infarction
P. Mone, F. Minicucci, A. Pansini, M. Rizzo, M. Carbonella, C. Mauro 181

Clinical Observations in Geriatrics

- A very unusual case of atlantoaxial dislocation
A. Tancredi, A. Giorgi..... 186
- How the systematic detection of delirium may help physicians
avoid a misdiagnosis of acute myocardial infarction: two case reports
M.C. Ferrara, F. Massariello, G. Annoni, G. Bellelli..... 190

A cross-sectional study to investigate dominant leg balance performance in healthy elderly individuals

B. Zeynalzadeh Ghoochani¹, S.A. Derakhshanrad^{1,2}, S.A. Hosseini³

¹ Department of Occupational Therapy, Shiraz University of Medical Sciences, Shiraz, Iran; ² Rehabilitation Sciences Research Center, Shiraz university of Medical Sciences, Shiraz, Iran; ³ Department of Occupational Therapy, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

Background. Examining underlying balance mechanism of the elderly can help identify their Achilles' heel of balance system. The research aim was to investigate the dominant leg balance characteristics of a sample of older adults while being challenged by sensory inputs and performing dual task.

Methods. This study was performed on 20 healthy elderly subjects during four conditions of one-leg standing with different levels of difficulty including: "open eyes", "dual task with open eyes", "closed eyes" and "dual task with closed eyes". Forceplate was used to evaluate postural control during standing on dominant leg measuring "Area" and "Velocity" as the dependent variables. Auditory Stroop task was used to simulate performing a secondary activity (dual task). Using Bonferoni post hoc test, Repeated Measurement Analysis of Variance was executed to find the differences between the conditions.

Results. Comparisons showed significant differences of "Area" [$F(3, 13) = 10.143, p = 0.001$] and "Velocity" [$F(9, 13) = 9.692, p = 0.001$]. Bonferoni test revealed that all four conditions had significant differences except two pairs including (a) "open eyes" with "dual task with open eyes", and (b) "closed eyes" with "dual task with closed eyes" ($p > 0.05$).

Conclusions. Results indicated that participants adopted a strategy to increase "Area" and "Velocity" during the challenge of standing on dominant leg with closed eyes. This is their tactic to maintain balance during the elimination of visual input. Exploring balance strategy would have important implications for developing long term fall prevention programs.

Key words: Balance, Dual task, Forceplate, Geriatrics, Visual input

BACKGROUND

Evaluating balance performance has become a favorite topic that can help identify Achilles' heel of the elderly balance mechanism so as to address their health care delivery systems. Balance performance is an essential issue in human motor control influencing most fields of daily living including work, leisure, and self-care. There are different laboratory systems that assist examiners to evaluate such performance. Forceplate seems to be one of the most suitable instruments that assess balance^{1,2}. As balance is known to be the inevitable

and crucial part of doing ordinary tasks of everyday life³, it is essential to have a trustworthy assessment instrument. Objective assessment of postural stability can be done by Forceplate⁴. Forceplate allows balance analysis and enables postural control stability monitoring through measurements of sway, and it is proved to have academic and clinical advantages.

In order to investigate postural stability, Forceplate technology provides researchers with informative center of pressure (COP) variables such as "Area" and "Velocity" used in this study. Until now, one single or more than one Forceplate⁵ has been used in different

■ Received: November 15, 2018 - Accepted: March 18, 2019

■ Correspondence: Seyed Alireza Derakhshanrad, Department of Occupational Therapy, Shiraz School of Rehabilitation Sciences, Abiverdi 1, Chamran Blvd, Shiraz, Fars, 7194733669, Iran. Tel. +98 71 36271551. Email: derakhshan@sums.ac.ir

studies for healthy⁶, athletes⁷, patients populations^{8,9} or balance-impaired elderly adults¹⁰ during standing¹¹, walking⁶ or jumping performance^{2,12}. To quantify the balance performance, people were studied during double leg¹³, feet together¹⁴, one-leg standing¹³⁻¹⁷, tandem^{4,8}, or standing on Forceplate with unstable surface¹⁸. Furthermore, studies with sensory manipulations¹⁹ such as open and closed eyes^{13,14} were also conducted.

Balance is supported by inputs from somatosensory, visual and vestibular systems along with neuromuscular, skeletal and cognitive sources. Dominant and non-dominant leg performance are prerequisite factors for studying balance performance. Some researchers studied balance during one-leg stance with Forceplate^{14,16} or without it^{20,21}, some have recruited dominant leg¹³ or preferred foot¹⁵. However, according to existing evidence little attention has been paid to investigate each lower limb contributions to balance capacity²². So, the present research is mainly focused on the dominant limb contributions so as to explore more about its substrate balance strategy during a number of challenging conditions.

Dual task performance is also thought to help researchers to explore more about the interaction of cognition and balance. There are variations in response to dual task which are linked to postural²³⁻²⁷ or the dual task nature^{28,29} and their level of difficulty. For instance, Vuillermé (2004)¹⁸ reported dual task cost (i.e. the interference of one task in doing another one) even in young gymnastic experts during one leg standing. However, having cost is not always the case when performing dual tasks³⁰⁻³². Elderly adults' balance was also a major target in many balance studies³³⁻³⁶. While some believe in age-related decline of elderly balance performance during dual task³⁷, others do not think so^{32,38}.

Visual input is another important and essential factor in the area of balance research. Therefore, visual input in elderly adults is considered as one important issue that is useful to be investigated more. Consequently, this research was conducted to examine the effect of visual input and dual task on healthy elderly balance performance and generate fresh insight into standing on dominant lower extremity. Characterization of dominant leg is important for our understanding of maintaining upright one leg standing. It is suggested that using this procedure would be useful as a challenge in selection of high risk individuals in the process of designing prevention protocols¹². This study aimed to contribute to this growing area of research by exploring the balance strategy of the elderly individuals. Therefore, this study made a major contribution to research on dominant leg performance by demonstrating change trend of center of pressure (COP), and it contributed to a deeper

understanding of older adults' responses during simulated difficult circumstances.

METHODS

PARTICIPANTS

Twenty healthy non-institutionalized elderly subjects (male = 14, female = 6, age = 61.15 ± 1.95 years, height = 166.9 ± 7.07 centimeters, weight = 73.9 ± 8.89 kilograms, with body mass index (BMI) average factor of 26.6 (SD = 2.8) participated in this cross-sectional study. The participants' Mini-Mental State Examination (MMSE) mean score was 28.25 (SD = 1.97). All the participants' dominant leg were the right ones.

The inclusion criteria includes being independent with an active life style. Not using sedative drugs, having no visual, auditory, verbal and sensory problems such as those secondary to diabetes were checked based on their medical history prior to the study. Participants who had any current lower extremity, trunk fractures, dislocations and surgery during the last six months were excluded. They must be free of any lower extremity injury that would limit the ability to maintain balance on one foot. Any problems during the data gathering process and recording such as fatigue, pain, dissatisfaction, fear of fall and instrumental deficit, which could cause the trial performance to be failed, were monitored.

PROCEDURES AND INSTRUMENTATION

This study consisted balance assessments of 4 trials performed on a 90" x 90" series Forceplate (Kistler -Switzerland), with sampling rate of 400 Hz and sensitivity of 10. The tasks included maintaining balance under varying stance conditions: single standing on dominant leg with open eyes on Forceplate (SO), single dominant leg standing with open eyes performing dual task (SOD), single dominant leg standing with closed eyes on Forceplate (SC), and single dominant leg with open eyes performing dual task (SCD).

Each trial was 20-seconds long and required the participant to maintain balance with standing on their dominant legs motionlessly. Each condition was separated by a five-minute rest interval preventing fatigue³. During one leg standing, the raised leg should not have any contact with Forceplate. The participants also were not allowed to jump in place and if they behaved out of standing protocol, the trial was considered failed. One major concern and percussion was to provide them with suitable control protection against unpredictable fall during one leg standing.

After describing the test procedure to the participants, they filled in the consent form, as Williams (2017) considered familiarization an inevitable and important part

of test procedures⁴. The trial conditions were performed with random order following completion of familiarization. Forceplate was unloaded and calibrated before each trial to guarantee accurate data gathering. In this study, dual task was the auditory Stroop task. During this task ‘high’ and ‘low’ words were played back with low and high tone pitch. The participants were required to answer by mentioning the tone regardless of words meaning itself. Wireless earphone and microphone (LEM-NP10, Taiwan) were used to execute auditory Stroop task. R2015a Matlab program and Microsoft Office Excel 2013 were also used.

Research setting was at University of Social Welfare and Rehabilitation Sciences (USWRS) laboratory setup. In the context of this sort of setup, closed eyes condition is believed to simulate real life situations in which people encounters difficulty accessing their visual input. Moreover, the Stroop task is somehow thought to detect reactions during performing dual task. This research project was approved by USWRS’s ethical committee.

MEASUREMENTS

Objective outputs of postural sway in this study were the dependent variables of COP; “Area” (CM²) and “Velocity” (CM/S), with higher values indicating worse balance. “Area”, the biomechanical stability parameter of overall COP displacement in all directions, was considered dependent variable by the means of which balance assessment was done in this study in four mentioned conditions. “Velocity” is also another parameter of COP in which displacement is considered along with time and is an index of postural control.

DATA ANALYSIS

Kolmogorov-Smirnov test was used to examine the normality and it showed the normal distribution of the data. Repeated measure analysis of variance were used for statistical analysis by the means of IBM SPSS statistics 20. The reference P-value was considered 0.05 to prove the significant differences. The Bonfferoni post-hoc analyses was used to define exact different conditions.

RESULTS

During the test procedure there were some participants who were unable to accomplish their balance performance trials. One failed to maintain balance during dual task condition with open eyes, two fell when their eyes were closed during performing single task, and one attempt was in vain at dual task condition with closed eyes. Kolmogorov-Smirnov test reported the “Area” and “Velocity” variables to be normally distributed in all conditions ($p > 0.05$). Mean Area (Fig. 1) and its standard

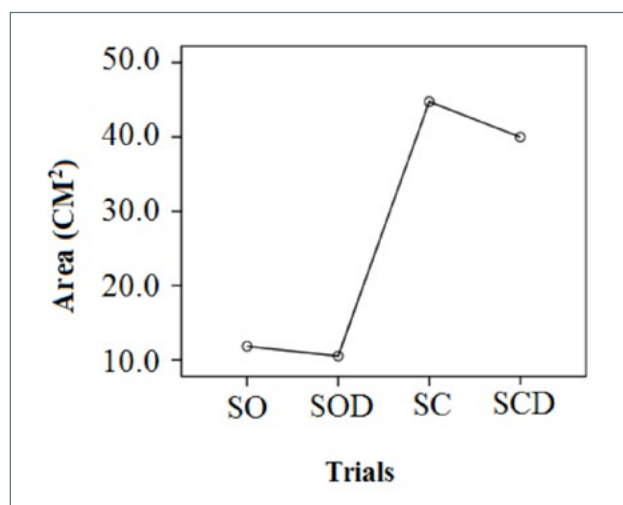


Figure 1. Mean “Area” during each specific condition.

deviation are presented as below: SO [11.84 (11.01)], SOD [10.52 (10.21)], SC [44.75 (28.702)] and SCD [39.98 (39.53)]. Repeated measurement analysis of variance results showed that there were significant differences between conditions mean Area [$F_{(3,13)} = 10.143$ $p = 0.001$]. Further analysis of paired comparisons have also detected the exact two conditions between which statistically significant differences existed (Tab. I).

Postural variable amounts are shown in Figure 1. This line graph reveals “Area” change pattern during four conditions of adding and removing visual input and dual task. Looking at the graph, it can be said that a hidden pattern of reactions and changes is evident in that Z-like fashion. There is a marginal decline of “Area” displacement from the SO condition to SOD condition. The least mean is related to the SOD trial. A sharp rise is displayed from SOD condition to the SC condition. This upward trend is statistically significant manifesting that COP displacement amount and its velocity would surge when visual input is omitted. The amount of “Area” in closed eyes conditions were much more than

Table I. Area paired comparisons to indicate in detail differences between each two conditions.

Trials	Mean difference	95% CI	P-value
SO and SOD	1.319	-7.67, 10.30	0.1
SO and SC*	32.91	9.50, 56.32	0.004
SO and SCD *	32.91	0.81, 55.46	0.04
SOD and SC *	34.23	11.40, 57.06	0.02
SOD and SCD*	29.46	4.58, 54.33	0.01
SC and SCD	4.77	- 29.67, 39.21	0.1

*The reference P-value was 0.05.

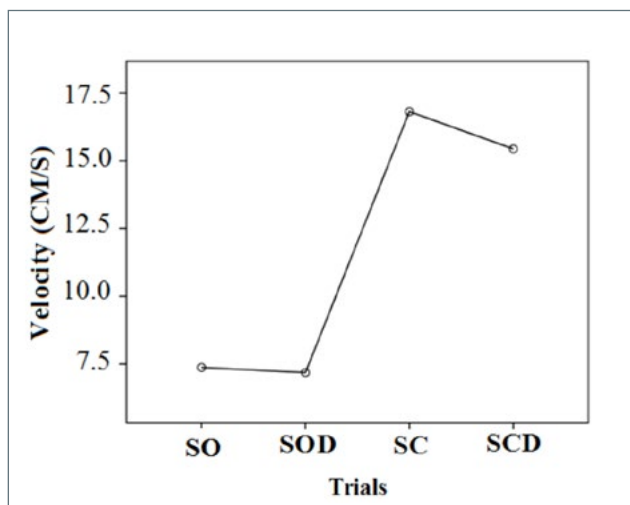


Figure 2. Mean “Velocity” during each specific condition.

open eyes conditions and its amount hits the highest point in single task with closed eyes condition. There is again a slight decrease from SC trial to SCD trial. However, mean “Area” in closed eyes conditions were significantly higher than means in open eyes conditions, regardless of dual task performance.

Mean Area (Fig. 2) and its standard deviation are presented as below: SO [7.3 (4.5)], SOD [7.1 (2.7)], SC [16.8 (8.1)] and SCD [15.4 (8.8)].

Repeated measurement analysis of variance results showed that there were significant differences between conditions mean “Velocity” [$F_{(9, 13)} = 9.692, p = 0.001$]. Further analysis of paired comparisons have also detected the exact two conditions between which statistically significant differences existed (Tab. II).

DISCUSSION

According to our findings, the four mentioned test conditions used in this study made the participants control

Table II. Velocity paired comparisons to indicate in detail differences between each two conditions.

Trials	Mean difference	95% CI	P-value
SO and SOD	0.002	-0.02, 0.03	1.0
SO and SC*	-0.094	-0.16, -0.02	0.003
SO and SCD *	-0.081	-0.14, -0.02	0.007
SOD and SC *	-0.09	-0.15, -0.03	0.002
SOD and SCD*	0.08	0.21, 0.14	0.006
SC and SCD	-0.01	- 0.09, 0.06	1.0

*The reference P-value was 0.05.

their center of gravity within their base of support. Some participants were unable to maintain their balance during some conditions with different levels of difficulty owing to the challenging nature of one leg standing. Those who accomplished their trials showed increased sway during closed eye condition. Undoubtedly, it can be inferred that visual input deprivation effect is more dominant than dual task effect on the “Area” and “Velocity” parameter in this study. With closed eyes condition standing on dominant limb, there would be a threat for centre of gravity to go beyond the base of support and it would be harder to restore COP, thus leading to an increase in “Area” and “Velocity” subsequently. It also conveys the importance of this input corporation and contribution to postural control and the countless dependency on that.

One of the concerns was that the higher “Area” and “Velocity” variables were, the more unsteady the participants were during the test (indicating greater instability during closed eyes conditions). These findings are consistent with the literature proving the inevitable effect of visual input on postural stability^{17, 39, 40}. Previous studies have shown increased “Area”^{39, 40} and “Velocity”⁴⁰ of COP displacements in blindfolded tasks which is in complied with the results of this study. According to Zeynalzadeh et al.’s study, whenever dual task and decreased visual input occur at the same time, the adopted strategy of increasing “Velocity” would emerge identifying the Achilles’ heel of the elderly during double leg standing¹¹.

In the case of standing on non-dominant leg in the elderly, weight bearing on only one leg is a difficult mission that requires a well-organized postural stability to endure the crucial declined somatosensory input of the other leg. During standing on non-dominant lower extremity, individuals are more prone to increase sway in closed eyes conditions. Therefore, Achilles’ heel of balance system during standing on non-dominant leg was the absence of visual input⁴⁰. This also accords with our earlier observations in this study, which showed that dominant leg standing balance was challenged when participants closed their eyes. During the course of this study the hardest situation of standing on dominant leg was eyes-closed conditions; as a result, these identified trials are recommended to be firmly tested to prevent an unsafe Achilles’ heel of equilibrium. It is accordingly recommended and would be better for these situations to be encompassed in screening, assessment, evaluation and future early fall preventive programs.

It is worth mentioning that the elderly participants in Zeynalzadeh et al.’s study were at the early stage of their senescence, meanwhile Era has reported that postural stability and control may encounter deficits especially when the elderly subjects are 75 to 80 years

old and their weak postural control may lead to subsequent balance issues³³. There are several possible explanations for this issue. A possible explanation for these may be implied in Maylor assumption. Maylor believes that balance performance and stability would be influenced and decreased in the process of aging as well³⁸. Another possible explanation in the same fashion, is Bohannon's reports who has reviewed studies which had reported that aging would lead to reduction of one leg standing duration²⁰. In addition, Lajoie reports that in comparison to fallers, healthy individuals have a slower sway³⁴. Teasdale mentioned that in the case of reducing sensory inputs, maintaining balance would be harder in elderly subjects²⁷.

Ruffieux declared that postural balance needs cognitive processing to some extent³⁷. As Ruffieux revealed and highlighted, this issue and these effects are yet to be investigated. So we aimed to find evidence in older adults during dual task performance. In the present study, under dual task conditions, participants showed tighter postural control to survive the challenge of one leg standing while confronting secondary imposed attention demanding task which was characterized by reduced sway (although not statistically significant).

The outcomes of this study are consistent with the results of past studies in which sway can be reduced by performing cognitive tasks, concluding that postural sway may be associated with cognitive operation³⁰. Soangra also believed that there is an interaction between postural task and the cognitive one in which exploring the interaction can help to prevent falling in healthy individuals with fall history. The result of Soangra's study specifies that dual task does not necessarily pose the risk of fall in healthy individuals and their new adaptive strategy can be called "Cautious Mode", which is not essentially destabilizing⁶. Our findings is consistent with that of Bonnet (2016) who described that during standing even in motionless conditions there is a constant sway, which would be different under dual task conditions (like a cognitive performance). Bonnet explained that in the particular setting of active visual tasks, young adults showed less sway⁴¹. As Maylor described, balance may be influenced by cognitive tasks in different ages and task types³⁸. According to the Andersson's study, changes of postural response were probable to be an adaptation strategy for lessening attentional demand and declining the risk of fall within restricted accessible attentional resources³⁰. There are similarities between the attitudes expressed by COP variables in this study and those described by Swan, who mentioned dual tasks (spatial or non-spatial memory tasks) can progress older adults balance during the hardest postural circumstances²⁸. Moreover, Pellicchia declared that attentional burden of cognitive task

can influence balance²⁹. Meanwhile, Brauer reported that postural retrieval was attention demanding, but the capability of healthy elderly subjects to pull through was not impacted by synchronized task burden¹⁰. On the contrary, Dai has found that imposed stimulus like cognitive task may decline postural performance¹².

One of the issues that emerges from these findings is the role of dominant leg. These findings may help us to understand the importance of visual input contribution to balance during one leg standing. While preliminary, this finding, suggests that routine assessment of healthy elderly balance on one leg should not be ignored. This study suggests that a protocol rich in sensory manipulation may help to detect weaknesses and prevent fall. These findings raise intriguing questions regarding the nature and extent of performing dual task. This combination of findings provides some support for the conceptual premise that visual input has one of the most vital capacities contributing to balance. Eliminating visual input would help to evaluate vestibular and somatosensory inputs contributions, since it brings in more vestibular and somatosensory inputs. The proper screening and early evaluation is a promising area in enabling, empowering and preventive care of people with apparently healthy aging. It also create a field to successfully test and identify older adults who are at risk of falling. The findings make an important contribution to the field of enhancing early intervention and global screening of general elderly balance. Active and community-living older adults were studied in this study, so those living in nursing homes or having inactive life style were missed. Accordingly, the latter population is also needed to be considered along with older healthy individuals in order for generalization of findings. According to this limitation, these findings cannot necessarily be extrapolated to different patients. Therefore, future research can focus more on balance-impaired elderly population.

CONCLUSIONS

Simulating real life conditions of dark environment, eliminating visual input, performing a secondary task and manipulating contribution of sensory system can possibly be provided if the protocol format of this study with four previously described conditions is applied. Therefore, the mentioned test conditions in this study can be suggested as the preferred test protocol and balance task assignment for healthy elderly population, helping identify the individuals with potential risk of falling. It is imperative to measure objective postural assessments and it should be incorporated into comprehensive evaluation to assess different domains of

balance function. The most paramount message of the present study is that visual input has a critical role in disturbing balance of even healthy elderly population during standing on dominant leg. Therefore, it is critical to modulate automatic and postural responses in order to gain some degree of adaptation. Vision as a corner stone must be monitored, so that its absence does not turn into Achilles' heel of balance performance and its usage in balance assessment is seriously suggested, using "Area" and "Velocity" parameters of COP by Forceplate technology. This may be of value in development of public balance empowering and health enhancement agendas.

CONFLICTS OF INTEREST

The Authors declare to have no conflict of interest this.

ACKNOWLEDGMENTS

Special thanks go to those who participated in this study.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. BZG has made contributions to acquisition of data. All authors have made contributions to analysis and interpretation of data. Finally, they have all contributed to the drafting and revision of the article, and the approval of the final version.

References

- 1 Peterson Silveira R, Stergiou P, Carpes FP, et al. *Validity of a portable force platform for assessing biomechanical parameters in three different tasks*. Sports Biomech 2017;16:177-86. Doi: 10.1080/14763141.2016.1213875
- 2 Baumgart C, Honisch F, Freiwald J, et al. *Differences and trial-to-trial reliability of vertical jump heights assessed by ultrasonic system, force-plate, and high-speed video analyses*. Asian J Sports Med 2017 (In Press). Doi: 10.5812/asjms.12921
- 3 Cogswell FD, Huang F, Dietze B. *The effects of upper-body and lower-body fatigue on standing balance*. WURJ: Health and Natural Sciences 2017;7:12. Doi: 10.5206/wurjhns.2016-17.11
- 4 Williams RM, Corvo MA, Lam KC, et al. *Test-retest reliability and practice effects of the stability evaluation test*. J Sport Rehabil 2017:1-13.
- 5 Kamono A, Kato M, Ogihara N. *Accuracy evaluation of a method to partition ground reaction force and center of pressure in cane-assisted gait using an instrumented cane with a triaxial force sensor*. Gait Posture 2018;60:141-7. Doi: 10.1016/j.gaitpost.2017.11.022
- 6 Soangra R, Lockhart TE. *Dual-task does not increase slip and fall risk in healthy young and older adults during walking*. Appl Bionics Biomech 2017;2017. Doi: 10.1155/2017/1014784
- 7 Howell DR, Hanson E, Sugimoto D, et al. *Assessment of the postural stability of female and male athletes*. Clin J Sport Med 2017;27:444-9. Doi: 10.1097/JSM.0000000000000374
- 8 Doherty C, Zhao L, Ryan J, et al. *Quantification of postural control deficits in patients with recent concussion: an inertial-sensor based approach*. Clin Biomech 2017;42:79-84. Doi: 10.1016/j.clinbiomech.2017.01.007
- 9 Shahmohammadi R, Sharifi G-R, Melvin JM, et al. *A comparison between aquatic and land-based physical exercise on postural sway and quality of life in people with parkinson's disease: a randomized controlled pilot study*. Sport Sci Health 2017:1-8. Doi: 10.1007/s11332-017-0363-8
- 10 Brauer SG, Woollacott M, Shumway-Cook A. *The interacting effects of cognitive demand and recovery of postural stability in balance-impaired elderly persons*. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2001;56:489-96. Doi: 10.1093/gerona/56.8.M489
- 11 Zeynalzadeh Ghoochani B, Hosseini SA, Talebian S, et al. *Healthy older adults balance pattern under dual task conditions: exploring the strategy and trend*. Health Promot Perspect 2016;6:207. Doi: 10.15171/hpp.2016.34
- 12 Dai B, Cook RF, Meyer EA, et al. *The effect of a secondary cognitive task on landing mechanics and jump performance*. Sports Biomechanics 2017:1-14. Doi: 10.1080/14763141.2016.1265579
- 13 Donath L, Roth R, Zahner Let al. *Testing single and double limb standing balance performance: comparison of cop path length evaluation between two devices*. Gait Posture 2012;36:439-43. Doi: 10.1016/j.gaitpost.2012.04.001
- 14 Bryant E, Trew M, Bruce A, et al. *Gender differences in balance performance at the time of retirement*. Clin Biomech 2005;20:330-5. Doi: 10.1016/j.clinbiomech.2004.11.006
- 15 Parreira RB, Boer MC, Rabello L, et al. *Age-related differences in center of pressure measures during one-leg stance are time dependent*. J Appl biomech 2013;29:312-6. Doi: 10.1123/jab.29.3.312
- 16 Hu M-H, Woollacott MH. *Multisensory training of standing balance in older adults: I. Postural stability and one-leg stance balance*. Journal of Gerontology 1994;49:52-61. Doi: 10.1093/geronj/49.2.M52
- 17 Sung PS, Zippel JT, Andraka JM, et al. *The kinetic and kinematic stability measures in healthy adult subjects with and without flat foot*. Foot 2017;30:21-6. Doi: 10.1016/j.foot.2017.01.010
- 18 Vuillerme N, Nougier V. *Attentional demand for regulating postural sway: the effect of expertise in gymnastics*. Brain Res Bull 2004;63:161-5. Doi:10.1016/j.brainres-bull.2004.02.006
- 19 Armistead-Jehle P, Lange BJ, Green P. *Comparison of neuropsychological and balance performance validity testing*. Appl Neuropsychol Adult 2017;24:190-7. Doi: 10.1080/23279095.2015.1132219
- 20 Bohannon RW. *One-legged balance test times*. Perceptual Motor Skills 1994;78(3 Pt 1):801. Doi: 10.1177/003151259407800322

- ²¹ Briggs RC, Gossman MR, Birch R, et al. *Balance performance among noninstitutionalized elderly women*. Phys Ther 1989;69:748-56. Doi: 10.1093/ptj/69.9.748
- ²² Tracey S-Y, Anderson DI, Hamel KA, et al. *Kicking performance in relation to balance ability over the support leg*. Hum Mov Sci 2012;31:1615-23. Doi: 10.1016/j.humov.2012.07.001
- ²³ Siu K-C, Lugade V, Chou L-S, et al. *Dual-task interference during obstacle clearance in healthy and balance-impaired older adults*. Aging Clin Exp Res 2008;20:349-54. Doi: 10.1007/BF03324867
- ²⁴ Marsh AP, Geel SE. *The effect of age on the attentional demands of postural control*. Gait Posture 2000;12:105-13. Doi: 10.1016/S0966-6362(00)00074-6
- ²⁵ Redfern MS, Jennings JR, Mendelson D, et al. *Perceptual inhibition is associated with sensory integration in standing postural control among older adults*. J Gerontol B Psychol Sci Soc Sci 2009;60. Doi: 10.1093/geronb/gbp060
- ²⁶ Lajoie YTN, Bard C, Fleury M. *Attentional demands for static and dynamic equilibrium*. Exp Brain Res 1993;97:139-44. Doi: 10.1007/BF00228824
- ²⁷ Teasdale N, Bard C, LaRue J, et al. *On the cognitive penetrability of posture control*. Exp Aging Res 1993;19:1-13. Doi: 10.1080/03610739308253919
- ²⁸ Swan L, Otani H, Loubert PV. *Reducing postural sway by manipulating the difficulty levels of a cognitive task and a balance task*. Gait Posture 2007;26:470-4. Doi: 10.1016/j.gaitpost.2006.11.201
- ²⁹ Pellecchia GL. *Postural sway increases with attentional demands of concurrent cognitive task*. Gaitpost 2003;18:29-34. Doi: 10.1016/S0966-6362(02)00138-8
- ³⁰ Andersson G, Hagman J, Talianzadeh R, et al. *Effect of cognitive load on postural control*. Brain Res Bul 2002;58:135-9. Doi: 10.1016/S0361-9230(02)00770-0
- ³¹ Dault MC YL, Frank JS. *Dose articulation contribute to modifications of postural control dual task paradigms?* Brain Res Cogn Brain Res 2003;16:434-40. Doi: 10.1016/S0926-6410(03)00058-2
- ³² Swan L, Otani H, Loubert PV, et al. *Improving balance by performing a secondary cognitive task*. Br J Psychol 2004;95:31-40. Doi: 10.1348/000712604322779442
- ³³ Era P, Heikkinen E, Gause-Nilsson I, et al. *Postural balance in elderly people: changes over a five-year follow-up and its predictive value for survival*. Aging Clin Exp Res 2002;14(Suppl 3):37-46. PMID:12475132
- ³⁴ Lajoie Y, Gallagher S. *Predicting falls within the elderly community: comparison of postural sway, reaction time, the berg balance scale and the activities-specific balance confidence (ABC) scale for comparing fallers and non-fallers*. Arch Gerontol Geriatr 2004;38:11-26. Doi: 10.1016/S0167-4943(03)00082-7
- ³⁵ Lundin-Olsson L, Nyberg L, Gustafson Y. *"Stops walking when talking" as a predictor of falls in elderly people*. Lancet 1997;349:617. Doi: 10.1016/S0140-6736(05)61565-6
- ³⁶ Lai C-H, Peng C-W, Chen Y-L, et al. *Effects of interactive video-game based system exercise on the balance of the elderly*. Gait Posture 2013;37:511-5. Doi: 10.1016/j.gaitpost.2012.09.003
- ³⁷ Ruffieux J, Keller M, Lauber B, et al. *Changes in standing and walking performance under dual-task conditions across the lifespan*. Sports Med 2015;45:1739-58. Doi: 10.1007/s40279-015-0369-9
- ³⁸ Maylor EA, Allison S, Wing AM. *Effects of spatial and non-spatial cognitive activity on postural stability*. Br J Psychol 2001;92:319-38. Doi: 10.1348/000712601162211
- ³⁹ Zeinalzadeh A, Talebian S, Naghdi S, et al. *Effects of vision and cognitive load on static postural control in subjects with and without patellofemoral pain syndrome*. Physiother Theory Pract 2017;1-10. Doi: 10.1080/09593985.2017.1391360
- ⁴⁰ Zeynalzadeh Ghoochani B, Derakhshanrad SA, Hosseini SA, et al. *Investigating the impact of dual task condition and visual manipulation on healthy young old during non-dominant leg stance*. Iranian Rehab J 2017;15:125-34. Doi: 10.18869/nrip.irj.15.2.125
- ⁴¹ Bonnet CT, Baudry S. *Active vision task and postural control in healthy, young adults: synergy and probably not duality*. Gait Posture 2016;48:57-63. Doi: 10.1016/j.gaitpost.2016.04.016

How to cite this article: Zeynalzadeh Ghoochani B, Derakhshanrad SA, Hosseini SA. *A cross-sectional study to investigate dominant leg balance performance in healthy elderly individuals*. Journal of Gerontology and Geriatrics 2019;67:141-7.

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

Effects of endurance, resistance and neuro-muscular electrical stimulation trainings to the anthropometric and functional mobility domains in elderly

T. Pietrangelo^{1,5}, C. Doria⁵, D. Bondi^{1,5}, E. Kinel², G. Renda¹, G. Neri¹, G. Fanò-Illic^{3,5}, V. Verratti⁴

¹ Department of Neuroscience, Imaging e Clinical Sciences, University "G. d'Annunzio" of Chieti-Pescara, Italy; ² Department of Rheumatology and Rehabilitation, Poznan University of Medical Sciences, Poznan, Poland; ³ Libera Università di Alcatraz, Gubbio, Italy; ⁴ Department of Psychological, Health and Territorial Sciences, Università "G. d'Annunzio" Chieti-Pescara, Italy; ⁵ Laboratory of Functional Evaluation, University "G. d'Annunzio" of Chieti-Pescara, Italy

Background and aims. There's the need to increase physical activity engagement to promote healthy ageing. Different training protocols elicit different morpho-functional effects: the comprehension of the related assessment tests is a key to improve the specific proposals and to monitor adequately the adaptations. We aimed to identify the functional adaptation processes basing on different training protocols.

Methods. 40 healthy elderly (28 males and 12 females, 70.7 ± 4.39 y) were randomly divided into 4 groups: endurance, resistance, Neuro-Muscular Electrical Stimulation and control, trained for 12 weeks and ex-post evaluated on anthropometric and functional domains.

Results. We found: significant effect for gender, time and time × protocols for Five Times Sit-to-Stand Test and Timed Up-and-Go test. Post-hoc analyses revealed effect for resistance and Neuro-Muscular Electrical Stimulation on Five Times Sit-to-Stand Test, and for endurance and Neuro-Muscular Electrical Stimulation on Timed Up-and-Go test. Correlations and factorial analysis linked Five Times Sit-to-Stand Test and Timed Up-and-Go test on the functional domain.

Conclusions. Medium-term physical interventions significantly modified functional characteristics of elderly. We found no ex-post effect on anthropometric parameters. The two functional tests are based on different underlying domains, our data therefore suggest to use both of them to specifically evaluate the training-induced functional adaptations in elderly. Our results promote the usefulness of evidence-based training.

Key words: Healthy ageing, Training, NMES, TUG, FTSST, Anthropometry

INTRODUCTION

Human ageing entails specific physiological modifications. Considering the current tendency towards an increase in the percentage of elderly population, the worthy focus is to understand deeply the course of healthy ageing: elderly need to avoid, inhibit or delay ageing-related chronic diseases, the loss of pro-activity and the loss of physical independence.

The engagement in physical activity is a cornerstone towards these aims, but the levels of participation are still low: one fourth of European population doesn't meet the minimum recommendations ¹, and the prevalence of physically inactive people drastically increases over 65 years-old age ².

The healthy effect of physical activity, facing with modern chronic disease is well known: the meta-analysis of Aune and colleagues shows that different subtypes of physical

■ Received: December 5, 2018 - Accepted: May 13, 2019

■ Correspondence: Tiziana Pietrangelo, Laboratory of Functional Evaluation, Department of Neuroscience, Imaging e Clinical Sciences, Università "G. d'Annunzio" Chieti-Pescara, via dei Vestini 31, 66100 Chieti, Italy. Tel. +39 0871 3554039. E-mail: tiziana.pietrangelo@unich.it

activity are strongly associated with a reduction in type 2 diabetes risk³. A recent work of Lachman and colleagues highlighted the protective effect of physical activity in older adults, even with low levels of engagement². In the healthy ageing paradigm, one of the key in later life is maintaining independence in the Activities of Daily Living (ADL), and different training protocols are effective in the attenuation of the disablement process⁴. Both endurance, resistance and Neuro-Muscular Electrical Stimulation (NMES) training protocols, if adequately proposed, showed their efficacy as Adapted Physical Activity (APA) for healthy elderly; however, different training protocols carry out the effects through specific physiological patterns, as demonstrated on neuro-motor level⁵, on circulating factors⁶, on transcriptional profile⁷, on regenerative system⁸. Monitoring the effects of the proposed protocols is a need: the implementation of functional evaluation is the key to understand and direct specific training plans, both for research purpose and health promotion. On this sight, Timed Up-and-Go test (TUG) and Five Times Sit-to-Stand test (FTSST, or 5STS, or FRSTST) have been widely using to evaluate functional mobility in older adults. In particular, TUG test is strongly related to the mobility status of elderly⁹, and it is useful as a tool for prevention¹⁰. FTSST permits to identify poor exercise tolerance and impaired functional performances¹¹, and it is useful as an outcome measure in rehabilitation¹². Chang and colleagues highlighted the usefulness of a physical performance battery for the early identification of frailty, among with the consideration of anthropometric parameters and taking into account the characteristics of the participants¹³. Lamb and Keene affirmed that the tests of physical capacity should be conducted under standardized environmental conditions, considering carefully the underlying construct and purposes¹⁴. We aimed to understand the functional adaptations related to different training protocols, in order to define the specificity of functional parameters of motor behaviour in elderly, as measured by widely used TUG test and FTSST. We also aimed to understand how training-induced functional adaptations were related to anthropometric parameters. We finally investigated the effect on gender on these adaptations.

MATERIAL AND METHODS

PARTICIPANTS

Putting $\alpha = 0.05$ and $1 - \beta = 0.8$, with an effect size of 0.3, the minimum number of participants was 36: we recruited 40 healthy subjects, in the age range of 62 to 82 years (Tab. I), reporting current physical inactivity during the initial interview. Exclusion criteria were: irregular ECG, osteo-articular pathologies, mild to medium cardio-circulatory pathologies, cancer, diabetes, non-controlled hypertension (diastolic pressure > 95 mmHg and/or systolic pressure > 150 mmHg), neurological or psychiatric disease, respiratory pathology, neuromuscular disease, genetic disease. All participants provided their written informed consent.

The study was conducted according to Helsinki declaration. The study was approved by the Ethics Committee of the University "G. d'Annunzio" of Chieti – Pescara, Italy (protocols no. 1634/07 COET and no. 1884/09 COET)

MEASURES

We measured the height and the body weight of the subjects, and calculated their Body Mass Index (BMI). We estimated the percentage of Fat Mass (%FM) using the plicometric method¹⁵.

Five Times Sit-to-Stand Test (FTSST) was applied according to a previous study¹⁶: at the signal of the evaluator, the subject stood up and sat down 5 times as quickly as possible, keeping the arms crossed on the chest. The evaluator provided preventively also the following instructions in order to standardize the execution: "Stand up fully and touch the chair in every repetition", "Do not touch your back to chair backrest". The subjects repeated the test three times and the best performance was considered.

Timed Up-and-Go (TUG) test was applied according to a previous study¹⁷: at the signal of the evaluator, the subject stood up from a chair, walked 3 m, turned beyond a ground line, walked back and sat down to the same chair. Two evaluators were positioned through the course to avoid any serious consequence in the case of a fall. The subjects repeated the test three times and the best performance was considered.

DESIGN AND PROCEDURES

We used an experimental longitudinal design to address the objectives. The subjects were divided randomly into

Table I. Participants. Descriptive characteristics of the recruited subjects; data are expressed as Mean \pm SD.

	Subjects	Age (years)	Weight (kg)	Height (m)
Overall	40	70.70 \pm 4.39	72.10 \pm 10.01	1.60 \pm 0.08
Males	28	71.10 \pm 5.05	75.90 \pm 8.55	1.64 \pm 0.07
Females	12	69.70 \pm 2.02	69.70 \pm 2.02	1.51 \pm 0.03

four groups: endurance training (n = 8, 5 M and 3 F), resistance training (n = 10, 7 M and 3 F), NMES (n = 10, 7 M and 3 F) and control (n = 12, 9 M and 3 F). Initially, they were clustered in 4 groups with an equal number of participants, but due to logistical impairments 2 subjects were moved from endurance group to control. All the following tests were executed before (t0) and after (t1) the completion of three different training protocols, below detailed. For the control group we respected the same time of other groups, executing t1 analysis after 12 weeks from t0. Participants of the control group were required to report the current physical activity engagement at the end of the experimental time, in order to confirm the physical inactivity status, such as in t0: all of them confirmed the same status.

The training plans were set coherently with the general recommendations for the age: in particular, considering our group as older adults who were not active, we used a multiple-months progressive intervention, with a regular monitoring and a re-evaluation of the plans in accordance with functional changes¹⁸.

The endurance training consisted of three sessions per week, for a period of 12 week. The training plan was set in accordance with the minimum recommendation for vigorous-intensity aerobic activity in older adults of 20 min on three days each week¹⁸. The subjects were trained on a cycloergometer, pedalling at a constant intensity monitored through Heart Rate (HR) by a HR monitor (Polar Accurex Plus, Polar, Finland). HR training (HR_{tr}) was calculated according with Karvonen formula (19): $(HR_{max} - HR_{rest}) \times Intensity + HR_{rest}$. HR_{max} was derived by Tanaka formula²⁰: $208 - (0.7 \times age-in-years)$. HR_{rest} was that one measured on ECG. Intensity was set at 0.6, 0.7 or 0.8 of HR_{tr} according to training plan. Intensity and duration were increased through the training period.

The resistance training consisted of three sessions per week, for a period of 12 week. The subjects were trained

on leg-press and leg-extension machines. Our plan met the minimum recommendation of two days each week for muscular strength in older adults, involving major muscle groups¹⁸. The subjects were trained with three series on leg-press and leg-extension machines. Intensity was based on the 1 Repetition Maximum (1RM) (Tab. II).

The NMES protocol consisted of a training program that lasted 18 min, with 40 passive isometric bilateral contractions that were stimulated isometrically by a NMES device (Genesy 1200 Pro; Globus Srl, Codognè, Italy) for three sessions per week over a 12-week period. Pre-load and post-load phases were set identically to the other protocols. During the NMES session, the subjects were seating on a leg extension machine with the knee joint at 90°. Two active electrodes were positioned over the motor points of the quadriceps muscles, closely to the motor point of the Vastus lateralis and Vastus medialis muscles: the specific positions were identified starting from the reference tables of the products and searching for personalized locations. A dispersive electrode was placed 5 cm to 7 cm below the inguinal crease, to close the stimulation loop. The electrical currents followed these characteristics: rectangular-wave (75 Hz every 400 μ s), rise time of 1.5 s, steady tetanic stimulation time of 4 s, fall time of 0.75 s, rest interval of 20 s between stimulations. The intensity was monitored throughout the time and it was gradually increased, keeping it close to the pain threshold of each subject, reaching at the end of the training period an intensity of 38 ± 9 mA.

STATISTICAL ANALYSIS

The calculations for statistical power were performed on G*Power software, version 3.1.9.3 (<http://www.gpower.hhu.de>). The statistical analyses were carried out using GraphPad Prism Software, version 7 (GraphPad Software, La Jolla, USA) and R-based open-source software Jamovi (<https://www.jamovi>).

Table II. Training protocols. Schedule and characteristics of the two training protocols; HRtr: Heart Rate training; 1RM: 1 Repetition Maximum; LP: Leg Press; LE: Leg Extension.

Protocol	Week	Intensity	Pre-load	Load	Post-load
Endurance	1-4	60-70% HR_{tr}	5' pedalling	30' pedalling	5' pedalling + 5' stretching
	5-8	60-70% HR_{tr}	5' pedalling	40' pedalling	5' pedalling + 5' stretching
	9-12	80% HR_{tr}	5' pedalling	40' pedalling	5' pedalling + 5' stretching
Resistance	1-4	60% 1RM	5' pedalling	3 series, 12 repetitions (both on LP and LE machine)	5' pedalling + 5' stretching
	5-8	70-75% 1RM	5' pedalling	3 series, 10 repetitions (both on LP and LE machine)	5' pedalling + 5' stretching
	9-12	80% 1RM	5' pedalling	3 series, 6-8 repetitions (both on LP and LE machine)	5' pedalling + 5' stretching

org). Identification of outliers was performed with ROUT method ($Q = 1\%$). Normality of the distributions was assessed with D'Agostino and Pearson omnibus test. Equality of variances was assessed with Levene's test. Data are reported as Mean (M) \pm Standard Deviation (SD). Three-way ANOVA for Repeated Measures was used to analyse differences between groups, gender and over the two time spots, in addition to Tukey (for time \times gender significance), and Sidak (for ex-post significance of each protocol) correction for multiple comparisons. We used correlation matrixes with Pearson method to test the correlations between parameters at t0 and t1. We ran Principal Component Analysis (PCA) analysis to evaluate the factorial relation between parameters (Oblimin rotation, number of components based on eigenvalues > 1 and scree plot). Significance was indicated as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Effect size was reported with partial η^2 . Given α , effect size and sample size, we calculated power ($1-\beta$).

RESULTS

All the participants performed TUG test, both at t0 and t1, with a better time than the cut-off value for normal mobility proposed by Bischoff and colleagues⁹. There were no significant differences in BMI. There was a tendency for the interaction effect (time \times protocol, $p = 0.068$). Post-hoc analyses revealed no significant differences (Fig. 1).

There was a significant effect for gender in the %FM ($p < 0.001$, partial $\eta^2=0.724$, $1-\beta=0.769$), and a

tendency for time effect ($p = 0.08$). Post-hoc analyses revealed females to have greater values, both at t0 ($p < 0.001$) and t1 ($p < 0.001$) (Fig. 2).

We found a significant reduction from t0 to t1 in FTSST values, with the effects of time ($p < 0.001$, partial $\eta^2 = 0.505$, $1-\beta = 0.193$), time \times protocol ($p = 0.030$, partial $\eta^2 = 0.241$, $1-\beta = 0.537$) and a tendency for protocol ($p = 0.064$). There was a gender effect ($p = 0.009$, partial $\eta^2 = 0.196$, $1-\beta = 0.231$, females have greater values than males). Post-hoc analyses revealed independent negative effect for resistance ($p = 0.035$), NMES ($p < 0.001$), males ($p < 0.001$) and females ($p = 0.003$) (Fig. 3). It is worth noting that a negative effect on this test means a functional improvement.

We found a significant reduction from t0 to t1 in TUG values, with the effects of time ($p < 0.001$, partial $\eta^2 = 0.373$, $1-\beta = 0.219$), time \times protocol ($p = 0.040$, partial $\eta^2 = 0.232$, $1-\beta = 0.563$). There was a gender effect ($p = 0.003$, partial $\eta^2 = 0.254$, $1-\beta = 0.191$, females have greater values than males). Post-hoc analyses revealed independent negative effect for endurance ($p = 0.037$), NMES ($p < 0.001$) and males ($p = 0.002$) (Fig. 4). It is worth noting that a negative effect on this test means a functional improvement.

Correlation matrixes (Tab. III) showed a good correlation between FTSST and TUG, and a light correlation between %FM and the two afore-mentioned tests.

Factorial analysis (Tab. IV) demonstrated the association of TUG and FTSST into the same functional domain, and the anthropometric domain to be separated into two different components. Thus, we identified the following three domains: Functional, Anthropometric BMI,

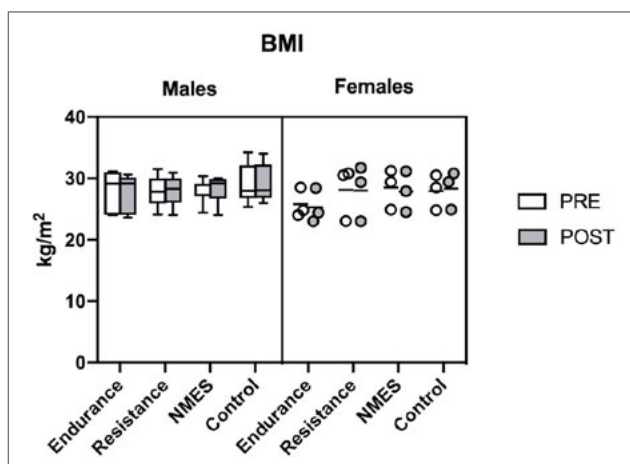


Figure 1. BMI. Results of the Body Mass Index calculations; white boxes and dots represent t0 values, grey boxes and dots represent t1 values; horizontal lines represent Mean; whiskers represent min to max; vertical line divides male and female data; NMES: Neuro-Muscular Electrical Stimulation; M: Males; F: Females.

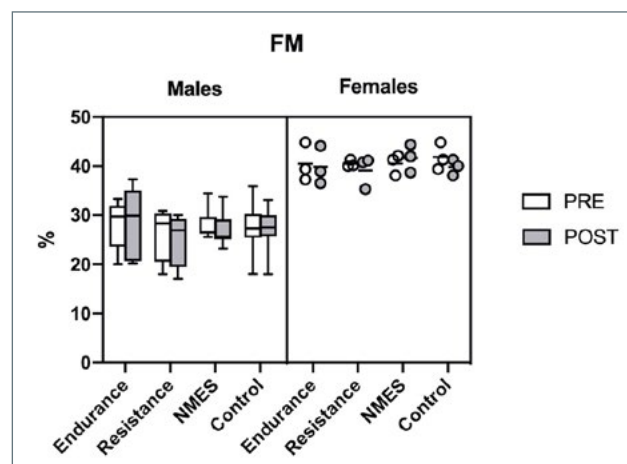


Figure 2. FM. Results of the percentage of Fat Mass estimation from plicometry; white boxes and dots represent t0 values, grey boxes and dots represent t1 values; horizontal lines represent Mean; whiskers represent min to max; vertical line divides male and female data; NMES: Neuro-Muscular Electrical Stimulation; M: Males; F: Females.

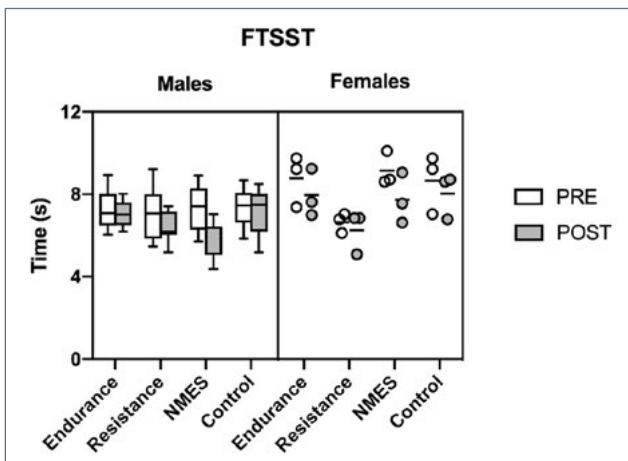


Figure 3. FTSST. Results of the Five Times Sit-to-Stand Test; white boxes and dots represent t0 values, grey boxes and dots represent t1 values; horizontal lines represent Mean; whiskers represent min to max; vertical line divides male and female data; NMES: Neuro-Muscular Electrical Stimulation; M: Males; F: Females.

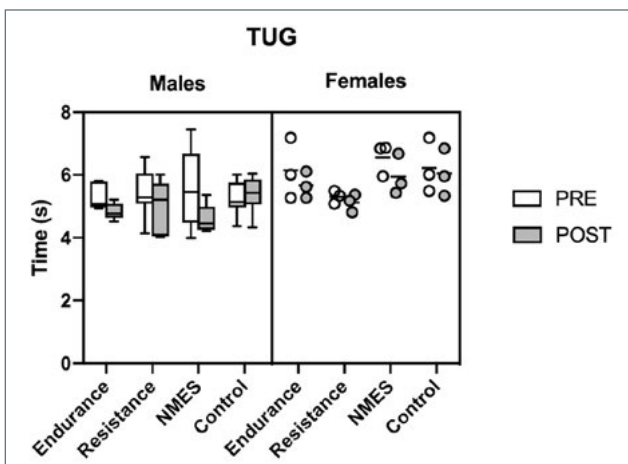


Figure 4. TUG. Results of the Timed Up-and-Go test; white boxes and dots represent t0 values, grey boxes and dots represent t1 values; horizontal lines represent Mean; whiskers represent min to max; vertical line divides male and female data; NMES: Neuro-Muscular Electrical Stimulation; M: Males; F: Females.

Anthropometric FM. Component correlations revealed a higher value in the comparison between Functional and Anthropometric FM, rather than between Functional and Anthropometric BMI.

DISCUSSION

Our recruited subjects demonstrated a good accomplishment and satisfaction on the course of study and on the perceived outcomes after training protocols. We did not find any significant difference in the

Table III. Correlations. Results of correlations (r values) test before (t0) and after (t1) the training period; BMI: Body Mass Index; %FM: percentage of Fat Mass; FTSST: Five Times Sit-to-Stand Test; TUG: Timed Up-and-Go test; *p < 0.05, **p < 0.01, ***p < 0.001.

t0	BMI	%FM	FTSST
%FM	0.192		
FTSST	0.135	0.389*	
TUG	0.120	0.374*	0.667***
t1	BMI	%FM	FTSST
%FM	0.249		
FTSST	0.209	0.452**	
TUG	0.204	0.496**	0.509**

Table IV. PCA. Principal component Analysis (KMO test for sampling adequacy 0.710) with all the parameters; the first table shows the component loadings, the second table shows the component summary, the third table shows the component correlations.

	Component		
	1	2	3
BMI t0		0.991	
%FM t0			1.016
FTSST t0	0.888		
TUG t0	0.892		
BMI t1		0.999	
%FM t1			0.947
FTSST t1	0.843		
TUG t1	0.628		
Component	% of variance	Cumulative	
1	34.3	34.3	
2	25.4	59.7	
3	25.1	84.7	
	2	3	
1	0.202	0.474	
2		0.240	

anthropometric characteristics from t0 to t1. Our results agree with that ones of Binns and colleagues, who reported no significant difference on Lean body Mass (LM) after 20 week (2 session/w) of High Velocity Resistance Training in healthy old subjects (77 ± 6.4 y), both in males and in females²¹. Thus, on healthy elderly, medium-term physical interventions are unable to significantly improve anthropometric characteristic. We should promote the long-term physical exercise engagement to see beneficial effects on anthropometric parameters of healthy older adults²².

Females have greater percentage of FM respect than males: other than the well-known hormonal traits, Tian and colleagues reported the same trend of age-related changes in body composition in a large cohort, with females having higher FM across the lifespan²³. The course of anthropometric adaptations improves the need to promote a long-term involvement in physical activity, beyond the duration of research protocol, in order to provide preventive morphological adaptations in healthy elderly. Surprisingly, factorial analyses revealed BMI values and FM values to be separated in the latent components. Furthermore, component correlations of factorial analysis and correlation matrixes revealed a higher correlation of functional domain with the domain of FM. Therefore, we should take into account which anthropometric domain has to be considered in the links to functional adaptations.

We found a significant interaction (time \times protocol) effect on both FTSST and TUG: different training protocol entail different effects. We expected that elderly trained with NMES and RT were more responsive on functional tests, especially on FTSST: surprisingly, we found similar tendencies for the effects on each group. This result could be explained considering that we found TUG and FTSST to be correlated. The high correlation support the idea of a functional articulated domain. Goldberg and colleagues also reported a correlation between the two afore-mentioned tests, suggesting the usefulness of FTSST as a measure of functional mobility in older adults²⁴. Interestingly, we found NMES group to be significantly responsive to both TUG and FTSST.

However, the low achieved power, due to high Coefficient of Variations (CVs) and limited number of participants in sub-groups, suggest us to take cautiously into account these results.

In particular, considering the independent effect of resistance and NMES on FTSST values, we consider this test more related to the local strength respect than TUG. This interpretation is in agreement with that one by Bohannon and colleagues, who highlight the relation of FTSST with lower limb strength; moreover, these authors found no correlation between FTSST and anthropometric profile²⁵.

Supporting the difference in functional sub-domain measure, we found independent effect of endurance and NMES, but not resistance, on TUG values: as affirmed by Maden-Wilkinson and colleagues, the changes in muscular mass and strength only partially explain the impairment in functional performance²⁶.

Considering the local increment of maximal isometric strength, as reported in previous study with the same protocol⁸, we expected to find a significance for NMES only on FTSST. Surprisingly, we found NMES to be effective on both the functional tests. Although we did not attempt

to determine the mechanisms, we may suggest these results to be related to a maintenance in neuroplasticity²⁷. As expected, we found gender differences in functional test (males exerted better performances), but not with an interaction effect with time and protocol. Ibrahim and colleagues affirmed that functional pattern course through ageing may be similar across genders²⁸. In our data, the number of females did not permit us to achieve adequate power in statistical comparisons of the functional tests, thus this limit did not permit us to propose a clear framework of gender-related adaptations: other studies with a large number of participants are required to go further in this topic.

FTSST and TUG are widely used tests to assess functional mobility in elderly: in our study, PCA and correlation matrixes revealed that there's a common base: however, our results revealed FTSST to be more related by a vigour performance and TUG more related to a more articulated motor behavior, as highlighted by the post-hoc effect of endurance training. Thus, we suggest the use of both of them to better characterize the course of functional adaptations in elderly.

Concerning the timeline of the evaluation, starting from the present findings, we suggest a multi-spot comprehensive interpretation with a sequential evaluation protocol, such as that one proposed by our group for the analysis of Maximal Voluntary Contraction (MVC) at t0, t4, t8, t12 e t28 (after 16 weeks of de-conditioning)⁷.

On the basis of recent results, demonstrating MVPA (Moderate-to-Vigorous Physical Activity) as a strong predictor for TUG and FTSST in healthy elderly²⁹, we should include the assessment of specific physical activity engagement in ex-post studies to improve the comprehension of multi-domain effect of specific exercise.

Considering our results, we suggest further studies with similar designs in order to go further in the identification of exercise-related adaptations, clustered by gender and age. Our results can be a base to suggest effective training protocols in healthy elderly.

In perspective, we could address other functional domain in elderly, such as balance³⁰, and the physiological adaptive main pathways implied in ageing³¹. We recently demonstrated a specific cross-talk between lower and upper limbs, the Bottom-Up Rise Strength Transfer (BURST), mainly linked to endurance training: we may therefore move forward in the comprehension of physiological mediators of training-related functional improvements³².

Considering the differences on the effect between training protocols and the evidence of gender differences, we should carry on towards an evidence-based physical activity training plans.

In conclusion, the results of the present study highlight and specify the effects of different trainings in elderly in

a functional mobility framework, bricking a piece in order to better promote adequate physical activity-based strategies towards an active and healthy ageing.

ACKNOWLEDGEMENTS

The authors would like to thank José Luiz Dantas who performed some FTSST and TUG tests and helped with some trainings. Special thanks go to all the elderly participants in the study.

FUNDING

This work was supported by 2012N8YJC3_003 PRIN and by grants of Università degli Studi “G. d’Annunzio” Chieti-Pescara to TP and WV.

CONFLICT OF INTEREST

The Authors declare to have no conflict of interest.

PUBLICATION STATEMENT

This manuscript has not been published elsewhere and it is not under consideration for publication elsewhere. Its publication is approved by all authors.

References

- Gerovasili V, Agaku IT, Vardavas CI, et al. *Levels of physical activity among adults 18-64 years old in 28 European countries*. *Prev Med* 2015;81:87-91.
- Lachman S, Boekholdt SM, Luben RN, et al. *Impact of physical activity on the risk of cardiovascular disease in middle-aged and older adults: EPIC Norfolk prospective population study*. *Eur J Prev Cardiol* 2018;25:200-8.
- Aune D, Norat T, Leitzmann M, et al. *Physical activity and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis*. *Eur J Epidemiol* 2015;30:529-42.
- Liu C-J, Xu H, Keith NR, et al. *Promoting ADL independence in vulnerable, community-dwelling older adults: a pilot RCT comparing 3-Step Workout for Life versus resistance exercise*. *Clin Interv Aging* 2017;12:1141-9.
- Leung M, Rantalainen T, Teo W-P, et al. *The ipsilateral corticospinal responses to cross-education are dependent upon the motor-training intervention*. *Exp Brain Res* 2018; Mar 6. [Epub head of print]
- Sapp RM, Shill DD, Roth SM, et al. *Circulating microRNAs in acute and chronic exercise: more than mere biomarkers*. *J Appl Physiol* 2016;122:702-17.
- Pietrangelo T, Mancinelli R, Doria C, et al. *Endurance and resistance training modifies the transcriptional profile of the vastus lateralis skeletal muscle in healthy elderly subjects*. *Sport Sci Health* 2012;7:19-27.
- Di Filippo ES, Mancinelli R, Marrone M, et al. *Neuromuscular electrical stimulation improves skeletal muscle regeneration through satellite cell fusion with myofibers in healthy elderly subjects*. *J Appl Physiol Bethesda Md* 1985; 2017;123:501-12.
- Bischoff HA, Stähelin HB, Monsch AU, et al. *Identifying a cut-off point for normal mobility: a comparison of the timed “up and go” test in community-dwelling and institutionalised elderly women*. *Age Ageing* 2003;32:315-20.
- Kang L, Han P, Wang J, et al. *Timed up and go test can predict recurrent falls: a longitudinal study of the community-dwelling elderly in China*. *Clin Interv Aging* 2017;12:2009-16.
- Bernabeu-Mora R, Medina-Mirapeix F, Llamazares-Herrán E, et al. *The accuracy with which the 5 times sit-to-stand test, versus gait speed, can identify poor exercise tolerance in patients with COPD: a cross-sectional study*. *Medicine (Baltimore)* 2016;95:e4740.
- Medina-Mirapeix F, Vivo-Fernández I, López-Cañizares J, et al. *Five times sit-to-stand test in subjects with total knee replacement: reliability and relationship with functional mobility tests*. *Gait Posture* 2018;59:258-60.
- Chang S-F, Yang R-S, Lin T-C, et al. *The discrimination of using the short physical performance battery to screen frailty for community-dwelling elderly people*. *J Nurs Scholarsh Off Publ Sigma Theta Tau Int Honor Soc Nurs* 2014;46:207-15.
- Lamb SE, Keene DJ. *Measuring physical capacity and performance in older people*. *Best Pract Res Clin Rheumatol* 2017;31:243-54.
- Durnin JV, Womersley J. *Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years*. *Br J Nutr* 1974;32:77-97.
- Whitney SL, Wisley DM, Marchetti GF, et al. *Clinical measurement of sit-to-stand performance in people with balance disorders: validity of data for the Five-Times-Sit-to-Stand Test*. *Phys Ther* 2005;85:1034-45.
- Podsiadlo D, Richardson S. *The timed “Up & Go”: a test of basic functional mobility for frail elderly persons*. *J Am Geriatr Soc* 1991;39:142-8.
- Nelson ME, Rejeski WJ, Blair SN, et al. *Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association*. *Circulation* 2007;116:1094-105.
- Karvonen MJ. *Physical activity for a healthy life*. *Res Q Exerc Sport* 1996;67:213-5.
- Tanaka H, Monahan KD, Seals DR. *Age-predicted maximal heart rate revisited*. *J Am Coll Cardiol* 2001;37:153-6.
- Binns A, Gray M, Henson AC, et al. *Changes in lean mass and serum myostatin with habitual protein intake and high-velocity resistance training*. *J Nutr Health Aging* 2017;21:1111-7.
- Rava A, Pihlak A, Ereline J, et al. *Body composition, neuromuscular performance, and mobility: comparison between regularly exercising and inactive older women*. *J Aging Phys Act* 2017;25:58-64.
- Tian S, Morio B, Denis J-B, et al. *Age-related changes in segmental body composition by ethnicity and history of weight change across the adult lifespan*. *Int J Environ Res Public Health* 2016;13 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4997507>).

- ²⁴ Goldberg A, Chavis M, Watkins J, et al. *The five-times-sit-to-stand test: validity, reliability and detectable change in older females*. Aging Clin Exp Res 2012;24:339-44.
- ²⁵ Bohannon RW, Bubela DJ, Magasi SR, et al. *Sit-to-stand test: performance and determinants across the age-span*. Isokinet Exerc Sci 2010;18:235-40.
- ²⁶ Maden-Wilkinson TM, McPhee JS, Jones DA, et al. *Age-related loss of muscle mass, strength, and power and their association with mobility in recreationally-active older adults in the United Kingdom*. J Aging Phys Act 2015;23:352-60.
- ²⁷ Barss TS, Pearcey GEP, Zehr EP. *Cross-education of strength and skill: an old idea with applications in the aging nervous system*. Yale J Biol Med 2016;89:81-6.
- ²⁸ Ibrahim A, Singh DKA, Shahar S. *'Timed Up and Go' test: age, gender and cognitive impairment stratified normative values of older adults*. PLoS One 2017;12 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5626462>).
- ²⁹ Rava A, Pihlak A, Kums T, et al. *Associations of distinct levels of physical activity with mobility in independent healthy older women*. Exp Gerontol 2018; Jun 8 [Epub head of print].
- ³⁰ Bernard PL, Blain H, Gerazime A, et al. *Relationship between a three-month physical conditioning "posture-balance-motricity and health education" (PBM-HE) program on postural and balance capacities of sedentary older adults: influence of initial motor profile*. Eur Rev Aging Phys Act 2018;15 (<https://eurapa.biomedcentral.com/articles/10.1186/s11556-018-0203-0>).
- ³¹ Di Giulio C, Antosiewicz J, Walski M, et al. *Physiological carotid body denervation during aging*. Adv Exp Med Biol 2009;648:257-63.
- ³² Pietrangelo T, Bondi D, Kinel E, et al. *The bottom-up rise strength transfer in elderly after endurance and resistance training: the BURST*. Front Physiol 2019;9 (https://www.frontiersin.org/articles/10.3389/fphys.2018.01944/full?utm_source=F-NTF&utm_medium=EMLX&utm_campaign=PRD_FEOPS_20170000_ARTICLE).

How to cite this article: Pietrangelo T, Doria C, Bondi D, et al. *Effects of endurance, resistance and neuro-muscular electrical stimulation trainings to the anthropometric and functional mobility domains in elderly*. Journal of Gerontology and Geriatrics 2019;67:148-55.

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

The caregivers' iceberg: qualitative narratives of Italian caregivers' roles and challenges

R. Papa, G. Lamura

IRCCS INRCA, Centre for Socio-Economic Research on Ageing, Ancona, Italy

Despite the crucial role of informal caregivers of dependent persons to ensure the sustainability of our welfare systems, only few European countries have so far recognized their pivotal role in care provision. The aim of this study is to provide additional evidence in this regard, based on the experience of Italian caregivers, analysed via a qualitative methodology, to take into account behaviours and perspectives of both spouses/partners and children/children-in-law. Six semi-structured face-to-face in-depth interviews were carried out. Five themes emerged: 1) the diseases and the need of information; 2) the caregiving role; 3) the organization of care; 4) the impact of caring; and 5) the social recognition of the role. The study confirms that the impact of caregiving can be enormous and affects all aspects of one's life and of our society as a whole, thus suggesting that appropriate measures are needed to provide accessible information and adequate support services to informal caregivers.

Key words: Informal caregivers, Qualitative interviews, Older people, Loneliness, Care burden

INTRODUCTION

BACKGROUND

Estimates suggest that 80% of care to dependent persons with chronic illnesses or disability is currently provided by informal caregivers, such as family members, friends or neighbours¹. This role, often taken for granted by governments, represents today an important component of welfare systems, which are facing major sustainability challenges due to the aging of the population². If, on one hand, the share of older people and the prevalence of chronic conditions and multimorbidity – now affecting about 50 million of European citizens³ – are both expected to increase in the next decades, on the other hand governments' financial constraints, demographic and social changes are leading to a decline in the number of people potentially able to provide care. This trend is due, for example, to the increase of old age dependency ratio, the decrease in

families' size, the increasing living distance between children and parents, and the growing women's employment rate⁴. Among the European countries, Italy is strongly affected by this phenomenon because is the country with the highest percentage of older people and with a tradition of a "family" model of care⁵.

To be effective, ageing in place and caring for older people in their homes, instead of use of residential care services, require remarkable joint efforts by families, public and private welfare organizations, and the voluntary sector⁶. Traditionally, informal caregivers are mainly represented by women aged 50 to 70 years, close relatives of the care recipients (e.g., partners or daughters), who are in charge of a wide range of activities, from health and personal care to financial and domestic management, mobility and emotional support⁷. Lack of homogeneous definitions and paucity of data have prevented reliable estimates of the size of this target group, which ranges, for the European Union only, from 19 to 100 million⁸.

■ Received: February 11, 2019 - Accepted: August 28, 2019

■ Correspondence: Roberta Papa, IRCCS INRCA, Centre for Socio-Economic Research on Ageing, via S. Margherita 5, 60124 Ancona, Italy. E-mail: r.papa@inrca.it

Despite the growing amount of care and support activities informal caregivers provide every day to their family members in need, only few European countries started to recognize their pivotal role in the care process⁹. In Italy, the Central Government recently established the "Fund to support the caring role of informal caregivers", whereas some Regions adopted specific laws to recognize the role of caregivers and provide them improved support services. In this context, the analysis of the challenges caregivers are facing, but also the contribution they are providing to the society, are important to support the development of adequate policies in this field. Moreover, the Italian situation offers interesting insights on how social and political trends of the last decades have influenced elder care provision.

THE ITALIAN CONTEXT

The last available official figures show that in Italy there are about 3.3 millions of informal caregivers aged 15-64 years¹⁰, a number that does not include the many over-65-years old who provide care to their partners or to other family members.

Although in Italy families have been traditionally the pillar of elderly care, demographic changes and the economic crisis contributed to gradually undermine this model⁵. On the one hand, the already low level of long-term care (LTC) public services was additionally reduced as an effect of fiscal austerity, except for the cash allowance provision - a universalistic measure targeted to completely dependent people - which increased of +3.1% in the period 2008-2014¹¹, and then decreased of -0.5% in the period 2013-2015¹². On the other hand, Italian families - who started to use privately hired home care workers as a response to the increasing women's engagement in the labour market¹¹ - have been suffering in recent times from the economic difficulties brought by the recent international economic crisis, struggling to sustain these expenses⁵. Moreover, it is worth mentioning that, apart from cash allowances (granted to about 12% of older people), older Italians refer only to a limited extent to social and health care services, these being affected by a high fragmentation and variability across regions, low accessibility (i.e., only 5 and 2% of older people using home care and residential care, respectively) and low intensity (i.e., about 20 hours *per year* of home care on average)¹³. In Marche region, where this study has been carried out, recent data show that health homecare is used by 2.9% of older people for a yearly average of 27 hours, whereas social homecare services are used by 0.7% of people aged 65 years and over (1.2% in Italy)¹². If residential care is considered, there are 2.2 beds every 100 persons aged 65 years and over. Finally, cash allowances are granted to 12.9% of older people, with a declining

trend since 2010. These data suggest that Marche region has a mixed cash-for-care model, dominated by cash allowances and integrated with homecare¹². When these services are not available, many families tend to seek help from privately hired migrant home care workers, estimated to reach about 830,000 in 2013¹⁴, even if most of them often do not have any specific training to carry out care activities, thus making it difficult to properly manage on a routine basis chronic illnesses like, for instance, Alzheimer's disease. The use of this solution is often not feasible for low-income people because the costs of a migrant care worker could be relatively high and the cash allowances, if received, usually cover only a part of it. As a consequence, the last decades have seen an increase of undeclared (and therefore cheaper) migrant care work¹⁴. These trends reflect, on the one hand, the efforts of Italian families to adjust their behaviours in the attempt to find the most suitable and sustainable solution to provide the best possible quality of care to their loved ones and, on the other hand, the still primary role of informal care.

IMPACT OF CAREGIVING

Informal caregiving could have positive benefits in terms of self-esteem and rewards, but also have a strong and negative impact on different aspects of life, such as health, family, work, and social inclusion. Becoming a caregiver means assuming the role of caring for a person in need, adapting and reinventing own life, with an uncertain future^{15 16}. Research has extensively documented that caring affects both psychological and physical health, showing that caregivers often suffer from stress, anxiety, depression and burden¹⁷, especially in the case of relatives suffering from Alzheimer's disease^{18 19}. Moreover, they can be at risk of physical problems (i.e. injuries, worsening of chronic conditions) or of unhealthy life-styles²⁰, especially in the case of older spouses caring for their partners because they are also exposed to their own health decline associated with aging. Caregivers living with the care recipient or those providing intensive care could also face problems with their work duties, requiring a reduction of working hours or even to quit job^{21 22}. In the same way, leisure time and family obligations are affected by the responsibilities associated with the role assumed. Thus, effects of caring are not only relevant for those providing care, but have a heavy impact also on the quality of care provided to the care recipients and on the society as a whole, with important implications in terms of costs and public expenditures.

It is not surprising, therefore, that in the last decades an increasing attention has been paid to the study of caregivers' needs and support services, although studies often focused on single aspects of caring^{23 24} or used

quantitative methods^{25 26}. A comprehensive view of the caregiver role should consider not only the different aspects of caregivers' life and the relationship among these aspects, but also the contextual aspects, such as the national organization of health and social service provision, and their impact on elder care. Availability of both individual and environmental resources and ability of the caregivers to use them are important elements to consider. For example, personal traits (e.g., optimism, self-esteem), presence of persons that can be called in case of need or that can be delegated to carry out some caring activities, assets, and accessible services, are all factors that can influence positively and significantly the perception of the caregiving experience²⁷. Conversely, in other situations, caregivers could avoid telling other persons about their situation, preventing the search for help, or could have problems in the relationship with the care recipient, creating barriers and conflicts in the management of care and support²⁸.

In the light of these considerations, this study aims, in the first place, to provide additional insight on the experiences of a sample of Italian caregivers, trying to grasp and illustrate their perspectives, needs and problems using a qualitative methodology. In particular, the study attempts to answer the following questions: How and why has caregiving started? How are care and assistance activities organized in relation to private life, work and family commitments? What kind of support do caregivers search for, receive, and from whom? What kind of difficulties do caregivers encounter? What perspectives and expectations do they have for the future? How do they feel with regard to the way their role is perceived by their closer social network and by society?

Secondly, given the crucial role played by social relations in this field, the study takes into account the kind of relationship existing between the caregiver and the care recipient, as potentially influencing the motivations, feelings, needs and caring strategies implemented²⁹. The relationship dynamics can be represented as an attempt of the caregiver to balance his/her needs and those of the care recipient, managing the changes occurring in the relationship, the motivations and the meanings of caregiving³⁰. Willingness of the caregiver to maintain the relationship with the care recipient (e.g. love relationship) could have positive effects, but failure to do so could provoke conflicting feelings (e.g., love and anger) and disruption. Indeed, spouses could suffer from not being able to do things together with their partners, and children could have problems in accepting the reversal of the role with their parents. There are also other characteristics influencing differences in caregiving experiences by kind of relationship. For example, spouses assisting their partners are usually older people themselves and have more time to dedicate to

caring as being retired, but have also reduced capabilities due to the health problems derived by the ageing process. On the contrary, children assisting a parent/grandfather are younger, but also likely to be employed and having other family commitments²².

MATERIALS AND METHODS

In this study, we used a qualitative methodology in order to gain a more comprehensive view of informal caregivers' experiences and thoughts^{31 32}.

SAMPLE

Participants were selected if they were family caregivers providing unpaid care – at least four hours per week of support, excluding financial support or companionship³³ – to a family member (adult or older people) with a chronic illness, disability or other long-lasting health or care need. The selection of participants was made in order to assure a certain degree of variation in terms of characteristics and conditions, thus providing a comprehensive view of caregivers' role, while looking at common patterns. Moreover, the sample was designed to include and be equally distributed between spouses/partners or sons/sons-in-law, in order to have some insights of the experiences and needs characterising the two groups. All participants lived in the Marche region (Central Italy) and were recruited in the facilities of the Italian National Institute of Health and Science on Ageing (IRCCS INRCA).

We interviewed six caregivers, 3 spouses (females) with an age ranging from 56 to 80 years, and 3 daughters/grandchildren (1 male and 2 females) from 46 to 54 years (Tab. I). Participants were the primary caregivers and in 4 out of 6 cases lived together with the care recipients. Duration of caring ranged from 8 to 22 years for the spouses, and from 5 to 10 years for daughters/grandchildren. Spouses were retired, except one still working full-time but going into early retirement within a year, whereas daughters/grandchildren were working part-time or full-time. Spouses were heavily committed to caring activities (e.g. 24 hours a day), mainly in surveillance and assistance with instrumental activities (e.g., shopping, transport, food preparation, medication) and, but to a lower extent, in assistance with basic activities (e.g., dressing, hygiene, walking). Although their partners were severely dependent, spouses tried to do things together and maintain as much as possible their autonomy. Daughters/grandchildren provided mainly assistance with instrumental activities, and to some extent surveillance, with variation among caregivers due to the presence of other persons taking care of the relative.

Table I. Characteristics of caregivers and care recipients.

Code	Caregivers ^a	Care recipients ^b
1	Female, 80 years, spouse , living with her husband, 3 children, retired, caring by 8 years	Male, 84 years, Alzheimer's disease, severely dependent
2	Female, 72 years, spouse , living with her husband, 2 children, retired, caring by 22 years	Male, 77 years, Parkinson's disease, severely dependent
3	Female, 56 years, spouse , living with her husband and 2 children, working full-time, caring by 9 years	Male, 56 years, Alzheimer's disease, moderately dependent
4	Male, 46 years, grandchild , living with his partner, working full-time, caring by 5 years	Female, 97 years, multimorbidity, moderately dependent
5	Female, 51 years, daughter , living with her husband and 1 child, working part-time, caring by 5 years	Female, 80 years, Parkinson's disease, severely dependent
6	Female, 54 years, daughter , living with her mother, working full-time, caring by 10 years	Female, 84 years, Alzheimer's disease, moderately dependent

^aGender, age, relationship with the care recipient, household condition, number of children (if any), working status, duration of caring; ^bGender, age, health condition, level of dependency

Care recipients were moderately or almost fully dependent, based upon the stage and progression of the diseases they suffered from.

DATA COLLECTION

Data were collected by semi-structured face-to-face qualitative interviews between November and December 2017. Prior to the interview, participants were informed about objectives of the study, criteria for inclusion and methods used. Moreover, it was clarified that the participation was voluntary, and that the information collected would have been treated as confidential. Before the beginning of the interview, it was asked permission to record the interview for subsequent analysis, and it was used ice-breaking conversation to put the caregiver at ease and create a relaxed atmosphere. The interview guide (Appendix 1) was composed of 6 sections: 1) basic socio-demographic information about caregiver and care recipient; 2) history of caring; 3) information about care and support; 4) care network; 5) challenges and rewards; 6) recognition and expectations. Topics and questions were derived from the review of the literature in the field³⁴⁻³⁶. The flexible structure of the interview gave the possibility to the participants to express their opinions and emotions, while letting the interviewer exercise some control over the topic studied. Interviews were carried out in a quiet room at IRCCS INRCA's premises, and lasted between 50 minutes and one hour.

DATA ANALYSIS

Due to the small sample size, data analysis was carried out manually. To this purpose, we used the Framework Analysis technique^{31,37}, consisting of five steps such as familiarization, identification of a thematic framework, indexing, charting, mapping, and interpretation.

Interviews were transcribed verbatim, read and re-read in order to become familiar with them. Main themes were then derived considering transcriptions and sections of the interview guide. One grid was used to analyse data of each theme, where columns represented participants and rows the sub-themes, analysing the transcripts of all participants both within and between cases.

The most meaningful statements, representing the main themes and describing the stories of the caregivers, were highlighted and translated. Quotes are reported in the text including the code of the caregiver (Tab. I); if relevant, it is also specified the degree of kinship with the care recipient.

RESULTS

Interviews provided rich material to understand caregivers' experiences and thoughts. Five themes emerged from the analysis, and results are presented following this structure: 1) the diseases and the need of information; 2) the caregiver role; 3) the organization of care; 4) the impact of caring; 5) the recognition of the role. Within each theme, several sub-themes were identified, as shown in Table II.

THE DISEASES AND THE NEED OF INFORMATION

Caregivers' histories began with the onset of the disease affecting the care recipients, which influenced their decisions, behaviours and assumption of the caregiver's role. For some of them the path to the diagnosis was easier, while for others it included a long list of visits and tests. Nevertheless, almost all participants described these moments with meticulous details. Some caregivers highlighted the difficulties encountered, often

Table II. Themes and sub-themes emerging from the interviews.

Themes	Sub-themes
Diseases and the need of information	<ul style="list-style-type: none"> • Disease's beginning and progression • The moment of the diagnosis • Need of information • Sources of information • Problems encountered
Caregiver role	<ul style="list-style-type: none"> • Reasons to provide care • Acceptance of the disease • Acceptance of the role • Changes of responsibilities
Organization of care	<ul style="list-style-type: none"> • Care plan • Care network • Time off from caring • Caregivers' support (spiritual aspects) • Caregiver style/coping strategies
Impact of caring	<ul style="list-style-type: none"> • Feelings and emotions • Relationship with the care recipient • Reconciliation with family and work commitments • Social isolation • Vision of the future • Positive aspects of caring
Recognition of the role	<ul style="list-style-type: none"> • Satisfaction with care provided • Possible improvements • Recognition of the role

related to the concomitant presence of other diseases/conditions affecting the care recipients, due to the ageing process.

The moment of the diagnosis was recalled by almost all participants as a crucial date, since it became for some of them the moment when they started realizing their situation:

The diagnosis a year ago... recently she begins to misfire and for me it's a stab, I'm crying, I'm venting by myself... these are small things you have to expect [from Alzheimer's disease], but for me the biggest sorrow is to accept the disease (P6).

From that moment onwards, an increasing need of information emerged, which was firstly addressed by the physician, followed by the reading of books, word-of-mouth with friends and other family members, and in few cases by on-line search. Different participants participated to ad hoc training courses for caregivers, which they evaluated as a positive experience:

There (caregiver's courses) they are always very nice... a relief valve and you find similar or opposite situations, you understand what kind of problems occur and you can find answers to your problems (P5).

However, caregivers struggled to find the right information about local services and voluntary associations, as well as about administrative procedures to get benefits and support:

The absurd thing is that with a diagnosis of Alzheimer's there isn't any standardized protocol... you have to tell me what I have to do, it cannot be that I'm at my wit's end (P3);

I have had enough of bureaucracy, those very complicated things... for some things the doctor told me, because otherwise I wouldn't have known it! (P4).

No differences emerged between spouses and daughters/grandchildren respect to the above issues.

CAREGIVER ROLE

Spouses and daughters/grandchildren reported different reasons to provide care. The first ones talked about choices of love, while the second ones often mentioned the necessity to do it, with the care recipient or other family members taking for granted this role:

When I got married, 50 years ago, I asked myself 'what will be of my life'... anyway I will accept it... 50 years have passed and we are still together... I could not imagine myself without him (P2, spouse);

It was a forced choice due to increasing needs linked to physical decline... but it is absolutely not for me [doing the caregiver], I don't have the time to spend on this thing and I don't like it, but for the sake of my grandmother I do this and more (P4, grandchildren);

I live with my mother and so I charged myself with burdens and honours of a life with a parent, it was automatic... she did so much for me when I needed it, so now it's my turn (P6, daughter).

A common issue was represented by the drastic changes in responsibilities inside the relationships, causing suffering and frustration in caregivers, and felt as something for which there are no alternatives and that should be managed in some way. Spouses were used to share with the partners duties and pleasures of life, while children were used to receive support and help from their parents. In the new situation, these traditional roles and division of responsibilities were completely reversed:

My mother has always been alone and independent, so for me it has become complicated because I had to take care of everything that she used to do previously and I'm not familiar with doing these things even for me (my husband thinks about it)... and so it happens that then certain things are missed (P5, daughter);

I don't have a husband like a husband anymore... a support... all the things he used to care for, I'm from an era in which the husband did some things and the wife others, so I had to re-invent myself with difficulty, but that's it (P1, spouse).

Acceptance of the disease/condition of the care recipients was mentioned by all caregivers as an important point in the process of assumption of the caregiver role, and those who were not able or did not yet achieved it were exposed to a deep suffering:

For me, to deal with the disease has been difficult and it's still difficult... it's a process of acceptance still in progress... for some things (which he makes) he irritates me, I don't remember that there's the disease... My father-in-law [which assists his wife, with Alzheimer, too] is an extraordinary caregiver and the comparison with him is terrible... he lives for his wife and I tell myself that I would not be able to do the same... I have another style... (P3).

ORGANIZATION OF CARE

Due to the level of dependence of care recipients, caring activities were quite demanding for almost all caregivers, independent of the kind of relationship with the care recipient. The tasks included personal care, management of therapies, assistance with mobility and transportation, emotional support, and administrative issues. Caregivers slowly became responsible for everything, and described a typical day with a well-organized and strict schedule of tasks to be carried out alone or with their loved ones. The main challenge for all interviewed was to maintain as long as possible the autonomy of the care recipients, keeping them busy with different activities and stimulating them continuously. This task, for which caregivers felt unprepared in some occasions, was described as quite heavy and requiring a lot of patience, self-control and physical efforts:

We go out every morning to do the ordinary things... I've become very patient, he comes out of the car many times, he puts up and remove the belt... very slow times... he has a good behaviour if you go along with it (P1).

Those not living with the care recipient (i.e. daughters and grandchildren) or working full-time had to rely on external supports – often not meeting the caregiver's expectations – or had to be managed in some other ways, both alternatives being partly unsatisfactory:

It's hard because I understand that she is there [the migrant care worker] 24 hours a day, I imagine it's heavy... but she's often on skype or on the phone, at most they're both watching television or do some exercises but she should do more (P5);

I work all the day so she stays all day alone... I ask her to do small things but then I don't know if she will do them... in the past I had a person who helped me but I had to renounce to it because I had not enough money to pay her (P6).

The general picture provided by the caregivers suggested a strong need to cope with an instable and unpredictable situation composed of good and bad days. For this reason, caregivers avoided any long-term plan and rather focused their attention on the present, preferring to deal with problems or difficulties as they come up. Hence, different coping strategies emerged, which

were heavily influenced by the acceptance of the disease and were aimed to maintain a serene relationship with the care recipients. For example, an experienced caregiver implemented the following approach:

It changed my life totally but I took it with simplicity... my Leitmotiv is: 'if I were in his shoes how would I have liked to be treated?'... this gives me the energy, the strength to go on, it is a continuous restart every day (P1).

The majority of caregivers admitted to be completely alone in their duties. Those receiving little support were helped by other family members, while 'strangers' were chosen if there were no alternatives. Although some care recipients were receiving cash allowances, caregivers preferred not to ask for external help. This argument was reported especially by the spouses, which were reluctant to ask help to their children because they didn't want to be a burden on them:

My children are busy, I can't pretend... of course if I call them they come, but I try to do so as little as possible (P2, spouse).

On the contrary, daughters expressed the need for support, but showed difficulties to involve their siblings in the care, especially if they were male:

My brother is completely absent, I live with her and the burden is mine... today he went on holiday and he told me just now... this makes me feel bad... (P6, daughter).

The burden of care produced stressful situations in caregivers, especially those in more demanding and longer caring situations such as the spouses, which felt to be like "prisoners". On the one hand, they all mentioned the need for some respite care to do some 'normal' activities, whereas on the other hand, they reported difficulties to create these occasions because these moments have to be taken away from care, causing in some cases a sense of guilt. The majority of caregivers reported feelings of loneliness and isolation, due to few psychological supports, and very few occasions to talk with some friends or other family members. In some cases, older caregivers mentioned the importance of the spiritual dimension:

We are religious people and we put everything on that level, in the trust of God that somehow will sustain ourselves (P2).

IMPACT OF CAREGIVING

Caring activities affected all areas of life, from psychological conditions to the reconciliation of work and private life. Different feelings emerged during the interviews, like distress, frustration, depression, anger, mental strain, burn-out and anxiety:

Two days ago, he read for half an hour with the intonation, I was astonished, then I asked him what he had read and he replied to me 'but I didn't read'... and then the world really crashes out on you (P1);

It's devastating, it's hard... the heavy thing is not showing that every time something happens it's a small knife to the heart (P3).

Sense of helplessness also emerged, causing sorrow and anger, because caregivers had to observe health decline of their loved ones without being able to do anything to avoid it:

For me it's a pain to not be able to get her out of this thing... every time she tells me that there is nothing to make her feel better, as if I had not been searching for... it's quite frustrating (P5).

The impact on private life was devastating, especially for those providing care 24 hours a day. Some differences emerged between spouses and daughters/grandchildren. Difficulties in reconciling caring tasks with everyday life commitments were reported by daughters, which sometimes experienced anger towards the situation:

I'm always angry, as my mother says. When I go there at the end of the day I am full of many things, probably I don't have the patience and time to dedicate to her as I would like... (P5, daughter).

For the spouses, health conditions of their partners prevented even the simplest activities normally done with them before the onset of the disease, causing a long list of renunciations:

I am so sorry to not be able to do things together like travel... There are so many things that we have not been doing since so much, and now I have understood that I will not be able to do them anymore, and this is terrible (P3, spouse);

I would like to go here, there... but it's complicated, you have to limit yourself, you have to renounce... how many times I say 'I would like to take a walk, it's too long that I don't take a walk', I really miss it (P2, spouse).

Despite these thoughts, some caregivers affirmed that they should not complain so much about their situation because there are always other persons in a worse situation compared to them.

As regards the impact on the other family members, this was particularly heavy in the case of young children living with the care recipient. In another case, a caregiver living with her mother confessed to have had no opportunity to create her own family because of her situation:

... the love life that I don't have but I don't want to... I feel alone in dealing with this situation but at the same time I wouldn't be able to manage my own life because it wasn't born... however now I don't have head for this (P6).

Social life as well was heavily affected by caring duties. Isolation and loneliness, accompanied by a sense of hopelessness, were the feelings most strongly expressed by the spouses, who have friends in common with their partners who now find difficult to interact with them given their conditions:

Loneliness is the biggest problem... we are alone, we had many friends but people, as they love you, do not hold up the situation, they feel embarrassed (P1, spouse).

On the contrary, daughters and grandchildren, especially those not living with their parents, seemed not to be affected by this problem, because they had the possibility of carving out some space to keep friendships despite caring activities.

Working caregivers with part-time or a flexible working time reported to have no major problems with their work duties, while those working full-time highlighted problems in reconcile work and care.

The difficulties associated with the caregiver role, together with the fear of the disease progression, produced in the caregivers the impossibility to think about the future. This feeling was reported by both spouses and daughters/grandchildren, and some were reluctant to speak about it:

I live day by day because I know that tomorrow will not be so good... I don't even want to think about it because otherwise I got chills... yesterday it passed and it was good, today we live in the present, tomorrow we don't know what to expect... what shall we do? (P2).

Moreover, older caregivers expressed the additional worry to not be able to continue providing care to their spouses, in case of a worsening of their own health conditions:

... then because I'm fairly well, because if I will feel poorly then yes, these is a big problem! (P2).

Despite the difficulties encountered, some positive feelings appeared to the mind of spouses as a part of their love relationship, while daughters/grandchildren were not able to identify any issue:

Days ago, he [the husband] said he was confused and I was suffering for that... so I told him 'Do you know that today are 55 years we are married and we are still together?'... in that moment he took my hand and kissed my wedding ring (P1, spouse)

At night, when I close the windows and it's just us I say 'how wonderful it is' (P2, spouse).

RECOGNITION OF THE CAREGIVING ROLE

Caregivers – both spouses and daughters/grandchildren – showed a moderate satisfaction with the care they were providing, mentioning the need to increase time for both caring and respite care, as well as to have someone with whom sharing the caring tasks. One caregiver highlighted the need to reduce and simplify the administrative procedures, in order to be able to have more time to enjoy the relationship with his relative.

The social recognition and acknowledgement of the caregiver role were poorly evaluated by all interviewed. Only in some cases other family members showed

comprehension about the activities performed, while friends showed often to not be able to understand the situation:

Friends tell me 'I'd never do what you do (for your husband)' and I'm used to answer 'I hope you never need' (P1).

Caregivers felt to be invisible for both society and institutions, and made a desperate cry for help due to the inadequate support and lack of information they felt. Both spouses and daughters/grandchildren explained that society is not aware of what they have to manage every day: *One who is not living the situation does not understand it, in my opinion they do not see them [people with Alzheimer's disease] as being sick, as it is a common thing and therefore there are no problems (P6, daughter); We are far behind, but not only for this issue... I don't hide my situation, on the contrary I tell my story to others but it does not generate so much feelings, people are admired but it ends up there (P1, spouse).*

DISCUSSION

This study, thanks to its qualitative methodology, offers a unique opportunity to gain an in-depth original insight into the experiences, feelings and thoughts of Italian family caregivers. The collected material allowed a two-fold analysis. Firstly, the themes emerged covered all main aspects caregivers have to deal with while caring for a family member and, while largely consistent with previous studies in the field, provided additional insights on the specific Italian situation and the existing contextual aspects. Secondly, the stories of the caregivers revealed different perspectives and difficulties between spouses and daughters/grandchildren.

Caregivers described in detail their stories and the circumstances that lead to the assumption of caregiver role. From that moment, they were responsible for a variety of activities and put efforts in maintaining the independence of their loved ones, through a constant level of assistance^{23 25 36}. These tasks required specific competencies, not always owned and in some cases developed by means of training courses and self-help groups, which are proved to enhance sense of confidence of caregivers about their role and skills^{35 38}. Moreover, management of the health conditions of the care recipients could be improved by the use of new technologies and e-health tools, especially in case of chronic conditions and multimorbidity^{39 40}. However, these solutions are not widely used in Italy, a country which performs in this regard quite poorly compared with most European countries¹¹.

Consistent with other studies^{15 17 24}, care burden was reported as increasing as long as the health conditions

of the family member were getting worse, producing psychological and physical distress, anxiety and depression, especially for caregivers of patients with Alzheimer's disease. These feelings were related not only to the demanding and mentally-exhausting nature of caring, but also to the close relationship with the family member, which often produced negative emotions like compassion and fear of loss^{17 23}. As showed by Gillhooly et al.³⁸, a common coping strategy, emerged also in this study, was that caregivers tended to deal with a problem when it arose, increasing in this way their knowledge base for subsequent similar situations. As expected, acceptance of the disease played an important role^{18 35 41} and followed a different path for each caregiver, based on their resilience and coping strategies adopted^{23 36 38 42}. Some caregivers referred also to have found comfort in spirituality and religious beliefs, which are positively associated with well-being, and with a better relationship with the care recipients^{42 43}. The need of information and the difficulties in find them emerged clearly from the interviews, producing a sense of isolation and frustration in caregivers. Information are usually sparse and scattered, difficult to find and not equally accessible to everyone^{19 33 35 36}. This phenomenon is particularly relevant in Italy because of its fragmented organization of services, on the one hand, and the digital divide and low health literacy of older people, on the other hand, which could be reduced by improving the integration among different services⁴⁴. As regards support received by others, our results showed, in line with other studies^{19 25 35 44}, that the majority of caregivers were women and were alone in this role, with a very limited support from family members or other persons. Moreover, although the severe level of dependence of the care recipients would require huge amount of care and support, only few were receiving cash allowances. In Italy cash benefits are accessible only to fully disabled people who are not able to perform autonomously any activities of daily living, and other kind of social and care services are accessible only to a small portion of people in need^{9 11}. Hence, those not receiving any allowance have to provide themselves for care and support – with all the limits they have due to work or other family commitments – because in many cases their economic situation does not allow them to pay for an external help. As a consequence, occasions of respite care and comfort from friends and support groups, essential to perform some 'normal' or leisure activity or to contain stress^{24 25 35 42}, were also limited. In general, caring for a loved person led to a radical change of life and a deviation from what had been considered 'normal' before the onset of the disease^{16 24 45}. Caregivers complained that they were missing very simple activities, like going out for a walk, visiting

friends, going to the cinema or on holiday. Moreover, care recipients and their spouses, due to their common social network, experienced a gradual and slow exclusion from society. Nevertheless, in an attempt to render the 'unmanageable situation manageable'⁴⁶, they tried sometimes to justify this behaviour as being a normal consequence of their situation, or saying that they knew people who were worse off. These themes are recurrent in literature, especially when co-residency caregivers are considered^{18 20 26 29}. Many of these micro-level difficulties reverberate often in a wider circle of consequences at a both meso level (i.e. within the caregivers' social networks) and macro level (i.e. within the wider society), that have to be managed in addition to the specific support and care provided to the ill person, undermining the sustainability of the whole system.

Invisibility and lack of recognition of the role by institutions and society represented additional burdens for caregivers, who explained to feel abandoned and not understood by service providers and close people^{25 47 48}. Older spouses appeared as the most vulnerable because they were affected also by their own health problems^{17 19 24}, which found difficult to manage, posing at risk the sustainability of their role and, as a consequence, of the quality of care granted to their loved ones.

The second objective of the study was to take into account kind of relationship between caregivers and care recipients in the analysis of the interviews. Spouses and children/grandchildren showed similarities in some aspects of their stories, such as the difficulties encountered in the first phases of the role assumption, the need of information, the burden of care activities, the expectations for the future and the recognition of their role by the society. However, also some differences emerged from the interviews. For example, they reported different reasons prompting family members to provide care. Older spouses were less likely to recognize themselves as caregivers, because they tended to see their role as a part of their marital commitment and a *choice of love*⁴⁸, whereas daughters/grandchildren explained to have started caring as an obligation or a necessity^{15 26}. As a consequence, the former ones were less likely to ask for help, assuming the complete supervision role, often 24 hours a day, whereas the latter had to reconcile caring activities with their own work and family duties, looking for the support of others or being forced to reduce the number of worked hours²¹⁻²³. Those in employment used to benefit from the paid leave to assist relatives in need, which in Italy foresees 3 days per month – for covering emergency situations or for small tasks (e.g., carrying the loved one to medical appointments) – and up to 24 months. In line with other studies, spouses appeared more affected by the

caring tasks compared with children, due to the high level of responsibilities, the older age and the spousal relationship^{17 20 29 48}. Notwithstanding, satisfaction for the care provided and moments of rewards were mentioned mainly by spouses²⁹, who tried to maintain as long as possible the love relationship with their partners and to do things together, even if their roles deeply changed^{18 23}. These results are in line with those of Bull⁴², who reported that, despite the burden produced by dementia, spouses were not able to imagine their life without their partners. On the contrary, daughters and grandchildren were more likely to suffer from this role, and often did not have the capacity to assist their loved ones in a successful way.

Finally, it should be underlined that, although the results obtained by this study are in line with previous research, confirming most of the evidence highlighted by the international literature also for the Italian context for the first time in such a detail, this investigation presents some limitations. Firstly, since it used a qualitative methodology, the small sample does not allow a generalization of the results to other contexts. Moreover, the recruitment of respondents was carried out by personal contacts and support groups, a strategy that does not permit to control for additional variables. Thirdly, it did not involve the perspective of service providers' representative who are daily in contact with informal caregivers, as their opinions might have contributed to better understand and contextualise the perspective of caregivers investigated here. Despite these limitations, we believe that our findings offer a useful, updated insight into the struggles and strengths of a core component of Italy's long-term care system.

CONCLUSIONS

The impact of caregiving is enormous and affects all aspects of one's life and society as a whole. When a person becomes a caregiver, he/she is at risk of high psychological distress and of social isolation, with heavy consequences also on the capacity to actively participate in the society. Our results confirm that caregivers are not a homogeneous group, with different needs and experiences that vary according to both caregiver's and care recipient's characteristics. Although these results cannot be generalized due to the small sample size, they provide important elements to be further explored as well as some suggestions for implementation in the clinical practice and for the planning of political and economic interventions. Hence, supporting caregivers in their tasks is a big societal challenge, requiring a holistic approach and specific tools. Moreover, as formal care is expensive and governments report increasing difficulties in providing adequate financing, supporting

informal care could represent an essential strategy to save costs and delay institutionalization²². Despite the high number of studies in this field, some critical issues remain and should be regarded as priorities by policy makers and researchers. These include an urgent need to reorganize health and social services in order to provide caregivers with more effective counselling and guidance, complete and accessible information, as well as psychological support and respite care services. More systematic and improved interventions in these areas would contribute to alleviate the burden of care and, as a consequence, increase the quality of care provided to the care recipients. Policy makers should therefore consider to further develop specific programmes to better recognize the role of caregivers and reduce their still remarkable social invisibility. In particular, they should promote measures to help caregivers in better reconciling caring activities with their private life and work in order to allow them to provide the best care for their family members, if they wish to do so, without having to stop being and feeling a member of the wider society. Although some steps in this direction have been already made by the Italian government, our findings clearly show that a lot still needs to be achieved in this country to set up a true partnership between citizens and institutions to protect the dignity of frail older people and of their family caregivers.

ACKNOWLEDGEMENTS

This study was partially supported by Ricerca Corrente funding from Italian Ministry of Health to IRCCS INRCA. We would like to thank also the caregivers interviewed for their availability to share with us their intimate feelings and unique experiences. They had the possibility to take some time off from care, while we had the opportunity to learn a lot from their stories.

CONFLICT OF INTEREST

The Authors declare to have no conflict of interest.

References

- Hoffmann F, Rodrigues R. *Informal carers: who takes care of them?* Policy Brief 2010;4 (<https://www.euro.centre.org/downloads/detail/1256>).
- Marin B, Zaidi A. *Trends and priorities of ageing policies in the UNEuropean Region*. Mainstreaming Ageing Indic to Monit Sustain Prog Policies 2017;1820.
- Struckmann V, Snoeijs S, Melchiorre MG, et al. *Caring for people with multiple chronic conditions in Europe*. Eurohealth INTERNATIONAL Eurohealth incorporating Euro Observer 2014;20 (<http://www.icare4eu.org/pdf/caring-for-people-with-multiple-chronic-conditions-in-Europe.pdf>).
- Redfoot D, Feinberg L, Houser AN. *The aging of the baby boom and the growing care gap: a look at future declines in the availability of family caregivers*. Washington, DC: AARP Public Policy Institute 2013 (https://www.aarp.org/content/dam/aarp/research/public_policy_institute/lrc/2013/baby-boom-and-the-growing-care-gap-insight-AARP-ppi-lrc.pdf).
- León M, Pavolini E. 'Social investment' or back to 'Familism': the impact of the economic crisis on family and care policies in Italy and Spain. *South Eur Soc Polit* 2014;19:353-69.
- Verbakel E. *How to understand informal caregiving patterns in Europe? The role of formal long-term care provisions and family care norms*. *Scand J Public Health* 2018;46:436-47.
- Triantafyllou J, Naiditch M, Repkova K, et al. *Informal care in the long-term care system European overview paper*, 2010 (<https://www.euro.centre.org/downloads/detail/768>).
- Colombo F, Llana-Nozal A, Mercier J, et al. *Help wanted?* OECD Publishing 2011 (OECD Health Policy Studies) (http://www.oecd-ilibrary.org/social-issues-migration-health/help-wanted_9789264097759-en).
- Courtin E, Jemai N, Mossialos E. *Mapping support policies for informal carers across the European Union*. *Health Policy (New York)* 2014;118:84-94.
- ISTAT. *La conciliazione tra lavoro e famiglia [Reconciling work and family life]*. 2011 (<https://www.istat.it/it/files/2011/12/stat-report-Conciliazione-lavoro-famiglia.pdf?title=Conciliazione+tra+lavoro+e+famiglia+-+28%2Fdic%2F2011+-+Testo+integrale.pdf>).
- Lamura G, Ranci C, Pavolini E. *Long-term care in Italy*. In: *Long-term care for the elderly in Europe*. New York, NY: Routledge 2016, pp. 89-106.
- Barbabella F, Poli A, Chiatti C, et al. *La bussola di NNA: lo stato dell'arte basato sui dati*. In: *L'assistenza agli anziani non autosufficienti in Italia, 6° Rapporto 2017/2018*. Santarcangelo di Romagna: Maggioli S.p.A. 2017, p. 22 (<https://www.maggioli.it/rna/pdf/9788891625175.pdf>).
- Barbabella F, Chiatti C, Rimland JM, et al. *Socioeconomic predictors of the employment of migrant care workers by Italian families assisting older Alzheimer's disease patients: evidence from the Up-Tech Study*. *J Gerontol B Psychol Sci Soc Sci* 2016;71:514-25.
- Pasquinelli S, Rusmini G. *Il punto sulle badanti [About care workers]*. In: *L'assistenza agli anziani non autosufficienti in Italia*, 2013, pp. 93-111 (https://www.maggioli.it/rna/2012/pdf/rapporto2012-assistenza_anziani.pdf).
- Saletti-Cuesta L, Tutton E, Langstaff D, et al. *Understanding informal carers' experiences of caring for older people with a hip fracture: a systematic review of qualitative studies*. *Disabil Rehabil* 2018;40:740-50.
- Lou S, Carstensen K, Jørgensen CR, et al. *Stroke patients' and informal carers' experiences with life after stroke: an overview of qualitative systematic reviews*. *Disabil Rehabil* 2017;39:301-13.
- Pinquart M, Sörensen S. *Associations of stressors and uplifts of caregiving with caregiver burden and depressive*

- mood: a meta-analysis. *J Gerontol B Psychol Sci Soc Sci* 2003;58:P112-28.
- 18 Feast A, Orrell M, Charlesworth G, et al. *Behavioural and psychological symptoms in dementia and the challenges for family carers: systematic review*. *Br J Psychiatry* 2016;208:429-34.
 - 19 McCabe M, You E, Tatangelo G. *Hearing their voice: a systematic review of dementia family caregivers' needs*. *Gerontologist* 2016;56:e70-88.
 - 20 Pinquart M, Sörensen S. *Correlates of physical health of informal caregivers: a meta-analysis*. *J Gerontol B Psychol Sci Soc Sci* 2007;62:P126-37.
 - 21 Lilly MB, Laporte A, Coyte PC. *Labor market work and home care's unpaid caregivers: a systematic review of labor force participation rates, predictors of labor market withdrawal, and hours of work*. *Milbank Q* 2007;85:641-90.
 - 22 Bauer JM, Sousa-Poza A. *Impacts of informal caregiving on caregiver employment, health, and family*. *J Popul Ageing* 2015;8:113-45.
 - 23 Plank A, Mazzoni V, Cavada L. *Becoming a caregiver: new family carers' experience during the transition from hospital to home*. *J Clin Nurs* 2012;21:2072-82.
 - 24 Ashworth M, Baker AH. "Time and space": carers' views about respite care. *Heal Soc Care Community* 2000;8:50-6.
 - 25 Raivio M, Eloniemi-Sulkava U, Laakkonen M-L, et al. *How do officially organized services meet the needs of elderly caregivers and their spouses with Alzheimer's disease?* *Am J Alzheimer's Dis Other Dementias* 2007;22:360-8.
 - 26 Amirkhanyan AA, Wolf DA. *Parent care and the stress process: findings from panel data*. *J Gerontol B Psychol Sci Soc Sci* 2006;61:S248-55.
 - 27 Clare L, Wu Y-T, Quinn C, et al. *A comprehensive model of factors associated with capability to "live well" for family caregivers of people living with mild-to-moderate dementia*. *Alzheimer Dis Assoc Disord* 2019;33:29-35.
 - 28 Toms GR, Quinn C, Anderson DE, et al. *Help yourself*. *Qual Health Res* 2015;25:87-98 ([http://journals.sagepub.com/Doi: 10.1177/1049732314549604](http://journals.sagepub.com/Doi:10.1177/1049732314549604)).
 - 29 Savage S, Bailey S. *The impact of caring on caregivers' mental health: a review of the literature*. *Aust Heal Rev* 2004;27:111.
 - 30 Quinn C, Clare L, Woods RT. *Balancing needs: the role of motivations, meanings and relationship dynamics in the experience of informal caregivers of people with dementia*. *Dementia* 2015;14:220-37.
 - 31 Ritchie J, Lewis J. *Qualitative research practice. A guide for social science students and researchers*. London, UK: SAGE Publications 2003, p. 350.
 - 32 Fioretti C, Mazzocco K, Riva S, et al. *Research studies on patients' illness experience using the narrative medicine approach: a systematic review*. *BMJ Open* 2016;6:e011220.
 - 33 Lamura G, Mnich E, Nolan M, et al. *Family carers' experiences using support services in Europe: empirical evidence from the EUROFAMCARE study*. *Gerontologist* 2008;48:752-71.
 - 34 Novais T, Dauphinot V, Krolak-Salmon P, et al. *How to explore the needs of informal caregivers of individuals with cognitive impairment in Alzheimer's disease or related diseases? A systematic review of quantitative and qualitative studies*. *BMC Geriatr* 2017;17:86.
 - 35 Fernandes CS, Angelo M. *Family caregivers: what do they need? An integrative review*. *Rev da Esc Enferm da USP* 2016;50:675-82.
 - 36 Teschendorf B, Schwartz C, Ferrans CE, et al. *Caregiver role stress: when families become providers*. *Cancer Control* 2007;14:183-9.
 - 37 Pope C, Ziebland S, Mays N. *Analysing qualitative data*. In: *Qualitative research in health care*. Oxford, UK: Blackwell Publishing Ltd 1999, pp. 63-81.
 - 38 Gilhooly KJ, Gilhooly MLM, Sullivan MP, et al. *A meta-review of stress, coping and interventions in dementia and dementia caregiving*. *BMC Geriatr* 2016;16:106.
 - 39 Barbabella F, Poli A, Andréasson F, et al. *A web-based psychosocial intervention for family caregivers of older people: results from a mixed-methods study in three European countries*. *JMIR Res Protoc* 2016;5:e196.
 - 40 Chi N-C, Demiris G. *A systematic review of telehealth tools and interventions to support family caregivers*. *J Telemed Telecare* 2015;21:37-44.
 - 41 Santini S, Andersson G, Lamura G. *Impact of incontinence on the quality of life of caregivers of older persons with incontinence: a qualitative study in four European countries*. *Arch Gerontol Geriatr* 2016;63:92-101.
 - 42 Bull MJ. *Strategies for sustaining self used by family caregivers for older adults with dementia*. *J Holist Nurs* 2014;32:127-35.
 - 43 Lopez J, Romero-Moreno R, Marquez-González M, et al. *Spirituality and self-efficacy in dementia family caregiving: trust in God and in yourself*. *Int Psychogeriatrics* 2012;24:1943-52.
 - 44 De Cola MC, Lo Buono V, Mento A, et al. *Unmet needs for family caregivers of elderly people with dementia living in Italy: what do we know so far and what should we do next?* *Inq J Heal Care Organ Provision, Financ* 2017;54:004695801771370.
 - 45 Daga E, Corvo E, Marucci A, et al. *L'esperienza dei caregiver primari che assistono a domicilio le persone affette dalla Malattia di Alzheimer [Alzheimer's disease and caregivers experience in home care]*. *Prof Inferm* 2014;67:5-14.
 - 46 Rose H, Bruce E. *Mutual care but differential esteem: caring between older couples*. *Connect Gend Ageing Sociol Approach* 1995;114-28.
 - 47 Sims-Gould J, Martin-Matthews A. *We share the care: family caregivers' experiences of their older relative receiving home support services*. *Health Soc Care Community* 2010;18:415-23.
 - 48 Russell R. *In sickness and in health: a qualitative study of elderly men who care for wives with dementia*. *J Aging Stud* 2001;15:351-67.

Appendix. Interview guide

- 1) Basic socio-demographic information about caregiver and care recipient:
 - a. Caregiver: gender; age; marital status; living arrangements; presence of children; working status (if retired, last work done); educational level; hobbies/interests;
 - b. Care recipient: gender; age; relationship with the caregiver; living arrangements (if in different household); health conditions; level of dependency (severely dependent, moderately dependent, slightly dependent, independent).
- 2) History of caregiving:
 - a. How and when did you start caring for your family member?
 - b. What were the reasons?
 - c. Now think about a typical day during which you provide assistance to your family member. Could you tell me about it? What activities do you do, how do these activities intertwine with your private life and your work? How many hours a week do you provide care to him/her? Do you provide care to other persons?
- 3) Information about care and support:
 - a. Now let's talk about information on health of your loved one, how it should be managed, useful contacts etc. Where do you get this information and how?
 - b. What are the main difficulties encountered, if any?
- 4) Care network:
 - a. Now think about all the people who are involved with you in caring to your family member, considering both other family members and external people like doctors, health workers, associations, friends, etc. Who are these people? What activities do they do and how?
 - b. Do you receive (or have recently requested and are awaiting a response) other external aids (e.g. economic) from social or health services, associations, other people outside the family? If yes, what are they?
 - c. Is there someone who supports you to deal with this situation? If yes, who and how?
- 5) Challenges and rewards:
 - a. How do you feel in the role of caregiver?
 - b. Did you have or do you currently have difficulty in reconciling your care activities with your private life / work etc.? If so, which ones? How do you deal with them?
 - c. Have you had or are you currently having difficulty managing your loved one's assistance activities? If so, which ones? How do you deal with them?
 - d. Did you have or do you currently have difficulty managing relationships with other people involved in caregiving activities? If so, which ones? How do you deal with them?
 - e. On the other hand, are there any positive aspect or things that make you satisfied? If yes, what are they?
- 6) Recognition and expectations:
 - a. Are you satisfied with the assistance you provide to your loved one?
 - b. Do you think your family understands your role and what you are doing for your family member?
 - c. And your employer and colleagues?
 - d. And society as a whole?
 - e. Given all that we have said so far, could you tell me what would you change / add to improve your quality of life and the care you provide to your loved one?
 - f. What are your wishes for the future?

How to cite this article: Papa R, Lamura G. *The caregivers' iceberg: qualitative narratives of Italian caregivers' roles and challenges*. Journal of Gerontology and Geriatrics 2019;67:156-67.

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

Differential diagnosis of nontraumatic purpura in the elderly – Have you considered acquired hemophilia?

M.A. Escobar¹, C.B. Dyer²

¹ Department of Hematology, Gulf States Hemophilia & Thrombophilia Center, University of Texas Health Science Center Houston, Texas, USA;

² Geriatric and Palliative Medicine, University of Texas Health Science Center Houston, Texas, USA

This clinical review discusses acquired hemophilia in the context of nontraumatic purpura in the elderly and highlights the most recent published data and guidelines. Acquired hemophilia is a rare bleeding disorder that occurs most frequently in the elderly population, and, is often associated with a high rate of morbidity and mortality. Identifying the underlying cause of bruising or bleeding to make an accurate diagnosis and implement appropriate management strategies can be complicated in the elderly patient where age-related comorbid conditions and use of pharmacologic agents, and sometimes dietary supplements, confound the differential diagnosis process. Delay in treatment can occur due to lack of awareness and challenges with the differential diagnosis. When bruising is not confined over bony prominences or appears in unusual places, it may be worth considering abuse, where bruises are more commonly located on the head, neck, trunk, and buttocks, as opposed to on the extremities. When bruises are larger or more numerous, or develop into hematomas, an underlying hematologic defect should be considered and include such disorders as undiagnosed congenital moderate/mild hemophilia A or an acquired inhibitor against a coagulation factor. Raising awareness of the signs and symptoms of acquired hemophilia and the steps to diagnosis may lead to timely and appropriate treatment of the elderly who present with unexplained bruising or bleeding and have no history of bruising or bleeding.

Key words: Acquired factor VIII inhibitor, Acquired hemophilia, Bruising, Bleeding, Coagulopathy

EPIDEMIOLOGY AND PATHOGENESIS OF BRUISING IN THE ELDERLY

There are several potential reasons for the onset of bruising or bleeding in the elderly, including physical trauma, coagulation disorders, systemic conditions and simple aging of the skin that can lead to alterations of the microvasculature. Hemorrhage, or macrovascular disruption, is often the result of major trauma that leads to alterations in blood volume and commonly presents with pain and shock. Conversely, there is generally no loss of blood volume or pressure associated with microvascular disruption; instead, petechiae and purpura

are the most common characteristics at presentation of microvascular disruption¹. Easy bruising has been estimated to occur in 12% to 55% of healthy adults²⁻⁴. While the bruising signs of microvascular disruption are fairly obvious, identifying the underlying cause to make an accurate diagnosis and implement appropriate management strategies can be complicated in the elderly patient where age-related comorbid conditions and use of pharmacologic agents, and sometimes dietary supplements, confound the differential diagnosis process. The differential diagnosis should include a patient history, the appearance and location of purpura, and findings from appropriate laboratory tests¹.

■ Received: January 2, 2019 - Accepted: March 27, 2019

■ Correspondence: Miguel A. Escobar, Department of Hematology, Gulf States Hemophilia & Thrombophilia Center, University of Texas Health Science Center Houston, 6655 Travis Street, Suite 400 HMC, 77030 Houston, Texas, USA. Tel. 713-500-8360. E-mail: miguel.escobar@uth.tmc.edu

The objective of this review is to provide an overview of purpura in the elderly and identification of the underlying microvascular causes, particularly those that are not obvious based on patient history, with a focus on findings from published data and guidelines on acquired hemophilia. Acquired hemophilia is a rare bleeding disorder that often goes undiagnosed, misdiagnosed, or has a clinically important delay in diagnosis, and, because so, has a high cost and high rate of morbidity and mortality. Increasing awareness of acquired hemophilia among those who care for the elderly may lead to a more timely and accurate diagnosis and appropriate acute and long-term management, especially when

referral to an experienced hematologist is considered early in the differential diagnosis process.

The potential underlying causes of purpura are many and varied. Table I provides a summary of each cause, location and appearance of purpura (eg, petechiae or purpura), and any unique characteristics that should be considered in the differential diagnosis in the elderly patient.

In many cases, the underlying microvascular pathology for the observed purpura is unknown. This includes senile purpura also called solar or actinic purpura seen in older adults (Fig. 1). The prevalence is as high as 10 to 12% in patients aged 70-90 year; it is more common

Table I. Potential causes, location, appearance, and diagnostic criterion by classification of purpura in the elderly (from Zumberg, Kitchens, 2007, mod.)¹.

Classification of purpura or microvascular lesion	Appearance and location of bruising	Diagnostic criterion or clues
Purpura with no known underlying microvascular pathology True purpuric lesion – presence of extravasated red cells		
Mechanical causes	<ul style="list-style-type: none"> • Petechiae on face and neck from increased venous pressure from vomiting or seizures, or hanging upside down (eg, to relieve back pain) • Purpura on palms/soles of feet from traumatic blows, such as falling from a tall ladder 	<ul style="list-style-type: none"> • History of activities prior to appearance of purpura • Formation of petechiae can be seen after choking, asphyxiation, seizure, barotrauma, electrocution • Facial or truncal bruises larger than 5 cm can indicate elder abuse
Factitious and psychogenic purpura	<ul style="list-style-type: none"> • Purpura is well demarcated; usually in areas readily accessible by the individual 	<ul style="list-style-type: none"> • History that is vague or not credible • Cause is self-infliction with various suction devices, tools etc. • Individuals often have major emotional disturbances and unresolved conflict
Purpura simplex	<ul style="list-style-type: none"> • Small bruises associated with daily life (eg, being pinched) • Often appear ~ 30 inches above the floor (ie, height of most furniture) 	<ul style="list-style-type: none"> • Nonpathologic normal process • More frequently reported by women
Senile purpura	<ul style="list-style-type: none"> • Arms and legs; sun-exposed areas • Non-blanching, red to purple 	<ul style="list-style-type: none"> • Age is the greatest risk factor • May occur spontaneously
Bruises and hematomas	<ul style="list-style-type: none"> • Bruises are not palpable and are flush with the surface of the skin • Can develop into larger bruises or even hematomas in presence of platelet or coagulation defects 	<ul style="list-style-type: none"> • Trauma, location, and appearance of bruising are key considerations • Bruising typically occurs over bony prominences • Unusual bruising: bruises NOT confined to bony prominences or in unusual places (eg, soles or palms) may raise concerns of abuse • Bruises that are larger or more numerous, and especially if palpable: consideration may be given to a hematologic defect as the underlying cause (eg, von Willebrand disease, acquired factor VIII inhibitor)
Progressive pigmented purpuras	<ul style="list-style-type: none"> • Characteristic collection of progressive purpuric lesions around the legs 	<ul style="list-style-type: none"> • Dermatologic conditions with no known underlying cause • CBC and immunologic test result normal • No known sequelae; treatment is cosmetic • Upon biopsy: absence of leukocytoclastic vasculitis; many display mononuclear pericapillaritis
Purpura associated with abnormalities of platelets		
Most commonly a result from mild trauma with profound thrombocytopenia ($\leq 20,000/\mu\text{L}$); also associated with qualitative platelet defects		
Thrombocytopenic purpura (autoimmune)	<ul style="list-style-type: none"> • Spontaneous purpura and epistaxis most frequently seen in severe thrombocytopenia • Petechial hemorrhage is the clinical hallmark of acute ITP 	<ul style="list-style-type: none"> • Platelet count $< 10,000/\text{dL}$



Classification of purpura or microvascular lesion	Appearance and location of bruising	Diagnostic criterion or clues
Purpura associated with abnormal platelet function	<ul style="list-style-type: none"> • Purpura or epistaxis due to platelet dysfunction 	<ul style="list-style-type: none"> • Use of antiplatelet agents: aspirin or newer agents used for ischemic heart disease (see Table III) • Use of dietary supplements; especially with an underlying platelet defect (see Table IV) • Congenital defects: Bernard-Soulier syndrome or Glanzmann's thrombasthenia (life-long history of bleeding)
Cutaneous vasculitis	<ul style="list-style-type: none"> • Palpable purpura 	<ul style="list-style-type: none"> • One of most common causes of nonthrombocytopenic purpura • Frequently associated with significant underlying medical disease • Main clinical attribute is palpable purpura • Histologic hallmark: leukocytoclastic vasculitis • Normal results for nearly all routine labs (eg, CBC, coagulation profile, serum studies for cryoglobulins, serologic studies for ANAs, serum complement levels, and ANCA); except, sedimentation rate is substantially elevated in most cases. • Causes are many; characterized as rheumatologic in origin and associated with requisite immune complexes • Majority of adult cases are from primary causes: idiopathic, upper respiratory viral or bacterial infection, and hypersensitivity to drugs such as penicillin, iodine, aspirin, antibiotics, analgesics, NSAIDs, thiazides, colchicine • Most common secondary causes in adults include: lupus erythematosus, cryoglobulinemia, chronic hepatitis C, Sjögren syndrome, polyarteritis nodosa, Churg-Strauss syndrome, rheumatoid arthritis, subacute bacterial endocarditis
Purpura associated with microbial endothelial damage Caused by residence and proliferation or direct attack by microorganisms		
Rickettsial disease	<ul style="list-style-type: none"> • Petechial rash may be detected the first day of illness, but more often third or fourth day • Spots become larger (5-6 mm diameter) than most petechiae and may have vague border that blend into erythema • Spots may appear on palms and soles 	<ul style="list-style-type: none"> • Rocky Mountain spotted fever by far the most common cause
Leptospiral disease	<ul style="list-style-type: none"> • Petechial rash 	<ul style="list-style-type: none"> • Petechial rash, sometimes modest thrombocytopenia, and DIC
Parvovirus B19 Infection	<ul style="list-style-type: none"> • Self-limiting "socks and gloves" petechial rash 	<ul style="list-style-type: none"> • Skin biopsy shows no evidence of vasculitis
Viral hemorrhagic fevers	<ul style="list-style-type: none"> • Petechiae • Hemorrhage in multiple organs 	<ul style="list-style-type: none"> • Global distribution in remote areas • Bleeding and accompanied thrombocytopenia or DIC
Purpura associated with decreased microvascular mechanical strength		
Scurvy	<ul style="list-style-type: none"> • Bleeding is characterized by perifollicular hemorrhage; large-huge, flat, plate-like ecchymoses; and hypertrophic spongy, bleeding gums 	<ul style="list-style-type: none"> • Diagnosed by its appearance
Hypercortisolism	<ul style="list-style-type: none"> • Purpura seen primarily on the extensor surfaces of the forearms and is the presenting sign in 25% of cases 	<ul style="list-style-type: none"> • Result of hypercortisolism
Senile, atrophic, or actinic purpura	<ul style="list-style-type: none"> • Purpura on the extensor surfaces of the forearms is characteristic, especially for those who work outdoors without adequate skin protection. 	<ul style="list-style-type: none"> • Hemostasis is normal • Skin is extremely thin in affected areas and if biopsied the dermal-epidermal junction will be thin and flattened • Slight trauma or stretching of the skin can physically rupture the skin with subcutaneous bleeding as a result • Common in older and debilitated individuals • Sometimes seen in healthy individuals with excessive exposure to the sun
Heritable disorders of connective tissue	<ul style="list-style-type: none"> • Large vessel hemorrhage • Subcutaneous hemorrhage may also occur, but is not of diagnostic importance 	<ul style="list-style-type: none"> • Bleeding as a result of tearing fragile subcutaneous tissues and skin as the result of spontaneous purpuric lesions. • No persistent coagulation or platelet abnormality • Healing is impaired



Classification of purpura or microvascular lesion	Appearance and location of bruising	Diagnostic criterion or clues
Amyloidosis	<ul style="list-style-type: none"> Purpuric bleeding with somewhat unusual distribution along pressure points, particularly in the periorbital area 	<ul style="list-style-type: none"> Coagulation abnormalities are frequent, multiple, and of varying patterns of amyloidosis, which can confound an accurate cause of the purpura (ie, deposition of amyloid)
Purpura associated with microthrombi		
Disseminated intravascular coagulation	<ul style="list-style-type: none"> Purpuric skin lesions and frank purpura fulminans 	<ul style="list-style-type: none"> Fibrin deposition in microcirculation Multiorgan dysfunction syndrome Abnormal coagulation studies and platelet count
Warfarin skin necrosis	<ul style="list-style-type: none"> Preceded by stinging or burning sensation ~ 2-4 days after initiation of warfarin therapy; site becomes hemorrhagic 1-2 days later More frequent in women than men (9:1), and develops in areas where generous adipose tissue is found (ie, thighs, buttocks, breasts). If not promptly treated, site become necrotic and appears as a large burn eschar 	<ul style="list-style-type: none"> Upon biopsy, fibrin deposition is prominent in dermal microcirculation
Fat embolism syndrome	<ul style="list-style-type: none"> Petechiae with unusual distribution scattered about the neck, shoulders, and axillary folds in the upper chest area; occasionally in conjunctivae 	<ul style="list-style-type: none"> Diagnosed based on presence and location of petechiae (60% of cases); shortness of breath (50% of cases) Fever is characteristic Peak incidence ~24-72 h after traumatic event. Associated with trauma: seen in 10-20% of all trauma cases when sought, specifically in cases of trauma and hypoxemia Seen in up to 60% autopsies involving blunt trauma
Blue toe syndrome, purple toe syndrome, and cholesterol emboli syndrome	<ul style="list-style-type: none"> Purple or blue discoloration of the toes Necrosis of toes and feet and significant soft tissues areas of the legs, or lower flank and back 	<ul style="list-style-type: none"> Occur during heparin or warfarin administration, following abdominal trauma or cardiac catheterization, or spontaneously All patients have significant underlying atherosclerosis and if lesions are biopsied cholesterol crystals in arterioles seen Differential diagnosis should focus on the arterial system: echocardiography with aortic arch, imaging aorta; ankle-to-brachial pressure index
Purpura associated with vascular malignancy		
Associated with AIDS	<ul style="list-style-type: none"> Most common form is Kaposi sarcoma: ecchymotic-appearing macular lesion that progresses to plaque or nodular lesions 	<ul style="list-style-type: none"> Key to diagnosis: early purpuric Kaposi sarcoma lesion does not blanch on external pressure Diagnosis may depend on biopsy, and can be done without risk of hemorrhage
Other hematovascular findings of hematologic interest		
Livedo reticularis	<ul style="list-style-type: none"> Dusky, ill-defined violaceous reticular pattern seen on legs and occasionally arms; some resemblance to blue/purple fishnet stockings 	<ul style="list-style-type: none"> May appear transiently in normal individuals in a cool environment; sometimes seen in lupus erythematosus, antiphospholipid antibody syndrome and other rheumatic disorders
Urticarial vasculitis	<ul style="list-style-type: none"> Similar appearance to typical urticaria, but with a substantial vasculitic component 	<ul style="list-style-type: none"> Lasts > 24 hours, painful, sometimes burning sensation; when lesions are clear some residual purpura is seen Can be associated with hypocomplementemia
Hemangiomas	<ul style="list-style-type: none"> Soft bluish tumors common in infants and spontaneously regresses Some are persistent, huge, cavernous and require aggressive treatment 	<ul style="list-style-type: none"> Can appear anywhere in the body, most commonly on the scalp, face, chest or back
Cherry angiomas	<ul style="list-style-type: none"> Small (1-3 mm), cherry-red, domed papules over upper abdomen and lower chest that occur in second-half of life 	<ul style="list-style-type: none"> Do not blanch as easily or completely as telangiectasias of HHT syndrome
Spiders	<ul style="list-style-type: none"> 1-3 cm legs that radiate from a 1-2 mm central body 	<ul style="list-style-type: none"> Gentle pressure collapses spider and legs Seen in aging, cirrhosis, and pregnancy
Erythema	<ul style="list-style-type: none"> Reddening of skin, notably on the face; no clear borders 	<ul style="list-style-type: none"> Blanches with pressure or application of cold May be result of hot environment, hyperthermia, fever, mild viral infection, or emotional reaction



Figure 1. Representative pictures of **A)** Senile purpura. **B)** Typical non-traumatic hematoma of soft tissue in an elderly individual with acquired hemophilia A. **C)** Subcutaneous hematoma from pressure from the brassiere in a patient with acquired hemophilia A. **D)** Extensive hand hematoma after venipuncture in a patient with acquired hemophilia A. **E)** Petechiae in a patient with immune thrombocytopenia (ITP) with platelet count $< 10,000$.

in women^{5,6}. The underlying cause of senile purpura is fragile skin due to aging, although secondary causes include solar damage, genetics, and long-term use of corticosteroids. These lesions may or may not be related to trauma as many older adults do not recall causative events⁷. Recommendations for prevention include protection from the sun, emollients, and adequate protein intake⁷.

Purpura simplex is due to blood vessel fragility and medication use irrespective of age. Mild day to day trauma can lead to purpura simplex, where small bruises associated with daily living appear over bony prominences. However, when bruising is not confined over bony prominences or appears in unusual places, it may be worth considering abuse. Abuse is more common when bruises are on the head, neck trunk and buttocks as opposed to extremities. Bruises due to abuse are more likely to be 5 cm or larger. The color of the bruise is not helpful in timing the traumatic event with accidental bruises or those associated with abuse⁸. Notably, when bruises are larger or more numerous, or develop into hematomas, an underlying hematologic defect should be considered and include such disorders as undiagnosed congenital moderate/mild hemophilia A or an acquired inhibitor against a coagulation factor (ie, FVIII or von Willebrand factor).

Acquired hemophilia is a rare (1-1.48 in 1 million⁹), but severe bleeding disorder that occurs when autoantibodies develop against clotting factors¹⁰, the most common of which is directed against FVIII¹¹. Patients with acquired hemophilia often present with large areas of subcutaneous hemorrhage (Fig. 1), which can be spontaneous or result from mild trauma or invasive procedures¹. Compartment syndrome can develop rapidly in acquired hemophilia when bleeding occurs into soft tissues¹². The bleeding pattern of acquired hemophilia is distinct from that of congenital hemophilia where bleeding occurs mostly in joints and appears in the form of a true hematoma. Acquired hemophilia is seen most commonly in the elderly population, with the exception in younger women of childbearing age¹³. Increasing age has been shown to be an independent predictor of death in people with acquired hemophilia^{9,13,14}, with those < 76.3 years at 16%, but 43% for those who are > 76.3 years¹³. The mortality rate may even be underestimated because, at least in part, data in the literature largely comes from centers of expertise where mortality rates would be expected to be lower than elsewhere. The European Acquired Hemophilia (EACH-2) registry is by far the largest prospective study of acquired hemophilia to date and included data from 501 patients (53 male, 47% female) with a median age at diagnosis of 73.9 years (IQR, 61.4-80.4 years) from 117 different centers in 13 countries¹³. The most common symptoms

of acquired hemophilia in the EACH-2 registry were subcutaneous bleeding (purpura) and soft tissue bleeds, including bleeding into skin (53%), musculoskeletal and retroperitoneal bleeding (50%), and mucosal bleeding (32%)¹³. While most bleeds were spontaneous (77%), some were attributed to trauma (8%), surgery (8%), and the peripartum period (4%)¹³. Similar findings were reported from the Hemostasis and Thrombosis Research Society (HTRS) registry, with the most common site of bleeding being subcutaneous bleeding (40%) followed by mucosal bleeding (33%), and most bleeds were spontaneous (70%), with others associated with trauma (18%), followed by dental (2%), surgical (2%), and other medical procedures (4%)¹⁵. Finding from the EACH-2 registry showed that a delay in diagnosis can result in subsequent delay in the initiation of hemostatic treatment with up to 35% of patients being diagnosed more than 7 days after the initial bleeding episode; and of these, 67% had severe bleeding¹³. Overall, there is a high rate of mortality (more the 20%) associated with acquired hemophilia in the elderly^{12,13,16}, which usually occurs within the first few weeks of the onset of bleeding symptoms¹². Age-related comorbidities, medications, and frailty that are common in elderly patients contribute to the situation¹².

Purpura that is associated with quantitative platelet abnormalities is most commonly a result of mild trauma with profound thrombocytopenia ($\leq 20,000 \mu\text{l}$). Acute idiopathic thrombocytopenic purpura with a platelet count < 10,000 μl usually presents as petechial hemorrhage. Qualitative platelet defects can also present as purpura because of effects of antiplatelet agents used for ischemic heart disease, use of dietary supplement, mostly in conjunction with an underlying platelet defect, or on rare occasions from congenital defects such as Bernard-Soulier syndrome or Glanzmann's thrombasthenia¹.

Side effects of anticoagulants and NSAIDs, both frequently prescribed to older patients, are some of the most common causes of bleeding in the elderly^{17,18}. Notably, while newer oral anticoagulants are administered at fixed doses and have some advantages over warfarin, the response between patients is highly variable and there is no reliable method of monitoring their activity¹⁹. Chronic administration of anticoagulants, especially in combination with antiplatelet agents, has been shown to increase the risk of bleeding that can range from skin bruising to intracranial and fatal hemorrhages^{20,21}. Table II provides a list of the common pharmacologic anticoagulant agents with their mechanism of action and parameters for increased risk of bleeding. Approximately half the US adult population regularly consumes a dietary supplement²⁸, some of which can lead to exacerbate bleeding in combination with other

Table II. Pharmacologic anticoagulant agents and bleeding risk parameters (from Altman, 2014, mod.)¹⁹.

Pharmacologic anticoagulants	Mechanism of action	Increased-risk of bleeding parameters
Warfarin	<ul style="list-style-type: none"> Inhibits vitamin K oxide reductase and thereby reduces vitamin K activity 	<ul style="list-style-type: none"> Narrow therapeutic window Slow onset/offset of action Interactions with food and drugs Unpredictable response, requires systematic monitoring and frequent dose modifications
Antiplatelets		
Aspirin	<ul style="list-style-type: none"> Inhibits COX enzymes Inhibits platelet generation of thromboxane A2 Weak inhibitor of platelet aggregation 	<ul style="list-style-type: none"> Increased risk of bleeding when combined with another antiplatelet or anticoagulant Antiplatelet combinations significantly prolong bleeding time and increase incidence of subcutaneous hematomas and epistaxis
Clopidogrel	<ul style="list-style-type: none"> Inhibits ADP receptors on the platelets 	
Dipyridimole	<ul style="list-style-type: none"> Inhibits platelet aggregation via inhibition of adenosine deaminase and phosphodiesterase activity 	
Anagrelide	<ul style="list-style-type: none"> Phosphodiesterase inhibitor²² Inhibits maturation of platelets from megakaryocytes²³ 	
Ticagrelor	<ul style="list-style-type: none"> Inhibits platelet aggregation²⁴ P2Y12 receptor antagonist²⁴ 	
Vorapaxar	<ul style="list-style-type: none"> PAR-1 receptor antagonist²⁵ Inhibits thrombin-related platelet aggregation via inhibition of thrombin-related platelet aggregation²⁵ Does not affect ADP-mediated platelet aggregation, coagulation parameters, or bleeding time²⁵ 	<ul style="list-style-type: none"> Used in combination with either aspirin or clopidogrel Increased risk of intracranial hemorrhage²⁶
Anticoagulants w/antithrombin activity		
Heparin	<ul style="list-style-type: none"> Activates antithrombin, which inactivates thrombin, factor Xa, and other proteases, and thereby inhibits thrombin formation 	<ul style="list-style-type: none"> Bleeding is a common side effect Heparin-induced thrombocytopenia is a serious side effect
Dabigatran	<ul style="list-style-type: none"> Direct thrombin inhibitor 	<ul style="list-style-type: none"> Lack of an effective and reliable clotting assay to measure anticoagulation
Rivaroxaban	<ul style="list-style-type: none"> Direct inhibitor of free and clot-bound activated coagulation factor X and prothrombinase activity 	<ul style="list-style-type: none"> Lack of an effective and reliable clotting assay to measure anticoagulation
Apixaban	<ul style="list-style-type: none"> Direct inhibitor of free and clot-bound activated coagulation factor X, and prothrombinase activity²⁷ 	<ul style="list-style-type: none"> Lack of an effective and reliable clotting assay to measure anticoagulation
Edoxaban	<ul style="list-style-type: none"> Inhibitor of activated coagulation factor X, and prothrombinase activity 	<ul style="list-style-type: none"> Lack of an effective and reliable clotting assay to measure anticoagulation

pharmacologic treatments. Further, many patients do not inform their physicians about their use of supplements. Popular dietary supplements such as fish oil, Ginkgo biloba, ginger, ginseng, and vitamin E can interfere with hemostasis, and adversely affect coagulation alone or in combination with an anticoagulant or antiplatelet medications such as NSAIDs, clopidogrel, or aspirin²⁹. Commonly used natural products, dietary supplements, and herbs and their anticoagulant activity and risk of bleeding are shown in Table III.

The most common cause of nonthrombocytopenic purpura is cutaneous vasculitis, which presents with palpable purpura and has a histologic hallmark of leukocytoclastic vasculitis. The underlying causes are many, but are typically rheumatologic in origin and associated with requisite immune complexes¹. Other underlying causes of purpura are more readily

known or identifiable, and include association with microbial endothelial damage, decreased microvascular mechanical strength, microthrombi (including thrombotic thrombocytopenic purpura), vascular malignancy, and other findings of hematologic interest (see Table I)¹.

DIAGNOSTIC APPROACH

The differential diagnosis for purpura in an elderly patient without a previous history of bleeding or known underlying microvascular pathology should include a detailed review of the patient's medical history along with appropriate laboratory tests. Considerations of the unknown cause of purpura should be given to trauma, complications from anticoagulants or NSAIDs, autoimmune disorders, cancers, and bleeding disorders such as von

Table III. Dietary supplements: mechanism of action and risk of bleeding (from Stanger, 2012, mod.)²⁹.

Dietary supplements ^a	Mechanism of action on platelets	Increased-risk of bleeding parameters
Ginkgo biloba	<ul style="list-style-type: none"> • reduced platelet aggregation 	<ul style="list-style-type: none"> • Used in combination with warfarin, anti-platelet agents or NSAIDs: cases of spontaneous intracerebral hemorrhage, retrobulbar hemorrhage, subarachnoid hemorrhage, subdural hematoma, and spontaneous hyphema have been reported
Ginger	<ul style="list-style-type: none"> • Alters thromboxane synthesis • Inhibits arachidonic acid-induced platelet activation 	<ul style="list-style-type: none"> • No confirmed anticoagulant properties
Ginseng	<ul style="list-style-type: none"> • Reduced platelet aggregation 	<ul style="list-style-type: none"> • When higher than recommended doses used (rude preparations of dried root powder 1-2 g for up to 3 months)³⁰ • Used in combination with anticoagulants, anti-platelet agents and NSAIDs
Fish oil	<ul style="list-style-type: none"> • Reduced platelet aggregation • Increased bleeding time 	<ul style="list-style-type: none"> • Bleeding time may increase when used in combination with NSAIDs or other anticoagulants
Vitamin E	<ul style="list-style-type: none"> • Reduced platelet adhesion to endothelial cells • Prevents platelet aggregation • Increased bleeding time 	<ul style="list-style-type: none"> • High doses may inhibit platelet aggregation (alpha or gamma-tocopherol)
Curcumin	<ul style="list-style-type: none"> • Inhibits platelet aggregation³¹ • Inhibits formation of thromboxane A₂³¹ 	<ul style="list-style-type: none"> • Increase risk of bleeding when used in combination with anticoagulant or in those with bleeding disorders

^aThese supplements can cause bleeding during surgical procedures.

Willebrand disease, moderate and mild congenital hemophilia, acquired platelet disorders, and acquired factor deficiencies like acquired hemophilia A¹. In the case of malignancy, differential diagnosis is important and can be challenging with several more common reasons for bleeding, such as DIC, thrombocytopenia, and localized bleeding from tumor tissue³². The differential diagnosis of purpura should involve consultation with and or referral to a hematologist with expertise in diagnosis of bleeding disorders and other causes of purpura that may complicate an accurate diagnosis and potentially delay effective treatment, which in some cases could result in death. Consult with a dermatologist is also merited as causes of purpura can include dermatologic conditions. The differential diagnosis process should start with a complete blood count and blood smear, along with prothrombin time (PT), partial thromboplastin time (PTT) and thrombin time (TT). Should these initial tests be inconclusive, then additional analyses such as fibrinogen level, platelet aggregation and analyses for fibrin degeneration products and D-dimers should be conducted. In obscure cases, blood cultures, viral studies, and even bone marrow biopsy may be warranted¹. Determining the underlying cause of purpura in an elderly patient with a malignancy can be difficult due to the number of potential causes^{33 34}. The potential underlying causes range from pre-existing conditions to cancer treatments or even the malignancy itself³². Causes of purpura due to the malignancy include thrombocytopenia resulting from bone marrow infiltration or

trauma to friable and/or highly vascularized malignant tissues³². Further, many chemotherapeutic agents are myelosuppressive, leading to thrombocytopenia and conditions (eg, infection and sepsis) that trigger DIC³². Notably, DIC is the most common cause of bleeding in the setting of malignancy³². On rare occasions, bleeding in patients with cancer results from the development of coagulation factor VIII inhibitors (ie, acquired hemophilia). In approximately 50% of cases, acquired FVIII inhibitors develop in patients with other underlying conditions, including malignancies³⁵. In the case of acquired hemophilia A, there are 3 important clues to consider for diagnosis: 1) new onset of bruising or bleeding, 2) no previous history of bruising or bleeding, and 3) an isolated prolonged PTT with normal results for thrombin and prothrombin times and platelet count. Similar test results can be seen with presence of a lupus anticoagulant, except that these patients usually do not present with bleeding symptoms. In the contrary, many of them will have thrombosis and/or miscarriages. The next step after having a prolonged PTT is performing a mixing study of the PTT with normal plasma. This test can be easily done in most laboratories that are performing basic coagulation tests. It is recommended to do an immediate (baseline) PTT followed by a PTT after an hour incubation at 37 C because some antibodies are time and temperature dependent. If the mixing study fully corrects the PTT, it is indicative of a deficiency of a coagulation factor in the intrinsic pathway (eg, FVIII, FIX, FXI, FXII). However, if the PTT does not correct, one

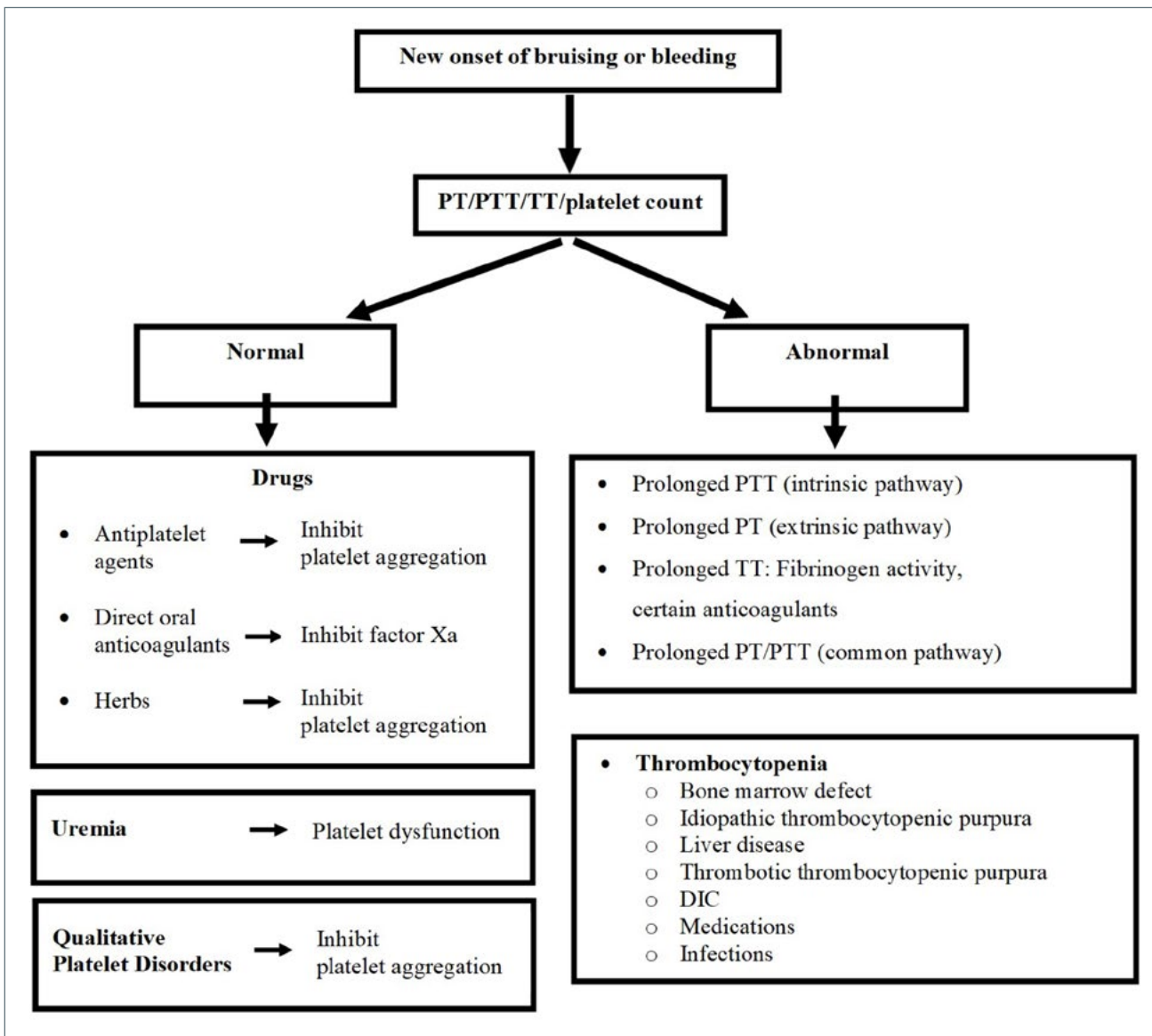


Figure 2. Clinical algorithm.

must consider the presence of an antibody against FXII, FXI, FIX, FVIII or a lupus anticoagulant. At this point in the differential diagnosis, analysis of specific factor levels can be performed. It is not usual for antibodies against FVIII to have a partial correction of the immediate PTT with a prolongation of this test after an hour incubation at 37°C. Lupus antibodies do not usually show this behavior. It should also be noted that heparin and direct oral anticoagulants (see Table II) may interfere with laboratory test results and can resemble FVIII inhibitors, thereby confounding laboratory test results and warrant specialized tests for exclusion^{36 37}. Measuring thrombin time may differentiate the effects of direct thrombin inhibitors from acquired FVIII inhibitors³⁷. Further, an anti-FXa assay

may differentiate the effects of anticoagulants that inhibit factor Xa from FVIII inhibitors³⁷. A clinical algorithm can be seen in Figure 2, and differential diagnostic approach when an acquired factor VIII inhibitor is suspected can be found in Figure 3.

THERAPEUTIC INTERVENTION

Treatment for many cases of purpura does not require hematologic intervention, while in other cases it is warranted. Regardless, the appropriate course of treatment requires an accurate diagnosis of the underlying cause of purpura. In many cases, a hematologist and

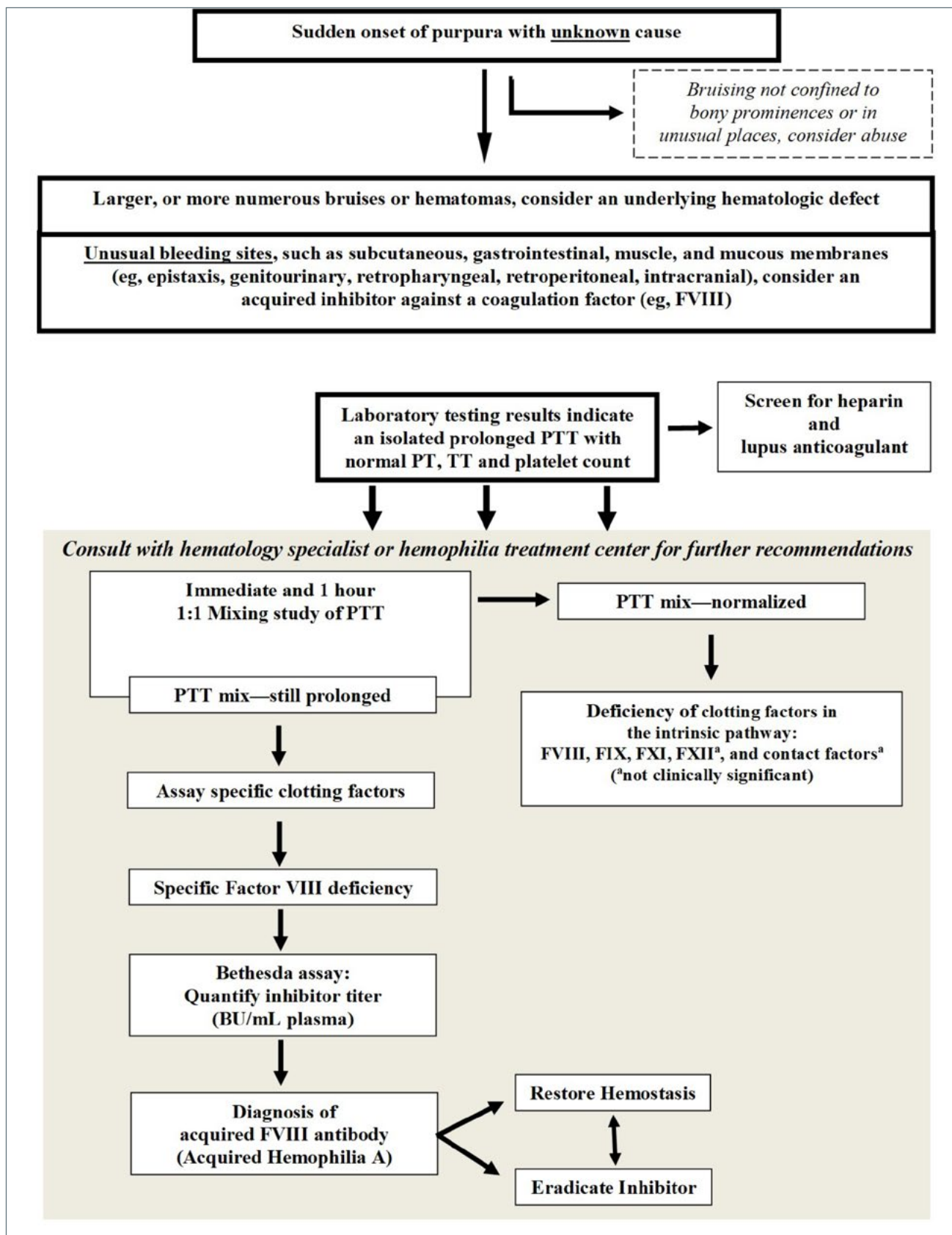


Figure 3. Differential diagnosis of acquired hemophilia A.

Table IV. General treatment approaches to nontraumatic purpura (from Zumberg, Kitchens, 2007, mod.)¹.

Treatment approach	Diagnosis
No hematologic treatment	Purpura simplex, progressive pigmented purpuras, primary cutaneous vasculitis
Hematologic treatment	Immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation
Nonhematologic treatment <i>Psychiatric evaluation</i> <i>Rheumatologic evaluation</i> <i>Antibiotics</i> <i>Dietary management</i>	Factitious purpura Secondary CV RMSF, subacute bacterial endocarditis, meningococemia Scurvy

dermatologist should be consulted in the differential diagnosis of the underlying cause of purpura. Table IV shows 3 general treatment approaches depending on the diagnosis of purpura.

In a case of acquired hemophilia, there are 2 treatment strategies undertaken. First, bypassing agents (ie, bypass the factors that are blocked by the inhibitor) or recombinant porcine FVIII are used to manage the acute bleeding, and then in most cases immunosuppressive therapy should be used to eradicate the antibody³⁸. Care should be taken when undergoing immunosuppressive therapy, as neutropenia is a serious concern in elderly patients who are often susceptible to infection because of underlying comorbidities.

PREVENTION

While purpura itself in many cases cannot be prevented, the morbidity and mortality associated with various causes of purpura can be reduced and even prevented with timely diagnosis and appropriate management. Upon presentation, proper diagnosis of the underlying cause of purpura in the older or elderly patient is often complicated by chronic comorbidities and medications that confound laboratory tests, among other reasons that are inherent in the elderly population. A key to a timely and accurate diagnosis, and prevention of unnecessary morbidity and mortality is awareness of rare conditions, such as acquired hemophilia A, and inclusion of an expert in bleeding disorders when one is suspected^{1 12 36}.

Generally, coagulation tests are not recommended for routine preoperative screening. A PT and PTT are indicated for patients with a history of bleeding disorders, on medications affecting coagulation like warfarin, or on hemodialysis. According to the American College of Surgery's National Surgical Quality Improvement Project with the American Geriatric Society, preoperative screening is indicated in patients undergoing "high risk procedures that involve arterial reconstruction, cardiac surgery, cancer operations, and ones in which small

amounts of bleeding can cause dramatic complications (neurosurgical or orthopedic spine procedures)". In addition, the prothrombin time is also indicated in patients with malnutrition, malabsorption, or liver disease³⁹.

SUMMARY AND CONCLUSIONS

Diagnosis of the underlying cause of nontraumatic purpura can be challenging in the elderly who often have additional chronic comorbid conditions that may require pharmacologic treatment that can also complicate laboratory testing. A multidisciplinary team of those experienced with identification of the underlying causes of purpura and subsequent treatment include a laboratory specialist, and, if a bleeding disorder is suspected, a hematologist with experience in diagnosing and treating patients with rare bleeding disorders such as acquired hemophilia A. Use of a detailed patient history, appearance and location of purpura, and laboratory findings are all important tools in the differential diagnosis process. Prompt diagnosis and treatment are key to a good outcome, as delays in the diagnosis of acquired hemophilia A often result in severe bleeding and high morbidity and mortality that otherwise could be avoided. Raising awareness of acquired hemophilia A among those who care for the elderly may lead to a more timely and accurate diagnosis and appropriate acute and long-term management.

CONFLICT OF INTEREST

Dr. Escobar has served as an advisory board participant, study investigator, and/or consultant for Bayer, CSL Behring, Genentech, Novo Nordisk, Pfizer, and Shire. Dr. Dyer has no conflicts of interest.

AUTHOR'S CONTRIBUTIONS

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Both authors, MAE and CBD, had substantial contributions to conception and design of this manuscript; and, the drafting of the outline and

subsequent drafts of the article, and critically revising it for important intellectual content; and reviewed and approved the final version for submission and to be published.

Independent editorial and medical writing support was provided by James Loss, PhD, and funded by the University of Texas Health Science Center at Houston.

References

- Zumberg M, Kitchens CS. *Purpura and other hematovascular disorders*. In: Kitchens CS, Alving BM, Kessler KM, Eds. *Consultative hemostasis and thrombosis*. 2th ed. Philadelphia, PA: Saunders, an imprint of Elsevier Inc. 2007, pp. 159-82.
- Mauer AC, Khazanov NA, Levenkova N, et al. *Impact of sex, age, race, ethnicity and aspirin use on bleeding symptoms in healthy adults*. *J Thromb Haemost* 2011;9:100-8.
- Wahlberg T, Blomback M, Hall P, et al. *Application of indicators, predictors and diagnostic indices in coagulation disorders. I. Evaluation of a self-administered questionnaire with binary questions*. *Methods Inf Med* 1980;19:194-200.
- Sramek A, Eikenboom JC, Briet E, et al. *Usefulness of patient interview in bleeding disorders*. *Arch Intern Med* 1995;155:1409-15.
- Kaya G, Saurat JH. *Dermatoporosis: a chronic cutaneous insufficiency/fragility syndrome. Clinicopathological features, mechanisms, prevention and potential treatments*. *Dermatology* 2007;215:284-94.
- Reszke R, Pelka D, Walasek A, et al. *Skin disorders in elderly subjects*. *Int J Dermatol* 2015;54:e332-8.
- Dyer JM, Miller RA. *Chronic skin fragility of aging: current concepts in the pathogenesis, recognition, and management of dermatoporosis*. *J Clin Aesthet Dermatol* 2018;11:13-8.
- Mosqueda L, Burnight K, Liao S. *The life cycle of bruises in older adults*. *J Am Geriatr Soc* 2005;53:1339-43.
- Collins PW, Hirsch S, Baglin TP, et al. *Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation*. *Blood* 2007;109:1870-7.
- Collins P, Baudo F, Huth-Kuhne A, et al. *Consensus recommendations for the diagnosis and treatment of acquired hemophilia A*. *BMC Res Notes* 2010;3:161.
- Coppola A, Favalaro EJ, Tufano A, et al. *Acquired inhibitors of coagulation factors: part I-acquired hemophilia A*. *Semin Thromb Hemost* 2012;38:433-46.
- Giangrande P. *Acquired hemophilia*. Montréal, Québec, Canada: World Federation Hemophilia 2012, pp. 1-7.
- Knoebel P, Marco P, Baudo F, et al. *Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)*. *J Thromb Haemost* 2012;10:622-31.
- Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, et al. *Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors*. *Br J Haematol* 2003;121:21-35.
- Ma AD, Kessler CM, Al-Mondhry HA, et al. *Use of recombinant activated factor VII for acute bleeding episodes in acquired hemophilia: final analysis from the Hemostasis and Thrombosis Research Society Registry acquired hemophilia study*. *Blood Coagul Fibrinolysis* 2016;27:753-60.
- Bitting RL, Bent S, Li Y, et al. *The prognosis and treatment of acquired hemophilia: a systematic review and meta-analysis*. *Blood Coagul Fibrinolysis* 2009;20:517-23.
- Barkin RL, Beckerman M, Blum SL, et al. *Should nonsteroidal anti-inflammatory drugs (NSAIDs) be prescribed to the older adult?* *Drugs Aging* 2010;27:775-89.
- Love DG. *Management of hemorrhagic events in patients receiving anticoagulant therapy*. *J Thromb Thrombolysis* 1999;7:149-52.
- Altman R. *New oral anticoagulants: are coagulation units still required?* *Thrombosis Journal* 2014;12:3.
- Alexander JH, Lopes RD, James S, et al. *Apixaban with antiplatelet therapy after acute coronary syndrome*. *N Engl J Med* 2011;365:699-708.
- Altman R, Rivas AJ, Gonzalez CD. *Bleeding tendency in dual antiplatelet therapy with aspirin/clopidogrel: rescue of the template bleeding time in a single-center prospective study*. *Thrombosis Journal* 2012;10:3.
- Petrides PE. *Anagrelide: what was new in 2004 and 2005?* *Semin Thromb Hemost* 2006;32(4 Pt 2):399-408.
- Jones GH, Venuti MC, Alvarez R, et al. *Inhibitors of cyclic AMP phosphodiesterase. 1. Analogues of cilostamide and anagrelide*. *J Medicinal Chemistry* 1987;30:295-303.
- Jacobson KA, Boeynaems JM. *P2Y nucleotide receptors: promise of therapeutic applications*. *Drug Discovery Today* 2010;15:570-8.
- Baker NC, Lipinski MJ, Lhermusier T, et al. *Overview of the 2014 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee meeting about vorapaxar*. *Circulation* 2014;130:1287-94.
- Morrow DA, Alberts MJ, Mohr JP, et al. *Efficacy and safety of vorapaxar in patients with prior ischemic stroke*. *Stroke* 2013;44:691-8.
- Frost C, Nepal S, Wang J, et al. *Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects*. *Brit J Clin Pharmacol* 2013;76:776-86.
- Radimer K, Bindewald B, Hughes J, et al. *Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000*. *Am J Epidemiol* 2004;160:339-49.
- Stanger MJ, Thompson LA, Young AJ, et al. *Anticoagulant activity of select dietary supplements*. *Nutr Rev* 2012;70:107-17.
- Blumenthal M, Gruenwald J, Hall T, et al., Eds. *The complete German commission e monographs: therapeutic monographs on medicinal plants for human use*. Austin, TX: American Botanical Council 1997.
- Shah BH, Nawaz Z, Pertani SA, et al. *Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor- and arachidonic acid-mediated platelet aggregation*

- through inhibition of thromboxane formation and Ca²⁺ signaling. *Biochemical Pharmacol* 1999;58:1167-72.
- ³² Escobar MA. *Bleeding in the patient with a malignancy: is it an acquired factor VIII inhibitor?* *Cancer* 2012;118:312-20.
- ³³ Green D. *Management of bleeding complications of hematologic malignancies.* *Semin Thromb Hemost* 2007;33:427-34.
- ³⁴ Mannucci PM. *Overview of bleeding in cancer patients.* *Pathophysiol Haemost Thromb* 2003;33(Suppl 1):44-5.
- ³⁵ Franchini M, Gandini G, Di Paolantonio T, et al. *Acquired hemophilia A: a concise review.* *Am J Hematol* 2005;80:55-63.
- ³⁶ Kruse-Jarres R, Kempton CL, Baudo F, et al. *Acquired hemophilia A: updated review of evidence and treatment guidance.* *Am J Hematol* 2017;92:695-705.
- ³⁷ Tiede A, Werwitzke S, Scharf RE. *Laboratory diagnosis of acquired hemophilia A: limitations, consequences, and challenges.* *Semin Thromb Hemost* 2014;40:803-11.
- ³⁸ Huth-Kuhne A, Baudo F, Collins P, et al. *International recommendations on the diagnosis and treatment of patients with acquired hemophilia A.* *Haematologica* 2009;94:566-75.
- ³⁹ *ACS NSQIP®/AGS BEST PRACTICE GUIDELINES: optimal preoperative assessment of the geriatric surgical patient, 2012* (Accessed August 27, 2018).

How to cite this article: Escobar MA, Dyer CB. *Differential diagnosis of nontraumatic purpura in the elderly – Have you considered acquired hemophilia?* *Journal of Gerontology and Geriatrics* 2019;67:168-80.

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REVIEW

Gait Speed test in physically frailty patients with ST-segment elevation myocardial infarction

P. Mone¹, F. Minicucci², A. Pansini², M. Rizzo³, M. Carbonella³, C. Mauro²

¹ Department of Medical, Surgical, Neurological, Aging and Metabolic Sciences, University of the Study of Campania "Luigi Vanvitelli", Naples, Italy;

² Department of Emergency, Cardarelli Hospital, Naples, Italy; ³ Department of Emergency, Maria SS Addolorata Hospital, Eboli, Italy

Coronary artery disease (CAD) is the most frequent cause of death worldwide and, approximately. Age is an important determinant of outcomes for patients with ST-segment elevation myocardial infarction (STEMI). Older adults are at particular risk of developing frailty, a biological syndrome of decreased physiological reserves resulting in increased vulnerability to stressors. When exposed to such stressors, frail patients are at risk for decompensation, adverse events, procedural complications, prolonged recovery, functional decline, disability and mortality. Frailty has become a priority section in cardiovascular medicine because of the aging and the comorbidities of these patients. There is no upper age limit with respect to reperfusion, especially with PPCI. In a 2013 study, Yasushi Matsuzawa et al. evidenced that slow gait speed was strongly associated with future cardiovascular events in STEMI patients who underwent successful primary percutaneous coronary intervention (PPCI). On the basis of existing literature, we may speculate that STEMI patients with frailty should be studied with 5 metres gait speed test before hospital discharge, for a better evaluation of physical status. The results of the test might indicate how to set the pharmacological strategy, cardiac rehabilitation and the time of follow-up, for improving quality of life of the patients, reducing mortality and hospitalization.

Key words: Gait Speed Test, STEMI, Frailty

BACKGROUND

Coronary artery disease (CAD) is the most frequent cause of death worldwide and, approximately, accounts for 1.8 million annual deaths in Europe, with natural variations between countries ¹. The relative incidence of ST-segment elevation myocardial infarction (STEMI) is decreasing but mortality and hospitalization for acute coronary syndrome (ACS) continue to be elevated ¹. The mortality in STEMI patients is influenced by many factors, among them: advanced age, Killip class, time delay to treatment, presence of emergency medical system (EMS)-based STEMI networks, treatment strategy, history of ACS, diabetes mellitus, renal failure, number of diseased coronary arteries and left ventricular ejection fraction (LVEF).

In particular, age is an important determinant of outcomes for patients with STEMI.

In fact, medically and surgically treated cardiovascular disease (CVD) lead the patients to a frailty status, but many patients are already frail before CVD ².

Older adults are at particular risk of developing frailty, a biological syndrome of decreased physiological reserves resulting in increased vulnerability to stressors. Stressors are broadly classified as acute or chronic illness (e.g., myocardial infarction) or iatrogenic (e.g., cardiac surgery) ^{2,3}. When exposed to such stressors, frail patients are at risk for decompensation, adverse events, procedural complications, prolonged recovery, functional decline, disability and mortality. Frailty has become a priority section in cardiovascular medicine because of the aging and the comorbidities of these patients ².

■ Received: February 11, 2019 - Accepted: March 21, 2019

■ Correspondence: Pasquale Mone, Department of Medical, Surgical, Neurological, Aging and Metabolic Sciences, University of the Study of Campania "Luigi Vanvitelli", piazza Miraglia 2, 80138 Naples, Italy. Tel. +39 081 5665110. E-mail: pasqualemone@hotmail.it

In the general critical care setting, about one-third of older adults are frail and frailty is associated with increased morbidity, mortality, and resource use, such as length of critical care unit stay and readmission rate^{2,4}. The adverse outcomes associated with frailty and CAD are clearly demonstrated in the existing literature and it is known that frailty patients with CAD have an higher risk of death and re-hospitalization for CVD.

FRAILITY ASSESSMENT

There are over 20 frailty tools to measure frailty. Most tools focus on 1 or more of the 5 core domains that define the frailty phenotype: slowness, weakness, low physical activity, exhaustion, and shrinking. Slowness is measured by a comfortable-pace gait speed test, weakness by a maximal handgrip strength test (using a dynamometer), and other domains by questionnaire or more specialized instruments⁵.

These domains may be considered individually or combined into a variety of scales. The Fried scale encompasses slowness, weakness, low physical activity, exhaustion, and shrinking (unintentional weight loss), with ≥ 3 of 5 criteria required for a diagnosis of frailty. This is the most frequently cited frailty scale and has been demonstrated to predict mortality and disability in large cohorts of elderly patients with CVD.

Whether cognition and mood should be considered as the sixth and seventh domains of frailty or as modulating factors remains an area of discussion^{5,6}.

There is a large and increasing body of evidence indicating that the prognosis of older patients is strongly related to the presence of concomitant diseases and to the degree of physical, cognitive, biological, and social impairment⁶⁻¹⁰. A multidimensional assessment is known to be useful for evaluating prognosis in these subjects^{8,10}.

The Short Physical Performance Battery (SPPB) encompasses slowness, weakness, and balance.

This is measured by a series of 3 timed physical performance tests (gait speed, chair rises, and tandem balance), each is scored 0 to 4 and a total score ≤ 5 of 12 is required for a diagnosis of frailty. In contrast to these multi-item frailty scales, 5-metres gait speed test has been proposed as a single-item measure of physical frailty¹¹.

FRAILITY STATUS WITH CARDIOVASCULAR DISEASES PROGNOSIS

Frail patients with CVD have a worse prognosis than non-frail patients. In 2011 study, 628 patients ≥ 65 years who underwent PCI at the Mayo Clinic, 3-year

mortality was 28% for frail patients compared with 6% for non-frail patients using the Fried criteria^{12,13}.

Frailty is strongly and independently associated with a risk for short-term outcomes for elderly Non ST-segment Elevation Myocardial Infarction) NSTEMI patients, including in-hospital mortality, 1-month mortality, prolonged hospital care^{14,15}.

Identifying frailty has important implications for clinical care. The presence of frailty, worse health status, and more comorbid conditions identify a subset of elderly patients at higher risk of dying during the follow-up, even after a successful procedure⁵.

The magnitude of risk associated with the frailty, comorbidity, and poor quality of life is greater than predicted from the risk models derived from conventional risk variables.

Identifying frailty can also prompt more comprehensive geriatric evaluation, and interventions to improve functional status. Reducing frailty is likely to both improve clinical outcomes and decrease healthcare utilization and costs⁵. Frailty is a strong predictor of mortality in patients with chronic heart failure. In patients admitted to hospital with acute decompensated heart failure, simple measures of physical function have been associated with length of hospital stay, reduced activities of daily living, higher readmissions, and mortality¹⁶⁻¹⁸.

In patients with severe symptomatic aortic stenosis treated by TAVR, frailty predicts need for institutional care and mortality 6–12 months after a successful procedure¹⁹⁻²¹.

FRAILITY STATUS AND STEMI

Frail patients receive lower rates of invasive cardiac care during ACS hospitalization. In a 2018 study, the investigators utilized the CONCORDANCE registry database to report the prevalence of frailty in older adults presenting with ACS²².

Increased frailty was independently associated with increased postdischarge all-cause mortality but not cardiac-specific mortality²⁻⁴. These findings inform identification of frailty during ACS hospitalization as a potential opportunity to address competing risks for mortality in this high-risk population. The SILVER-AMI Study evaluated the impact of frailty alongside other risk factors in older adults hospitalized with acute myocardial infarction (AMI), for creating a more personalized assessment of risk and identify potential targets for interventions²³.

In a 2013 study, Yasushi Matsuzawa et al. evidenced that slow gait speed was strongly associated with future cardiovascular events in STEMI patients who underwent successful primary percutaneous coronary intervention (PPCI)²⁴.

These findings indicated that the clinical assessment of gait speed could identify the subsets of patients at a higher risk for cardiovascular events after STEMI²⁴. Interestingly, in a 2010 and 2016 study, Afilalo J. et al. showed how gait speed test may predict mortality in older adults, after cardiac surgery^{25,26}. Therefore, it should be consequential to correlate gait speed test to STEMI evaluation for better tailoring therapy and setting follow-up.

TREATMENT IN FRAILTY STEMI

The leading therapeutic choice in frailty patients with STEMI is PPCI but these patients may present with atypical symptoms, the diagnosis of STEMI may be delayed or missed. In addition, the elderly have more comorbidities and are less likely to receive reperfusion therapy compared with younger patients^{27,28}.

Elderly and frailty patients are also at particular risk of bleeding and other complications from acute therapies because bleeding risk increases with age, renal function tends to decrease, and the prevalence of comorbidities is strong. Observational studies have shown frequent excess dosing of antithrombotic therapies in elderly and frailty patients^{29,30}. These observational studies, principally focused their attention on NSTEMI but they describe in STEMI too.

Furthermore, these patients have a higher risk of mechanical complications. It is important to use specific strategies to reduce bleeding risk; these include paying attention to proper dosing of antithrombotic therapies, particularly in relation to frailty status. It is better to use radial access whenever possible. There is no upper age limit with respect to reperfusion, especially with PPCI.

GAIT SPEED TEST IN THE CARDIOVASCULAR CARE OF OLDER ADULTS

Gait speed is a quick, inexpensive, reliable measure of functional capacity with well-documented predictive value for major health-related outcomes. Numerous studies have documented gait speed in older people³¹⁻³³.

In a 2014 JACC review, Afilalo J. et al. analyzed that 5-meter gait speed that has been advocated as a single-item measure of frailty⁵.

The gait speed test has been shown to have excellent inter-rater reliability (intraclass coefficient 0.88 to 0.96) and test-retest reliability (intraclass coefficient 0.86 to 0.91). It is responsive to change, with meaningful improvements in gait speed (estimated at 0.05 to 0.2 m/s)^{5,32,33} predicting positive outcomes on a population level but not necessarily an individual patient level.

The walking distance has varied between 3 and 10

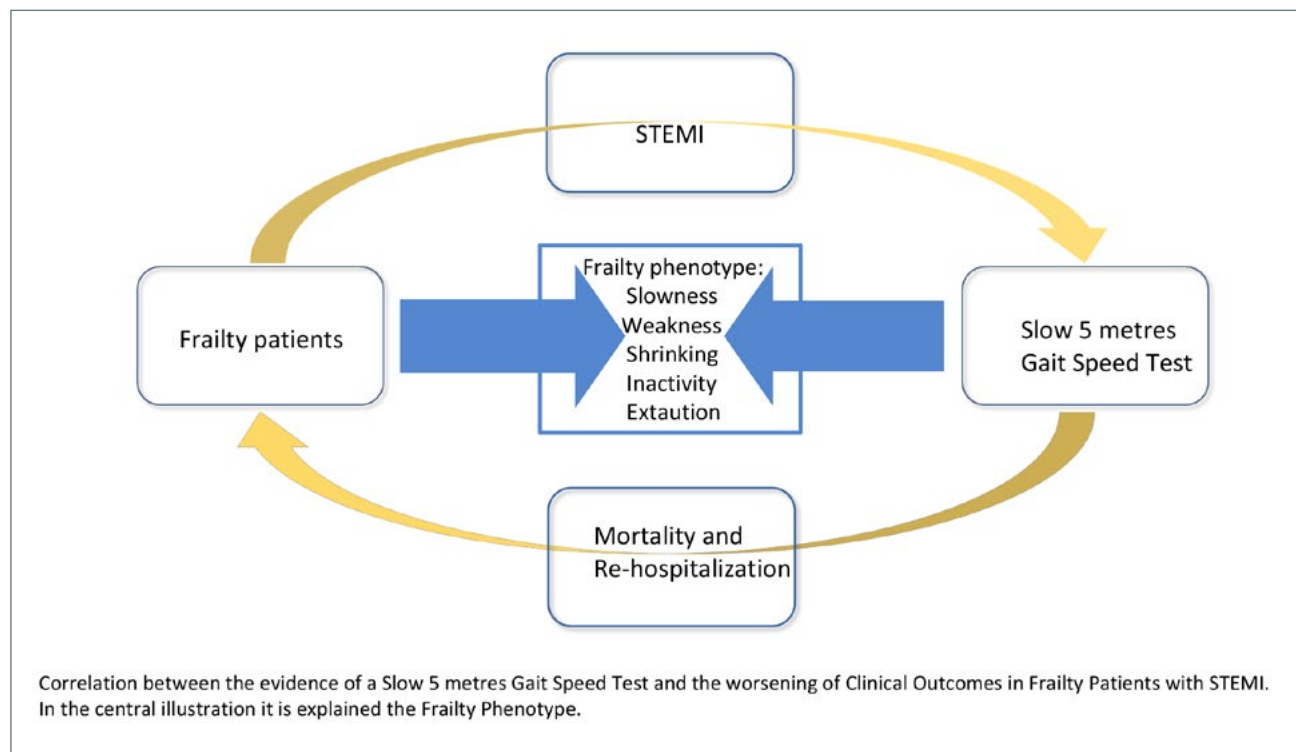


Figure 1. Slow Gait Speed Test and Clinical Outcomes in Frailty Patients with STEMI.

m, although the distance has little effect on measured speed³⁴. The 5-metres distance has been adopted by large registries and is a good balance between allowing patients to achieve a steady walking speed without eliciting cardiopulmonary symptoms, because of its shorter duration⁵.

The short distance and comfortable pace, in fact, are well below cardiopulmonary limitations, making the focus of this test different than a typical stress test or 6-min walk test¹².

Finally, slow gait speed, along with other frailty measures, has been associated with all-cause mortality, hospital re-admission, adverse surgical outcomes, and incident disability and cardiovascular disease^{5,24,35-37,39}.

The most effective treatment for improving the outcomes of patients with slow gait speed and cardiovascular disease is not clear.

Exercise is the most studied intervention but remains underused because of lack of widespread screening and logistical challenges in designing exercise programs specific to older frail patients. Cardiac rehabilitation (CR) combines exercise and lifestyle interventions, and it is a guideline-recommended therapy after acute myocardial infarction (AMI)³⁶⁻³⁸.

CONCLUSIONS

On the basis of existing literature, we may speculate that STEMI patients with frailty should be studied with 5 metres gait speed test before hospital discharge, for a better evaluation of physical status. In a 2012 study, Cacciatore F et al. showed how $EF \geq 50\%$ and $6MWT \geq 300$ m independently protect against mortality in CABG patients before CR, but their protective role was age dependent. In fact, $EF \geq 50\%$ was protective in adults but not in elderly while $6MWT \geq 300$ m was protective in elderly but not in adult patients³⁹. In this context, we may speculate that 5 metres gait speed test should be important in physical frailty patients evaluation.

The results of the test might indicate how to set the pharmacological strategy, CR and the time of follow-up, for improving quality of life of the patients, reducing mortality and Hospitalization⁴⁰⁻⁴². Future studies are needed for filling the gap, with particular attention to senescence's biomarkers.

ACKNOWLEDGEMENTS

All authors have read and approved the submission to Journal of Gerontology and Geriatrics.

CONFLICT OF INTEREST

The Authors declare to have no conflict of interest.

References

- 1 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2017;00:1-66.
- 2 Flint K. Which came first, the frailty or the heart disease? Exploring the vicious cycle. *J Am Coll Cardiol* 2015;10.
- 3 Bergman H, Ferrucci L, Guralnik J, et al. *Frailty: an emerging research and clinical paradigm issues and controversies*. *J Gerontol A Biol Sci Med Sci* 2007;62:731-7.
- 4 Goldfarb M, Afilalo J, Chan A, et al. *Early mobility in frail and non-frail older adults admitted to the cardiovascular intensive care unit*. *J Crit Care* 2018;47:9-14.
- 5 Afilalo J, Alexander KP, Mack MJ, et al. *Frailty assessment in the cardiovascular care of older adults*. *J Am Coll Cardiol* 2014;63:747-62.
- 6 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:M146-56.
- 7 Gill TM, Gahbauer EA, Han L, et al. *Trajectories of disability in the last year of life*. *N Engl J Med* 2010;362:1173-80.
- 8 Clegg A, Young J, Iliffe S, et al. *Frailty in elderly people*. *Lancet* 2013;381:752-62.
- 9 Pilotto A, Ferrucci L, Franceschi M, et al. *Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients*. *Rejuvenation Res* 2008;11:151-61.
- 10 Pilotto A, Sancarlo D, Daragjati J, et al. *Perspective: the challenge of clinical decision-making for drug treatment in older people. The role of multidimensional assessment and prognosis*. *Front Med* 2014;1:61.
- 11 Guralnik JM, Ferrucci L, Simonsick EM, et al. *Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability*. *N Engl J Med* 1995;332:556-61.
- 12 Singh M, Stewart R, White H. *Importance of frailty in patients with cardiovascular disease*. *Eur Heart J* 2014;35:1726-31.
- 13 Singh M, Rihal CS, Lennon RJ, et al. *Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization*. *Circ Cardiovasc Qual Outcomes* 2011;4:496-502.
- 14 Ekerstad N, Swahn E, Janzon M, et al. *Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction*. *Circ Cardiovasc Qual Outcomes* 2011;124:2397-404.
- 15 Alexander KP, Roe MT, Chen AY, et al. *Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes*. *J Am Coll Cardiol* 2005;46:1479-87.
- 16 Volpato S, Cavalieri M, Sioulis F, et al. *Predictive value of the short physical performance battery following hospitalization in older patients*. *J Gerontol A Biol Sci Med Sci* 2011;66:89-96.
- 17 Chaudhry SI, McAvay G, Chen S, et al. *Risk factors for hospital admission among older persons with newly*

- diagnosed heart failure: findings from the Cardiovascular Health study. *J Am Coll Cardiol* 2013;61:635-42.
- 18 Pittman JG, Cohen P. *The pathogenesis of cardiac cachexia*. *N Engl J Med* 1964;271:453-60.
 - 19 Stortecky S, Schoenenberger AW, Moser A, et al. *Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation*. *J Am Coll Cardiol* 2012;5:489-96.
 - 20 Drudi LM, Ades M, Asgar A, et al. *Interaction between frailty and access site in older adults undergoing transcatheter aortic valve replacement*. *J Am Coll Cardiol* 2018;12;11:2185-92.
 - 21 Afilalo J, et al. *Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR study*. *J Am Coll Cardiol* 2017;70:689-700
 - 22 Patel A, Goodman SG, Yan AT, et al. *Frailty and outcomes after myocardial infarction: insights from the CONCORDANCE registry*. *JAMA* 2018;7:e009859.
 - 23 Dodson JA, Geda M, Krumholz HM, et al. *Design and rationale of the comprehensive evaluation of risk factors in older patients with AMI (SILVER-AMI) study*. *BMC Health Serv Res* 2014;14:506.
 - 24 Matsuzawa Y, Konishi M, Akiyama E, et al. *Association between gait speed as a measure of frailty and risk of cardiovascular events after myocardial infarction*. *J Am Coll Cardiol* 2013;61:1964-72.
 - 25 Afilalo J, Eisenberg MJ, Morin JF, et al. *Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery*. *J Am Coll Cardiol* 2010;56:1668-76.
 - 26 Afilalo J, Kim S, O'Brien S, et al. *Gait speed and operative mortality in older adults following cardiac surgery*. *JAMA Cardiol*. 2016;1:314-21.
 - 27 Toleva O, Ibrahim Q, Brass N, et al. *Treatment choices in elderly patients with ST-elevation myocardial infarction-insights from the Vital Heart Response registry*. *Open Heart* 2015;2:e000235.
 - 28 Malkin CJ, Prakash R, Chew DP. *The impact of increased age on outcome from a strategy of early invasive management and revascularisation in patients with acute coronary syndromes: retrospective analysis study from the ACACIA registry*. *BMJ Open* 2012;2:e000540.
 - 29 Alexander KP, Chen AY, Roe MT, et al.; CRUSADE Investigators. *Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes*. *JAMA* 2005;294:3108-116.
 - 30 Bueno H, Betriu A, Heras M, et al.; TRIANA Investigators. *Primary angioplasty vs fibrinolysis in very old patients with acute myocardial infarction: TRIANA (TRatamiento del Infarto Agudo de miocardio en Ancianos) randomized trial and pooled analysis with previous studies*. *Eur Heart J* 2011;32:51-60.
 - 31 Peel NM, Kuys SS, Klein K. *Gait speed as a measure in geriatric assessment in clinical settings: a systematic review*. *J Gerontol A Biol Sci Med Sci* 2012;68:39-46.
 - 32 Hardy SE, Perera S, Roumani YF, et al. *Improvement in usual gait speed predicts better survival in older adults*. *J Am Geriatr Soc* 2007;55:1727-34.
 - 33 Perera S, Mody SH, Woodman RC, et al. *Meaningful change and responsiveness in common physical performance measures in older adults*. *J Am Geriatr Soc* 2006;54:743-9.
 - 34 Rikkert MGM, van Iersel MB, Munneke M, et al. *Gait velocity and the timed-up-and-go test were sensitive to changes in mobility in frail elderly patients*. *J Clin Epidemiol* 2008;61:186-91.
 - 35 Dumurgier J, Elbaz A, Ducimetière P, et al. *Slow walking speed and cardiovascular death in well functioning older adults: prospective cohort study*. *BMJ* 2009;339:b4460.
 - 36 Anderson L, Thompson DR, Oldridge N, et al. *Exercise-based cardiac rehabilitation for coronary heart disease*. *Cochrane Database System Rev* 2016:CD001800.
 - 37 Flint K, Kennedy K, Arnold SV, et al. *Slow gait speed and cardiac rehabilitation participation in older adults after acute myocardial infarction*. *JAMA* 2018;7:e008296.
 - 38 Dodson JA, Arnold SV, Gosch KL, et al. *Slow gait speed test and risk of mortality or hospital readmission after myocardial infarction in the translational research investigating underlying disparities in recovery from acute myocardial infarction: Patients' Health Status registry*. *J Am Geriatr Soc* 2016;64:596-601.
 - 39 Cacciatore F, Abete P, Mazzella F. *Six-minute walking test but not ejection fraction predicts mortality in elderly patients undergoing cardiac rehabilitation following coronary artery bypass grafting*. *Eur J Prev Cardiol* 2012;19:1401-9.
 - 40 Herrman M, Witassek F, Erne P, et al. *Impact of cardiac rehabilitation referral on one-year outcome after discharge of patients with acute myocardial infarction*. *Eur J Prev Cardiol* 2018;26:138-44.
 - 41 Lawler PR, Filion KB, Eisenberg MJ, et al. *Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials*. *Am Heart J* 2011;162:571-84.e2.
 - 42 Parashar S, Spertus JA, Tang F. *Predictors of early and late enrollment in cardiac rehabilitation, among those referred, after acute myocardial infarction*. *Circulation* 2012;126:1587-95.

How to cite this article: Mone P, Minicucci F, Pansini A, et al. *Gait Speed test in physically frailty patients with ST-segment elevation myocardial infarction*. *Journal of Gerontology and Geriatrics* 2019;67:181-5.

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

A very unusual case of atlantoaxial dislocation

A. Tancredi¹, A. Giorgi²

¹ Department of Neurosurgery, San Filippo Neri Hospital, Rome, Italy; ² Department of Internal Medicine, San Filippo Neri Hospital, Rome, Italy

Atlantoaxial dislocation is a rare disorder of the craniocervical junction characterized by C1-C2 instability and loss of normal articulation. Causes may be traumatic, inflammatory, congenital or multifactorial. Congenital malformations are usually early recognized. This is the case of an elderly, tetraparetic patient affected by a previously undetected atlantoaxial dislocation associated with very rare anomalies such as os odontoideum and malformation of C1. CT/MR scans showed also severe foramen magnum stenosis and myelopathy. The role of a superimposed traumatic injury of the upper cervical spine is unclear. In patients harboring congenital deformities of the craniocervical junction even a minor head-neck trauma can precipitate the onset of severe-to-catastrophic neurologic syndrome. The great importance of timely detection and management of craniocervical anomalies is discussed.

Key words: Atlantoaxial joint, Dislocation, Atlas, Os odontoideum, Cervical spine

INTRODUCTION

Atlantoaxial dislocation (AAD) is a pathologic condition caused by C1-C2 instability and consequent loss of normal articulation. Causes for loss of stability may be traumatic, inflammatory (rheumatoid arthritis), congenital or multifactorial. Pure traumatic atlantoaxial dislocations, which means in the absence of predisposing risk factors, are very rare. Congenital deformities of the craniocervical joint, which can occur in genetic and non genetic disorders (Down syndrome, Goldenhar syndrome, Ehler-Danlos and Marfan syndrome, skeletal dysplasias, mucopolysaccharidosis, osseous abnormalities), are usually early diagnosed. We are reporting the unusual case of an elderly patient affected by a previously undetected symptomatic AAD associated with rare disorders such as dystopic os odontoideum (OO) and unfused anterior and posterior arch of C1. The great importance of timely detection and management of patients with craniocervical junction abnormalities is also discussed.

CASE REPORT

This 78 year-old-woman was admitted to the department of internal medicine for a subocclusive intestinal syndrome. Besides congestive cardiomyopathy, pleural effusion and moderate cognitive impairment, mild tetraparesis and marked head movement restriction were pointed out. Chronic neck pain was reported. Our patient had lived for a long time in a catholic assisted living community and had no relatives. We had information about a few falls occurring in the past followed by the application of a cervical collar for a short period of time and progressive decline in mobility. Static CT/RM imaging studies of the cervical spine showed a severe AAD associated with dystopic OO, congenital malformation of C1 (unfused anterior arch and hypoplasia of the posterior arch), severe foramen magnum/upper cervical spine stenosis and myelopathy (Figs. 1-2). Evoked potential studies were moderately abnormal. Craniometric values – Skull Basal Angle and Clivus Canal Angle – were within normal limits ¹. Since

■ Received: February 21, 2019 - Accepted: June 14, 2019

■ Correspondence: Angelo Tancredi, Department of Neurosurgery, San Filippo Neri Hospital, ASL Roma 1, via Martinotti, 00135 Roma, Italy. E-mail: at.antan@virgilio.it

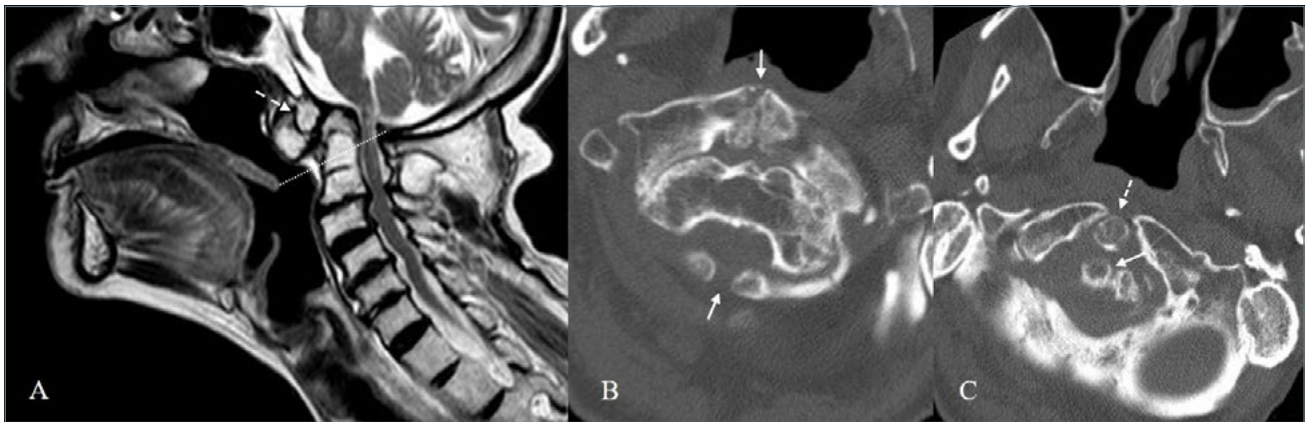


Figure 1. **A.** Foramen magnum stenosis, parenchymal enhancement of the medulla oblongata and upper cervical myelopathy. Increased atlanto-dental interval (6 mm). Dystopic os odontoideum (→) and basilar invagination (---- Chamberlain line). **B.** Unfused anterior and posterior arch of C1. Anterior arch is hypertrophic. **C.** Odontoid process (→) and os odontoideum (→).

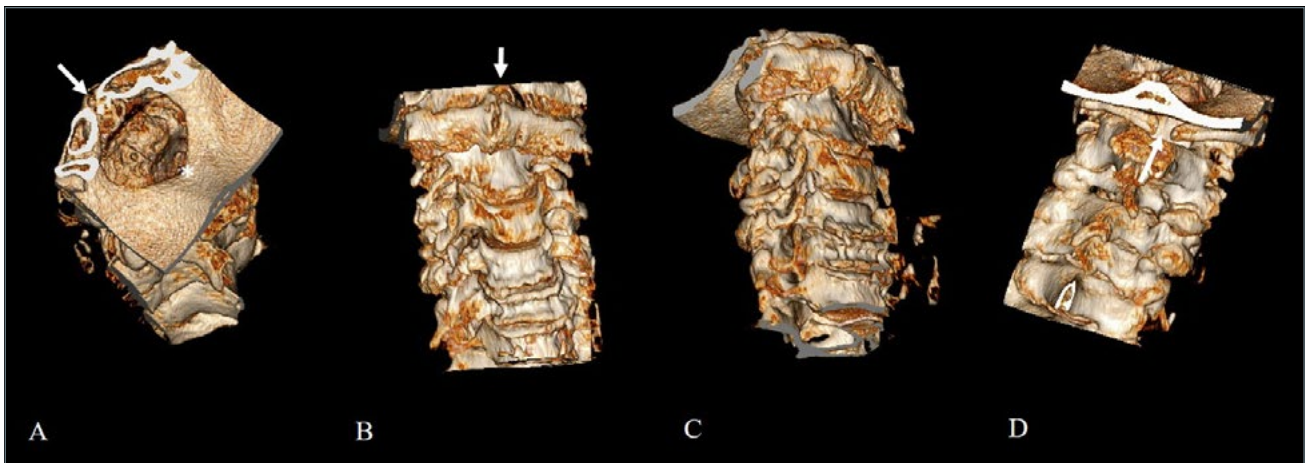


Figure 2. **A.** Dystopic os odontoideum (→). Severe foramen magnum stenosis (*). **B.** Os odontoideum (→). Unfused anterior arch of C1 which is also hypertrophic. **C.** Note the significant separation of the odontoid from the anterior arch of C1. **D.** Hypoplasia of the posterior arch of the atlas (type A) (→).

a poor clinical condition precluded surgical procedures, external immobilization with neck brace was applied. The patient died for sepsis two months after hospitalization.

DISCUSSION

Late diagnosis of a severe symptomatic malformation of the atlantoaxial joint is very unusual considering advances in medical care, innovation in healthcare technology, and heightened public awareness.

In this patient AAD is part of a complex congenital malformation of the craniocervical joint; however, the possible role of a superimposed traumatic injury of the upper cervical spine remains unclear. Unfortunately,

earlier radiological studies are lacking and if they had been performed, it is very likely that the malformation was overlooked or improperly interpreted.

Etiology of OO, which is generally early diagnosed, is still controversial. For this poorly understood condition both traumatic and congenital causes have been hypothesized by several authors^{2,3}. OO has been classified in two anatomical types – orthotopic and dystopic – based on the position of the dens tip⁴: orthotopic OO lies in the location of the normal odontoid process and moves with C2 and the anterior arch of the atlas; dystopic OO is displaced and generally fused to the basion or to the anterior ring of C1. The natural history of OO is variable. Although it can be associated with atlantoaxial instability, predictors of patient deterioration have not yet been clearly identified⁴. Coexistence of OO

and bipartite atlas is quite rare. Midline anterior cleft of the atlas is a very rare congenital anomaly; it is present in 0,1-0,3% of population^{5,6} whereas the incidence of posterior arch anomalies ranges from 0,7 to 4%^{5,7,8}; posterior and anterior arch anomalies can sometimes coexist⁹. Congenital bipartition of the atlas in the absence of other malformations is generally a coincidental finding and requires no specific treatment.

Until now, various classification systems of AAD have been published^{10,11}. First proposed in 1968, Greenberg's classification in two groups – reducible and non reducible – each connected to different treatment modality, has been generally adopted even though treatment strategies still remain quite controversial¹². Of course, due to the limited number of cases, preparation of universally accepted guidelines is a demanding objective. Currently, management of AAD and associated neural compression – with or without OO – includes three key-stages: closed reduction attempt (cervical traction), orthotic immobilization and surgery in case of persistent instability or recurrence of deformity after a period of immobilization^{4,10,12}. Nonoperative management with cervical traction and/or orthotic immobilization is considered a viable option only for asymptomatic patients provided that atlanto-dental interval is less than 5 mm in adults and less than 4 mm in children¹²; in these cases longitudinal radiological surveillance is also recommended. Surgical options include anterior approaches (odontoidectomy, transoral reduction plate, anterior transarticular C1-C2 screw fixation) posterior approaches (trans-articular and pedicle C1-C2 screw fixation, occipitocervical stabilization, bone decompression) and combined approaches. The best surgical technique is still debated; however, posterior fusion is regarded as the treatment of choice for reducible atlantoaxial deformity.

CONCLUSIONS

This case should serve as reminder that subtle, frequently age-related and slowly progressive signs and symptoms such as head-neck movement restriction, neck pain and headache, unsteady gate, numbness, weakness, lightheadedness, lower cranial nerves dysfunction, sphincter dysfunction, presyncopal events need to be thoroughly considered and properly investigated. In patients harboring congenital or acquired unstable deformities of the craniocervical junction consequences of neglect may be extremely serious. Since even a minor head-neck trauma can precipitate the onset of a catastrophic neurologic syndrome with quadriplegia or death^{12,13}, early detection, although challenging, is critical to ensure timely treatment and

to prevent major complications. Plain radiographs, CT scans and MRI of the cervical spine provide all the information needed to plan appropriate treatment (upper cervical spine anatomy, presence of bony fusion, myelopathy, instability); if foramen magnum stenosis is diagnosed, Transcranial Doppler Ultrasound allows for noninvasive evaluation of vertebral arteries hemodynamics. On the other hand, it should be kept in mind that congenital anomalies of the craniovertebral joint as well as fragility/traumatic cervical fractures may be silent^{12,13}. According to the Canadian C-Spine Rule, individuals over 65 years of age should always undergo a good quality 3 view X-ray study of the cervical spine (AP, lateral, odontoid) in the case of cervical trauma no matter the absence of specific symptoms¹⁴.

As upper and lower cervical segments are the most difficult to visualize on radiographs, CT scan (or MRI) which is essential in the event of abnormal or doubtful X-ray findings, is strongly advisable also in the presence of incomplete radiological examination^{13,15}.

CONFLICT OF INTEREST

The Authors declare to have no conflict of interest.

References

- 1 Koenigsberg RA, Vakil N, Hong TA, et al. *Evaluation of platybasia with MR imaging*. AJNR 2005;26:89-92.
- 2 Stevens JM, Chong WK, Barber C, et al. *A new appraisal of abnormalities of odontoid process associated with atlantoaxial subluxation and neurological disability*. Brain 1994;117:133-48.
- 3 Fielding JW, Hensinger RN, Hawkins RJ. *Os odontoideum*. J Bone Joint Surg Am 1980;62:376-83.
- 4 Rozzelle JC, Aarabi B, Dhall SS, et al. *Os odontoideum*. Neurosurgery 2013;72:159-69.
- 5 Martirosyan NL, Cavalcanti DD, Kalani MY, et al. *Aplasia of the anterior arch of atlas associated with multiple congenital disorders*. Neurosurgery 2011;69:1317-20.
- 6 Osti M, Philipp H, Meusburger B, et al. *Os odontoideum with bipartite atlas and segmental instability*. Eur Spine J 2006;15:564-67.
- 7 Senoglu M, Safavi-Abbasi S, Theodore N, et al. *The frequency and clinical significance of congenital defects of the posterior and anterior arch of the atlas*. J Neurosurg Spine 2007;7:339-402.
- 8 Currarino G, Rollins N, Diehl JT. *Congenital defects of the posterior arch of the atlas: a report of seven cases including an affected mother and son*. AJNR. 1994;15:249-54.
- 9 Hosalkar HS, Gerardi JA, Shaw BA. *Combined asymptomatic congenital anterior and posterior deficiency of the atlas*. Pediatr Radiol 2001;31:810-3.
- 10 Greenberg AD. *Atlanto-axial dislocations*. Brain 1968;91:655-84.

- ¹¹ Wang S, Wang C, Yan M, et al. *Novel surgical classification and treatment strategy for atlantoaxial dislocations*. Spine 2013;38:E1348-56.
- ¹² Yang SY, Boniello AI, Poorman CE, et al. *A review of the diagnosis and treatment of atlantoaxial dislocations*. Global Spine 2014;4:197-210.
- ¹³ Sengupta DK. *Neglected spinal injuries*. Clin Orthop Relat Res 2005;431:93-103.
- ¹⁴ Stiell IG, Clement CM, McKnight RD, et al. *The Canadian C-Spine Rule versus the NEXUS Low-Risk Criteria in patients with trauma*. N Engl J Med 2003;349:2510-8.
- ¹⁵ Ryan MD, Taylor TK. *Odontoid fractures in the elderly*. J Spinal Disord 1993;6:397-401.

How to cite this article: Tancredi A, Giorgi A. *A very unusual case of atlantoaxial dislocation*. Journal of Gerontology and Geriatrics 2019;67:186-9.

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

How the systematic detection of delirium may help physicians avoid a misdiagnosis of acute myocardial infarction: two case reports

M.C. Ferrara, F. Massariello, G. Annoni, G. Bellelli

Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; Acute Geriatric Unit, San Gerardo hospital, Monza, Italy

A 93-year-old female and an 81-year-old female presented to the Emergency Department (ED) with hypoactive delirium. In both cases, a quite common delirium-precipitating factor was initially thought to be found by the ED physicians. However, a proactive searching for all medical reasons potentially underlying delirium enabled the physicians of our Acute Geriatric Unit to unveil a diagnosis of acute myocardial infarction. These cases illustrate the complexity of detecting delirium and its etiology, especially in frail patients. We suggest that a systematic diagnostic workup should be performed in all patients presenting with delirium, including an EKG and enzymes measurement even in the absence of typical cardiovascular symptoms.

Key words: Delirium, Myocardial infarction, Underdetection, Older

INTRODUCTION

Delirium is a common and serious disorder of cognition, usually resulting from an underlying medical condition¹. According to the DSM-5, key diagnostic features include an acute onset and fluctuating course of symptoms, inattention, impaired level of consciousness, and disturbance of cognition indicating disorganization of thought¹. Delirium is associated with several negative outcomes, including worsening of cognitive and functional status, increasing patients' and caregivers' burden and elevated mortality in the middle to long term^{2,3}. Despite the toll of these negative outcomes, delirium is frequently undetected in clinical practice and its diagnostic still remains a critical area of need⁴. Here, we report two cases of old females in whom the diagnosis of acute myocardial infarction was obtained after a process of active searching of the underlying causes of delirium.

CASE PRESENTATION N°1

A 93-year-old Caucasian female was admitted to the Emergency Department (ED) of our hospital because

of an altered level of consciousness. On admission, her caregiver reported a subtle though progressive and significant impairment of patient's baseline mental and motor status occurring in the last week. The patient was reported fully dependent in all the activities of daily life, except for self-feeding which was still preserved. She had a history of major tobacco consumption (one packet/day since she was very young). Despite a history of falls, for which she underwent hip-surgery about ten years before, she was still able to walk at home with assistance until the previous week. She had no relevant disease but an uninvestigated cognitive impairment with behavioral disorders, for which she was prescribed low dosage of benzodiazepines and haloperidol. In the last few days, her caregiver also noticed foul-smelling urine. General practitioner was called home and suggested bringing her to the hospital.

At ED presentation, the patient was lethargic, with temperature as high as 36.7°C, blood pressure (BP) was 95/60 mmHg, heart rate (HR) 110/min, respiratory rate (RR) 30 breaths/min while arterial oxygen saturation was normal. Cardiovascular, thoracic and abdominal

■ Received: March 3, 2019 - Accepted: March 18, 2019

■ Correspondence: Giuseppe Bellelli, Department of Medicine and Surgery, University of Milano-Bicocca, piazza dell'Ateneo Nuovo 1, 20126, Milan, Italy. E-mail: giuseppe.bellelli@unimib.it

examinations were unremarkable. Laboratory investigations revealed elevated levels of leucocytes (17.800/mmc, with 78% of neutrophils), elevated C-reactive protein (21.71 mg/dl), and creatin-kinase (589 U/l), whereas the chest X-ray did not find pneumonia but mild pleural effusion. Intravenous fluid therapy and empiric antibiotic therapy with ceftazidime were started, soon after urine and blood cultures collection and, on the same day of ED arrival, the patient was transferred to our Acute Geriatric Unit (AGU) with a suspected diagnosis of urinary tract infection.

On admission to the AGU, she was still difficult to wake, scoring -3 at the modified Richmond Agitation and Sedation (m-RASS) ⁵, and she was unable to direct, focus and sustain attention. Accordingly ⁵, a diagnosis of hypoactive delirium was made, and soon the underlying causes of delirium were actively searched. To this aim, an electrocardiogram (EKG) was run, showing QS and RS complexes with persistent ST-segment elevation in the anterior and septal leads (V1-V4). Cardiac enzymes were elevated - TroponinT-hs (TnT-hs) 3852 ng/l, creatin-kinase-mb-isoenzyme (CK-MB) 33.94 ng/ml – and an echocardiography showed a complete apical and septal akinesia (LVEF 25-30%) in addition to moderate mitral valvular regurgitation. ST-Elevation Myocardial Infarction (STEMI) was then diagnosed and both antiplatelet and beta-blocker were started. Moreover, antibiotic therapy was shifted to Ampicillin/Sulbactam, as urine culture resulted positive for *Enterococcus Faecalis*.

Patient's arousal gradually improved and delirium finally resolved on third day after AGU admission. There was a progressive normalization of the EKG pathologic findings and a corresponding decline of troponin and CK-MB serum levels. A return to pre-hospital health conditions was achieved over the next fortnight and the patient was discharged home with stable clinical conditions and normal arousal.

CASE PRESENTATION N°2

An 81-year-old Caucasian female affected by severe Alzheimer's disease (AD) was admitted to the ED of our hospital because of trauma due to a fall occurring at home. According to her caregiver's report, there was a progressive impairment of patient's baseline mental status starting in the last few days before admission. The patient was fully dependent in all the activities of daily life; except for AD, the only remarkable disease was a type 2 diabetes mellitus. No drug was prescribed at home.

At ED presentation, the patient was lethargic, with normal BP, HR and RR values. Cardiovascular, thoracic and abdominal examinations were unremarkable. Laboratory investigations revealed nothing but elevated

CK values (298 U/l), which was initially considered consequence of recent fall, and the EKG did not reveal abnormal findings. On the same day of ED arrival, she was transferred to our AGU for observation and treatment.

On admission to the AGU, she was lethargic, with m-RASS scoring -3, and unable to direct, focus and sustain attention. A diagnosis of hypoactive delirium was done in this case as in the previous one ⁵, and the somatic causes underlying delirium were actively searched. To this aim, laboratory investigations were re-checked and an important elevation of CK (2840U/l) was found. Thus, specific cardiac enzymes were collected, finding elevation of TnT-hs and CK-MB values (TnT-hs 8647 ng/l and CK-MB 75.68 ng/ml, respectively). A new EKG showed T-wave inversions in the infero-posterior and lateral leads, associated with ST depressions in the anterior leads. Therefore, a diagnosis of Non-ST-Elevation Myocardial Infarction (NSTEMI) was done and both antiplatelet and beta-blocker treatment was started.

In the following days, there was a progressive reduction of Tn-T-hs and CK-MB serum levels and a corresponding normalization of the EKG pathologic findings. Patient's arousal gradually improved and delirium resolved. The patient was discharged home with stable clinical conditions and normal arousal.

DISCUSSION

Delirium is a multifactorial disorder, depending on complex interactions between predisposing and precipitating factors ^{1 2}. Infections, metabolic derangements, drugs, dehydration and immobility are commonly accepted delirium precipitating factors. Predisposing factors include baseline cognitive impairment or dementia, multimorbidity and older age ². A recent systematic review and meta-analysis has also shown that frailty significantly predisposes to subsequent delirium, contributing to the individual's susceptibility towards various negative outcomes ⁶. From a geriatric perspective, delirium may therefore be considered as one of the syndromic presentations of an individual's underlying condition of frailty ⁶.

Since cardiac diseases as well as other conditions can present with atypical signs/symptoms including delirium ⁷⁻⁹ in older people, all patients at risk (i.e., the frail patients) should undergo a systematic assessment of delirium to detect especially the hypoactive subtypes ¹⁰. In fact, although many clinicians think of patients with delirium as being agitated, hyperactive delirium represents only 20% of cases, with the others having hypoactive ("quiet") delirium ^{10 11}. Importantly, hypoactive delirium is associated with a significantly worse prognosis at short-term than hyperactive or no delirium ³. Many

screening tools have been validated in recent years¹², but their use is still missed in clinical practice. However, without detecting delirium, many acute clinical conditions may go under-recognized in clinical practice. Once delirium is detected or suspected, a proactive searching for possible causes is imperative to guide diagnostic investigations and to avoid risk of missed diagnosis. Since an acute change in the level of consciousness is often the first clue of delirium, patient's baseline mental status and a prior diagnosis of dementia must be assessed from an adequate interview with caregiver, which information is not always easy to gather (delirium superimposed on dementia has significant prognostic implications if compared with dementia alone)^{1,2}.

To the best of our knowledge, only few studies and a small number of case-reports have been published on the association between delirium and acute myocardial infarction (AMI), which is one of the most common causes of death worldwide, particularly among the older population¹³. For example, Grosmaître et al. retrospectively reviewed 255 patients aged 75 years and older with ST-Elevation Myocardial Infarction, finding that delirium and impaired general conditions were the main presenting symptoms in nearly 12% of all patients⁷. Anyway, the method to detect delirium in this study is not reported and it is likely that a standardized assessment with proper tools has not been done. Another retrospective study including patients aged 90 years and older, reported delirium or agitation being present in more than a quarter of AMI hospitalized patients⁸; this finding was probably an underestimation of the true prevalence since stupor and coma were not always classified as possible manifestations of delirium⁸. Atypical symptoms are even much more frequent among patients with pre-existing cognitive impairment or communication difficulties, since these symptoms seem to be associated with vulnerability criteria such as dementia, functional dependence and impaired communication skills^{7,9,11,13}.

The importance to detect atypical presentation (and then delirium) in older patients with AMI is evident. Based on data from the NRMI-2, Canto et al. have shown that patients with atypical symptoms are at risk of delayed diagnosis, incorrect management and inappropriate discharge, and are less likely to receive reperfusion therapy^{9,13}. According to a recent editorial¹⁴, age discrimination in the management of acute coronary syndrome is still present in clinical practice, whereas current evidence suggests older people with AMI should normally be referred to an interventional cardiologist for consideration of invasive treatment. The After Eighty Study¹⁵ also remind that there is no place for discriminatory clinical practices based on age alone, stressing the need for individually tailored approach.

In conclusion, a systematic detection of delirium should be done in all frail patients once they arrive at an ED. The detection of delirium may rapidly enable clinicians to start a diagnostic workup including an EKG and enzymes measurement, even in the absence of cardiovascular symptoms.

Summarizing, the goal of this report is to highlight the critical importance of 1) detecting delirium systematically in older patients on ED arrival, 2) proactively searching for delirium causes and 3) underscoring the critical gaps existing in knowledge of the relationship between delirium and AMI. Future research is needed to advance in this field.

CONFLICT OF INTEREST

The Authors declare to have no conflict of interest.

References

- 1 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Society 2013.
- 2 Morandi A, Lucchi E, Turco R, et al. *Delirium superimposed on dementia: a quantitative and qualitative evaluation of informal caregivers and health care staff experience*. J Psychosom Res 2015;79:272-80. Doi: 10.1016/j.jpsychores.2015.06.012.
- 3 Bellelli G, Carnevali L, Corsi M, et al. *The impact of psychomotor subtypes and duration of delirium on 6-month mortality in hip-fractured elderly patients*. Int J Geriatr Psychiatry 2018; May 31. Doi: 10.1002/gps.4914. [Epub ahead of print]
- 4 Bellelli G, Nobili A, Annoni G, et al. *Under-detection of delirium and impact of neurocognitive deficits on in-hospital mortality among acute geriatric and medical wards*. Eur J Intern Med 2015;26:696-704. Doi: 10.1016/j.ejim.2015.08.006
- 5 Morandi A, Han JH, Meagher D, et al. *Detecting delirium superimposed on dementia: evaluation of the diagnostic performance of the Richmond Agitation and Sedation scale*. J Am Med Dir Assoc 2016;17:828-33. Doi: 10.1016/j.jamda.2016.05.010.
- 6 Persico I, Cesari M, Morandi A, et al. *Frailty and delirium in older adults: a systematic review and meta-analysis of the literature*. J Am Geriatr Soc 2018;66:2022-30.
- 7 Groismaître P, Le Vavasseur O, Yachouh E, et al. *Significance of atypical symptoms for the diagnosis and management of myocardial infarction in elderly patients admitted to emergency departments*. Arch Cardiovasc Dis 2013;106:586-92.
- 8 Malone ML, Rosen LB, Goodwin JS. *Complications of acute myocardial infarction in patients > 90 years of age*. Am J Cardiol 1998;81:638-41.
- 9 Canto JG, Shlipak MG, Rogers WJ, et al. *Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain*. JAMA 2000;283:3223-9.

- ¹⁰ Marcantonio ER. *Delirium in hospitalized older adults*. N Engl J Med 2017;377:1456-66.
- ¹¹ Morandi A, Di Santo SG, Cherubini A, et al.; ISGoD Group. *Clinical features associated with delirium motor subtypes in older inpatients: results of a multicenter study*. Am J Geriatr Psychiatry 2017;25:1064-71. Doi: 10.1016/j.jagp.2017.05.003.
- ¹² Jones RN, Cizginer S, Pavlech L, et al. *Assessment of instruments for measurement of delirium severity: a systematic review*. JAMA Intern Med 2019;179:231-9. Doi: 10.1001/jamainternmed.2018.6975
- ¹³ Uguz F, Kayrak M, Cicek E, et al. *Delirium following acute myocardial infarction: incidence, clinical profiles, and predictors*. Persp Psych Care 2010;46. Doi: 10.1111/j.1744-6163.2010.00249.x
- ¹⁴ Soiza RL. *Management of acute coronary syndromes in older people*. Age Ageing 2018;47:2-3. Doi: 10.1093/ageing/afx160
- ¹⁵ Tegn N, Abdelnoor M, Aaberge L, et al. *Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial*. Lancet 2016;387:1057-65.

How to cite this article: Ferrara MC, Massariello F, Annoni G, et al. *How the systematic detection of delirium may help physicians avoid a misdiagnosis of acute myocardial infarction: two case reports*. Journal of Gerontology and Geriatrics 2019;67:190-3.

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.