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Oral condition assessment among a nursing home population. Analysis of the association between tooth loss and cognitive impairment: an observational study

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Background & aims. Several studies report that a low number of teeth is strictly associated with a higher risk of cognitive impairment. Aim of this study is to evaluate the oral condition of a nursing home population, in order to clarify the possible association between tooth loss and cognitive decline.

Methods. 444 patients were selected; clinical information were excerpted from their hospital records. Subjects were visited in their nursing home unit, paying particular attention to number of teeth, prosthesis and soft tissues.

Results. 378 subjects were visited, 277 with formal diagnosis of dementia and 101 with mild or no impairment in cognition. Age was similar in both group, while education level, MMSE and number of teeth were significantly lower among people with dementia. There was an inverse correlation between age and number of remaining teeth, while MMSE did not seem to be associated with tooth loss. School level was positively associated with number of teeth.

Conclusions. There is a significant difference in number of teeth, school level and MMSE between patients with and without dementia. Maybe due to the high prevalence of people with severe cognitive impairment, a significant association between MMSE and number of teeth was not found. The presence of compromise oral conditions is relevant.

Key words: Alzheimer’s disease, epidemiology, oral health, prosthesis, cerebrovascular dementia, teeth, geriatrics, gerontology, nursing home

INTRODUCTION

The constant increase in the average age is determining an increasing epidemiological relevance of different types of cognitive impairment, in particular dementia. In 2018, about 50 million people suffered from some kind of dementia, with an annual incidence of 9.9 million¹; over the next 20 years, these numbers will nearly double, up to 152 million in 2050. From a socio-economic point of view, the impact of these conditions is considerable: not only patients and their families, but also all public health
is affected. Despite the clinical manifestations have been recognized, risk factors of dementia remain unclear, especially of Alzheimer’s disease (involving about two-thirds of the sufferers).

Recently, a growing number of research studies have focused on the link between oral health and cognitive status. In particular, it seems possible to assess the association between tooth loss and an increased risk of developing dementia in the elderly. Several research studies report how the reduced and the difficult chewing activity (following a widespread edentulism) and the state of chronic inflammation (typical of periodontal disease) predispose the patient to an increased risk of developing dementia and losing cerebral volume in the areas devoted to memorisation (hippocampus, caudate nucleus and temporal lobe).

A poor oral health and the resulting dietary poverty are also associated with the weakening of systemic health, which can contribute to the onset and progression of dementia. In preparation for a larger population study, the purpose of the current pilot phase is the evaluation of oral conditions – with particular reference to the number of teeth – in an institutionalized population, comparing the results with the anamnesis taken from clinical documentation. Through the investigation of a large number of patients, the aim of this study is clarifying the correlation between a reduced number of teeth and the level of cognitive decline, considering the possible influence of factors such as age and level of education.

PATIENTS AND METHODS

Participants
This study was conducted between November 2017 and April 2018 at the Palazzolo Geriatric Institute (Don Carlo Gnocchi Foundation) in Milan. 444 patients were enrolled in the study, all of them selected from 9 Nursing Home (NH) units and the Alzheimer Special Care Unit of the Institute. During the visits, 66 patients were excluded: 21 for their unstable medical condition and 45 who refused to submit to the study (Fig. 1). From the medical records of every patient, the diagnostic profile and the coexistence of potentially confounding variables were evaluated: upcoming and remote conditions (hypertension, diabetes mellitus compensated or not, stroke), drug therapy, habits (smoking and alcohol abuse), level of education, SOSIA score (indicative for daily living abilities, cognition/behaviour, comorbidities) and the results obtained with test for cognitive assessment and autonomy (MMSE index and Barthel Index, considering the latest performance). If present, the reports of dental services at the Institute’s Dental Centre was considered.

Procedures
Age and sex were used as demographic characteristics; we defined a low education level as less than 10 years of schooling. We classified the group under evaluation in patients with or without cognitive impairment; among patients with dementia, we made a further distinction based on neurodegenerative disease: Alzheimer's disease, cerebrovascular dementia, dementia of other kind. As regards their achievements in the MMSE, we used the NICE classification (2015): 11 points, normal; 26-21 points, mild impairment; 20-10 points, impairment; ≤ 9 points, severe impairment. We considered edentulous subjects with no teeth, only root or non-osteointegrated implant prosthesis. The visits took place in the ward, with patient in bed or on a wheelchair. For the inspection of the oral cavity a sterile set (mirror, probe and tweezers) and a tongue depressor were used; each control lasted few minutes. In case of good compliance, a photographic documentation of the oral cavity was taken. For each patients, residual teeth (number of teeth, mobility, integrity, any prosthetic rehabilitations fixed, implants), removable dentures (full or partial, fair or unstable, cleaning) and soft tissues (presence of plaque and Tartar, gum bleeding or typical oral lesions such as candida and hypertrophy of lingual papillae) were evaluated. A written report of the visit was attached to the medical records of patients.

Analysis
Descriptive statistics (mean, median, IQR, kurt) were used to characterize the patients. Analysis of distribution of some data (age, school level, MMSE, number of teeth) was tested using Kolmogorov-Smirnov normality Test; almost all variables considered did not follow a normal distribution. Because of that, Mann-Whitney Test was used for analysis of difference between groups (patients with and without Dementia) in age, school level, MMSE and number of teeth. Analysis of correlation has been carried out with non-parametric Spearman Test. The level of significance was assumed to be p < 0.05 or p < 0.01. SPSS (IBM Corp. Armonk, NY) was used for the analysis.

Results
378 individuals were visited (Tab. I). The range of age was between 59 and 104 years old, with mean age of 85.96 ± 7.97 (86.47 ± 7.68 in the cognitively impaired group and 85.79 ± 8.89 in the cognitively normal group). 357 patients (94.4%) were 75 years old or older. The sample consisted of 298 women (78.8%) and 80 men (21.2%). On average, level of schooling...
Oral condition assessment among a nursing home population

Figure 1. Flowchart. Description of the procedure for the patients'selection.

- Patients selection:
  - patients of RSA ward
  - all patients of Alzheimer Centre
  \( N = 444 \)

- Is patient in good clinical conditions?
  \( \text{NO} \)

- Is patient collaborative?
  \( \text{NO} \)

- Patients excluded
  \( N = 21 \)

- Patients excluded
  \( N = 45 \)

- Patients included in the study
  \( N = 378 \)

- Oral examination

- Analysis of anamnestic information

- Age
- Sex
- Level of schooling
- Hypertension
- Diabetes
- Stroke
- Smoke
- Alcoholism
- Cognitive evaluation (MMSE, Barthel index)

- in the NH unit and Alzheimer Special Care Unit
- evaluation of:
  - Soft tissues
  - Oral Hygiene
  - Residual Teeth
  - Removable denture
was 7.29 ± 3.53 year; 306 participants (80.9%) had a school level lower than 10 years. 277 patients (73.3%), which previously received a formal diagnosis of dementia, were mainly in the moderate or severe stage of the disease; among them, there were 60 subjects with Alzheimer’s disease, 144 with Cerebrovascular Dementia, 73 with other kind of cognitive impairment. The remaining 101 patients (26.7%) had no formal diagnosis of dementia in their clinical file or received a diagnosis of Mild Cognitive Impairment (MCI). Among them, just according to cognitive performance, some patient could be reasonably considered in the mild stage of a dementia condition (Tab. I). On average, MMSE score was 10.67 ± 9.03 (7.20 ± 6.85 for subjects with dementia and 20.68 ± 6.36 for patients without a formal diagnosis of dementia or MCI).

Across the population, 205 subjects had hypertension, 54 diabetes, 33 a history of stroke, 29 were smoker or formers smoker, 8 patients had previous history of alcoholism.

The mean number of teeth was 5.70 ± 8.17; 39 patients had more than 20 teeth left, 45 had a number of teeth between 19 and 10, 110 from 9 to 1 tooth, 184 were completely edentulous. 99 subjects 026.2%) used regularly a denture; among them, 91 had a full removable denture, while 8 patients had a partial prosthesis.

Distribution of age, school level, MMSE and number of teeth was analysed with Kolmogorov-Smirnov Test. Because these variables did not have a normal distribution, the comparison between patients was done with Mann-Whitney Test (Tab. II). Patients with diagnosis of dementia had a significantly lower level of education than patients with no formal diagnosis of dementia or MCI (U = 11356.000, z = -2.338, p < 0.05); similarly, MMSE score (U = 2310.000, z = -12.578, p < 0.05) and number of teeth (U = 11210.000, z = -3.13, p < 0.05) were significantly lower among patients with dementia. These two groups did not differ by mean age (U = 12311.000, z = -1.786, ns): on average, age was similar between patients with and without dementia.

A significant negative association was found between age and number of residual teeth (rs = -0.209, p < 0.01), while MMSE score did not correlate significantly with the amount of teeth (rs = 0.082, p = ns). There was a mild correlation between number of teeth and level of schooling (rs = 0.149, p < 0.01). A slight negative correlation was found between SOSIA score and number of teeth: the higher was the class and the level of complexity care, the lower was the number of residual teeth (rs = -0.111, p < 0.05).

**DISCUSSION**

The present study allowed to evaluate general and clinical conditions and state of oral health, showing significant differences between patients with and without a formal diagnosis of cognitive impairment. Despite the average being similar in the groups, the number of teeth was lower among people with dementia, as well as level of education and, subsequently, the MMSE score. These findings are in agreement with literature: patients with dementia tend to have a lower level of education (aspect that is recognized as a risk factor) and lower results in cognitive test. The number of teeth appears

**Table I.** Descriptive characteristics: anamnesis, comorbidity, cognitive status and oral conditions were used to describe the group.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anamnesis</td>
<td></td>
</tr>
<tr>
<td>≥ 75 aa</td>
<td>339</td>
</tr>
<tr>
<td>M</td>
<td>78</td>
</tr>
<tr>
<td>F</td>
<td>286</td>
</tr>
<tr>
<td>Level of schooling ≤ 10 years</td>
<td>306</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>205</td>
</tr>
<tr>
<td>Diabetes</td>
<td>54</td>
</tr>
<tr>
<td>Stroke</td>
<td>33</td>
</tr>
<tr>
<td>Smoker</td>
<td>29</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>8</td>
</tr>
<tr>
<td>Cognitive status</td>
<td></td>
</tr>
<tr>
<td>Non-formalized diagnosis</td>
<td>101</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>60</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>144</td>
</tr>
<tr>
<td>Other kind of dementia</td>
<td>73</td>
</tr>
<tr>
<td>Residual teeth</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>184</td>
</tr>
<tr>
<td>1-9</td>
<td>110</td>
</tr>
<tr>
<td>10-19</td>
<td>45</td>
</tr>
<tr>
<td>≥ 20</td>
<td>39</td>
</tr>
<tr>
<td>Mobile denture</td>
<td></td>
</tr>
<tr>
<td>Totale</td>
<td>91</td>
</tr>
<tr>
<td>Rimovibile</td>
<td>8</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
</tr>
<tr>
<td>≤ 9</td>
<td>174</td>
</tr>
<tr>
<td>10-20</td>
<td>128</td>
</tr>
<tr>
<td>21-26</td>
<td>56</td>
</tr>
<tr>
<td>≥ 27</td>
<td>19</td>
</tr>
<tr>
<td>Bartehl/ADL</td>
<td></td>
</tr>
<tr>
<td>0-24</td>
<td>228</td>
</tr>
<tr>
<td>25-49</td>
<td>29</td>
</tr>
<tr>
<td>50-74</td>
<td>18</td>
</tr>
<tr>
<td>75-90</td>
<td>2</td>
</tr>
<tr>
<td>91-100</td>
<td>/</td>
</tr>
</tbody>
</table>
to be reduced in patients with dementia, either as a result of a reduced ability of maintaining hygiene or as predisposing factor \(^1\). In the studied population, very poor attention to oral hygiene was observed on the part of caregivers and a specialized monitoring was totally lacking. There was an inverse correlation between age and number of teeth: increasing the years, patients (with and without cognitive impairment) had a higher number of edentulous areas. These results can be ascribed to not only poor general physical condition of the elderly, but also to reduced ability of cleaning, that requires more support and help \(^12\).

Regardless of level of cognitive impairment, a higher degree of schooling was associated with an increased amount of remaining teeth. People with higher education, and probably higher social background, may have had access to adequate dental care since before admission, continuing to maintain good oral health when admitted in NH.

Several studies have examined the possible mechanisms of association between tooth loss and progression of cognitive impairment \(^13\): a reduced masticatory efficiency and the involvement of periodontal pathogens in the development of inflammatory processes of the brain seem to be, currently, the most accredited pathways. However, in the present study, no correlation between MMSE and residual teeth number seems to emerge, perhaps due to the presence, in the studied population, of a high percentage of subjects with low MMSE score and severe cognitive impairment. Thus, the distribution of patients could have invalidate an analysis in this direction.

The constant use of denture was limited to a low percentage of patients; most subjects with partial or total edentulism did not have prosthesis or had incongruous denture, not cleaned or, in some cases, not their own. A severe cognitive impairment may have influenced, since before admission, the maintenance of proper oral hygiene and patient adaptation for eventual restoration.

It is possible that both variables (poor oral condition and inadequacy of the prosthesis) influenced and influence even during hospitalization the nutritional status of patients. Some studies have shown an association between masticatory efficiency (guaranteed by the use of implants or from natural teeth), nutrition quality and cognitive status. Optimal chewing performance positively influences not only the maintenance of an appropriate nutritional intake, but also the regulation of cerebral blood flow, helping to reduce the risk of cognitive decline \(^14\).

Correlation study made it possible to identify a negative association between SOSIA score and number of teeth:

**Table II.** Comparison: age, education, MMSE and number of teeth were used to compare patients with and without formal diagnosis of dementia. Mann-Whitney Test was used for the analysis. P-value < 0.05. (NS = not significant).

<table>
<thead>
<tr>
<th></th>
<th>Formal diagnosis of dementia (n = 277)</th>
<th>No formal diagnosis of dementia of MCI (n = 101)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>86.47</td>
<td>84.79</td>
<td>NS</td>
</tr>
<tr>
<td>Median</td>
<td>87</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>7.67</td>
<td>8.89</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>10</td>
<td>11.25</td>
<td></td>
</tr>
<tr>
<td><strong>Schooling</strong></td>
<td></td>
<td></td>
<td>0.019</td>
</tr>
<tr>
<td>Mean</td>
<td>7.022</td>
<td>8.06</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>3.29</td>
<td>4.02</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>7.2</td>
<td>20.69</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>6.85</td>
<td>6.36</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Residual teeth</strong></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Mean</td>
<td>4.64</td>
<td>8.79</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>7.18</td>
<td>9.94</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>6</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>
a higher level of complexity of care is associated with a lower number of residual teeth. As already mentioned, the total or partial edentulism can be expression of poor general physical condition; on the other hand, a growing number of studies are investigating the report and the predictability of tooth loss on the onset of diseases such as diabetes, cardiovascular disease and obesity, signalling significant correlations. The difference in number of residual teeth between patients with and without dementia might have been influenced by other factors, such as general surgical conditions and the level of education.

CONCLUSIONS

Based on a considerable sample of hospitalized patients and on a timely analysis of individual clinical history, this study highlight significant differences among subjects with a formal diagnosis of dementia and patients with MCI or without a formal diagnosis of dementia. Oral health conditions were very poor, with abundant deposits of plaque and tartar and badly preserved dentures, particularly among patients with advanced cognitive decline. In this group of patients, attention to hygienic aspect is poor, with possible repercussions on the quality of life (self-perception, socialization, relationship with neighbours) and nutritional status. This underestimation of the oral cavity hygiene should be considered and examined in depth, in order to improve the competence of caregivers. Despite the limits of this study (presence of patients with advanced cognitive decline, absence of a control group), we can still get a confirmation of the relationship between oral conditions and dementia, in line with the literature. Correlations among the number of teeth and level of cognitive impairment with other variables should be taken into account and analysed, including comorbidity and socio-economic conditions, which could play a potential confounding role.

References

Chest ultrasound in Italian geriatric wards: use, applications and clinicians’ attitudes

Andrea Ticinesi1, Fulvio Lauretani1, Antonio Nouvenne1, Andrea Ungar2, Raffaele Antonelli Incalzi2, Simone Scarlata2, On behalf of the GRETA (Gruppo di Ricerca sull’Ecografia Toracica nell’Anziano) Group of the Italian Society of Gerontology and Geriatrics (SIGG)

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INTRODUCTION

Point-of-care ultrasonography is becoming more and more popular in acute-care hospital wards, quickly providing diagnostic information directly at the bedside and exactly at the moment of need, and assisting clinicians in guiding invasive procedures. Although the acoustic impedance...
of the lungs does not allow direct visualization of most chest anatomical structures, chest ultrasound has proven useful for assisting the diagnostic process of the main cardio-respiratory diseases that can be found in acute-care medicine, including pneumonia, pleural effusion, heart failure and pneumothorax. Each of these conditions may in fact be associated with specific ultrasonographic patterns, that help solving a wide range of diagnostic dilemmas raised by patient history and physical examination.

Critical care physicians increasingly perceive ultrasound as an essential complement to physical examination, emphasizing its importance for altering clinical decision making and improving patient care. However, the availability of chest ultrasonography in the hospital care of developed countries is still inhomogeneous, particularly outside EDs and ICUs. The diffusion of point-of-care ultrasound and practice of chest ultrasound in geriatric wards is still unknown. Despite increasing interest in the topic, ultrasonography is perhaps less popular among geriatricians than any other specialists dealing with acute care. Mobility limitations, reduced collaboration due to cognitive impairment, multimorbidity and age-related modifications of the respiratory system, typical of geriatric patients, are probably the most important barriers to chest ultrasonography diffusion in geriatric wards. Changes of acoustic impedance of the chest wall related to aging and age-related chronic diseases should be also considered as another important factor limiting the use of thoracic ultrasound in geriatric medicine. However, the scientific literature supports the use of chest ultrasound even in older patients with the worst clinical conditions and performance status for assisting the diagnostic workup of respiratory diseases, implying several positive consequences on clinical decision making.

In 2018, the Italian Society of Gerontology and Geriatrics (SIGG) has promoted a research group on chest ultrasound in geriatrics (Gruppo di Ricerca sull’Ecografia Toracica nell’Anziano – GRETA), to improve the understanding of the current use of chest ultrasound in Italian geriatric wards and promote research projects on this theme. The aim of the present investigation was thus to assess availability, uses and applications of chest ultrasonography in a convenience sample of Italian geriatric wards, and understand geriatricians’ attitudes towards it.

METHODS

Basing on the current literature state-of-the-art, a questionnaire was developed to explore the topics of interest of chest ultrasound application in Italian geriatric wards. After reviewing the available literature up to April 2018, GRETA members selected six topics of interest (see the following paragraph) which were discussed and approved by the full GRETA board. All the members of the board were involved in producing the questions, which were submitted and further revised by two external reviewers with experience in geriatric care and ultrasound practice. A convenience sample of 25 Italian geriatric hospital wards, located throughout the entire nation, was selected. The head doctors of each unit were contacted by e-mail and requested to fill an online form hosted by the SIGG web site. The questionnaire explored these areas (see Supplementary Material for a sample):

- availability of equipment for performing thoracic ultrasound;
- location where ultrasound is generally performed (i.e., at the bedside vs in a dedicated room);
- expertise of ward physicians on thoracic ultrasound and frequency of utilization;
- most frequent indications for performing thoracic ultrasound in clinical practice;
- perceived or codified role of this technique in different diagnostic paths, with special regard to its integration with X-ray and CT diagnostics;
- impact of thoracic ultrasound on the timing and quality of management of selected conditions and diagnoses (acute dyspnea, volemic state, pleural effusion, pneumonia, acute heart failure).

Data were analyzed anonymously and in aggregated way, as number and percentages, in order to obtain a description of the current chest ultrasound practice and perception in Italian geriatric hospital wards. The software SAS (version 8.2; SAS Institute Inc., Cary, NC, USA) was used for analyses.

RESULTS

The geriatric hospital units, that participated to the survey, are mainly located in academic hospitals (18/25), and host an overall number of 680 beds. A portable
ultrasound equipment for performing bedside examinations was present, and used in everyday practice, in 23/25 wards (92%). Bedside ultrasonography was performed systematically in all patients with pertinent clinical indications in fifteen wards (58%), while in the remaining wards ultrasound was performed only sporadically, basing on clinical presentation of patients or due to limitations in the availability of equipment (Figure 1A). Among those who performed bedside ultrasound, chest examinations were performed in the majority of cases (19/23, 82%). However, the ultrasonographic assessment was considered routine in only 10 wards out of 19 (52%), while in other cases it was applied only in selected situations (Fig. 1B).

The number of team members able to perform chest ultrasound was limited: three or less physicians in 13/19 wards (68%), more than 3 physicians in 6/19 wards (32%). However, in 15 academic wards some residents were able to perform thoracic ultrasound. The main setting of application of thoracic ultrasound was acute-care beds in most cases (17 out of 19), but in some wards the technique was also applied in subintensive care beds, long-term care beds and even outpatient clinics (4 wards each). In 75% of wards, chest ultrasonography was performed directly at the bedside, while in the remaining wards the setting was a dedicated room outside the ward.

The main indications of chest ultrasound are summarized in Table I. Most head doctors declared that chest ultrasound is performed as a complement to chest X-ray (18/19), either routinely (15/19) or only in case of inconclusive X-ray results (3/19). In one unit, ultrasound was even considered a substitute for X-ray in selected clinical situations. The timing of ultrasound examination is summarized in Table II.

Chest ultrasound was integrated with bedside echocardiography in 14 out of 19 wards (77%). Diaphragmatic ultrasound evaluation was performed in only 4 wards (21%).

With respect of traditional radiography, most head doctors (16/19, 84%) perceived that chest ultrasound can ameliorate the diagnostic process in all cases, while

Figure 1. Pie charts showing the availability of ultrasound equipment (A) and the practice of bedside chest ultrasound (B) in a convenience sample of 25 Italian geriatric wards.

### Table I

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of wards</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential diagnosis of acute dyspnea</td>
<td>10/19</td>
<td>53%</td>
</tr>
<tr>
<td>Evaluation of volemic state (dry or wet?)</td>
<td>15/19</td>
<td>79%</td>
</tr>
<tr>
<td>Diagnosis and follow-up of pleural effusion</td>
<td>18/19</td>
<td>95%</td>
</tr>
<tr>
<td>Diagnosis and follow-up of pneumonia</td>
<td>13/19</td>
<td>68%</td>
</tr>
<tr>
<td>Diagnosis and follow-up of acute heart failure</td>
<td>17/19</td>
<td>89%</td>
</tr>
<tr>
<td>Clinical follow-up of respiratory diseases diagnosed with other methods</td>
<td>9/19</td>
<td>47%</td>
</tr>
<tr>
<td>Invasive procedures (thoracentesis, central venous lines)</td>
<td>15/19</td>
<td>79%</td>
</tr>
<tr>
<td>Diaphragmatic motility assessment during noninvasive mechanical ventilation</td>
<td>2/19</td>
<td>11%</td>
</tr>
</tbody>
</table>
others declared that ultrasound can be useful only in selected cases according to their clinical experience. Forty-seven percent of head doctors (9/19) declared that ultrasound results determined a change in the patient management in a substantial proportion of cases, while 53% (10/19) felt that the diagnostic pathway can benefit from ultrasound results only in selected cases.

DISCUSSION AND CONCLUSIONS

Our survey demonstrated that, in a convenience sample of 25 Italian geriatric hospital wards, bedside ultrasound is generally available, and quite used for exploring the chest in case of respiratory symptoms. However, thoracic ultrasound is not widely applied as a complement to physical examination in around one third of wards, being executed only in selected situations such as assistance to invasive procedures, diagnosis of heart failure and monitoring of pleural effusions. These situations represent the most conventional and consolidated applications of chest ultrasonography.

The use of chest ultrasound in emergency-urgency situations in Italian geriatric wards is limited, since around a half of questionnaire responders declared that this technique is not routinely used for the diagnostic workup of acute dyspnea. This circumstance is probably a consequence of the reduced number of geriatricians trained in chest ultrasonography, since in most wards only three or less staff members are able to perform the examination. It may also be the consequence of a limited confidence in the diagnostic capacity of chest ultrasound. In fact, around a half of geriatric head doctors felt that chest ultrasound was able to change the patient management in only selected cases. However, ultrasound was recognized as potentially able to improve the diagnostic pathway of respiratory diseases by most questionnaire responders. Thus, in a significant percentage of wards chest ultrasound is considered a promising diagnostic examination, but it has not completely entered everyday clinical practice.

This cautious attitude towards chest ultrasound is not in accordance with some of the most recent literature findings, supporting the usefulness of chest ultrasonography in guiding clinical reasoning in the management of acute dyspnea and for improving the clinical and radiological diagnosis of heart failure, pneumonia, pneumothorax and pleural effusion. These findings however come from studies performed in EDs, with a case-mix that may not be completely overlapping with geriatric wards. The cautious attitude of Italian geriatricians towards chest ultrasound could also depend on the knowledge of some intrinsic limitations of the technique, that may be emphasized in older patients. In fact, ultrasound cannot investigate deeper regions of the chest and as much as 30% of the pleural surface, leading to a significant number of false negative scans in pneumonia, lung cancer and pneumothorax. For example, according to a recent study, in a large series of chest radiography-confirmed pneumonia, thoracic ultrasound missed the detection of 26.5% of lesions, proving useful only for follow-up of viewable consolidations. Moreover, B-lines, the comet-tail artifacts commonly associated with pulmonary congestion, do not allow to distinguish pulmonary edema from alternative causes of congestion in a small, but significant number of cases.

Besides this attitude, there is also a significant number of wards where chest ultrasound is performed in many different clinical situations, including also advanced applications, such as diaphragm ultrasound assessment during non-invasive ventilation and integration with transthoracic echocardiography. M-mode diaphragm ultrasound is a highly reproducible technique that can help to predict the outcome of mechanical ventilation even in geriatric patients. In one ward, the integration of chest ultrasound with clinical data could even be utilized as a replacement for X-ray, especially for monitoring the course of different respiratory diseases. This advanced utilization is supported by data from the scientific literature, highlighting that the diagnostic capacity, in terms of Area Under the Receiver Operating Characteristic curve, of ultrasound for the diagnosis of pneumonia is significantly better than that of traditional X-ray.

Chest ultrasound is also particularly popular among young geriatricians and geriatricians in training. In two thirds of the wards participating to the survey, residents are trained in chest ultrasonography. This circumstance is particularly qualifying for Italian post-graduate

<table>
<thead>
<tr>
<th>Timing</th>
<th>Number of wards</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>During physical examination, at the moment of the first evaluation of the patient</td>
<td>13/19</td>
<td>68%</td>
</tr>
<tr>
<td>In case of need, during emergency/urgency situations</td>
<td>13/19</td>
<td>68%</td>
</tr>
<tr>
<td>In election, following a scheduled agenda</td>
<td>8/19</td>
<td>42%</td>
</tr>
<tr>
<td>During clinical follow-up of inflammatory or hemodynamic conditions</td>
<td>12/19</td>
<td>63%</td>
</tr>
</tbody>
</table>
Chest ultrasound in Italian geriatric wards: use, applications and clinicians’ attitudes

geriatric training courses, and adherent to the most recent recommendations by scientific societies that support the necessity of providing ultrasound training to young physicians. However, the ultrasound training of geriatric residents is not generally formalized into a scheduled education program. The recent development of a European curriculum in Geriatric Emergency Medicine, identifying the essential skills of geriatricians delivering acute care, should represent a great opportunity to include chest ultrasound training in geriatric education.

Chest ultrasound is useful for assisting the diagnostic process even in the hands of physicians in training with limited clinical and ultrasonographic experience, particularly when the integration of ultrasound with clinical data suggests a focused diagnostic question. Unlike abdominal ultrasound, a limited number of examinations seems to be required to achieve a sufficient level of competency in basic chest ultrasound while prolonged and continuous training is of course necessary for advanced applications. This is probably one of the most important points of strength of this technique, that should be particularly developed in the geriatric setting, where the complexity of patients in many cases prevents the prescription of advanced imaging tests. Standardization of training methods and rigorous definition of reporting is however required, to avoid inhomogeneity and misuse of applications.

Our survey has certain some limitations, due to the relatively reduced number of participating wards and methodology of data collection (e-mailed questionnaire). However, we believe that it provides a quite reliable pictures of the current utilization of chest ultrasound, and attitudes towards it, in Italian acute-care geriatric wards. Some critical issues highlighted by our survey (reduced number of trained physicians, lack of a formalized training pathway, disparity in utilization) consistently overlap with the findings of similar surveys conducted in EDs, ICUs and acute-care units of other countries. However, the attitude of geriatricians towards chest ultrasound is generally more cautious than that of emergency physicians, that consider this technique as an essential skill for everyday practice. Chest ultrasound should therefore be implemented in geriatric practice and research, promoting training courses among geriatricians and making them aware of the advantages of this diagnostic method in the patient care. The GRETA Group is currently planning research and training initiatives to spread chest ultrasound techniques in geriatric wards, standardize its applications and promote education for young geriatricians, with the ultimate aims of advancing knowledge for a better patient care and filling the gap of ultrasound competency with other internal medicine specialties.

References

SURVEY ON THORACIC ULTRASOUND AVAILABILITY, PRACTICE AND PERCEPTION IN ITALIAN GERIATRIC WARDS

Number of ward beds __________________

Academic Hospital: YES NO
Teaching ward: YES NO

1. Is portable ultrasound equipment available in your ward?
   • YES
   • NO

2. Is clinical bedside ultrasound (abdomen, vascular, thyroid, fast protocols for trauma assessment) performed in your ward?
   • YES
   • NO

3. If yes, how much frequently?
   • Every day, in all patients who have a clinical indication for it
   • Only in selected situations and not every day, based on clinical conditions and ultrasound availability
   • Not applicable

4. Is bedside chest ultrasound performed in your ward?
   • YES
   • NO

If no, please go to question number 20.
5. If yes, how much frequently is chest ultrasound performed?
   • Every day, in all patients who have a clinical indication for it
   • Only in selected situations and not every day, based on clinical conditions and ultrasound availability

6. How many physicians are able to perform chest ultrasound in your ward? ________

7. In your ward, are there any physicians in training or residents able to perform chest ultrasound under the supervision of a tutor?
   • YES
   • NO

8. In which clinical setting is chest ultrasound performed in your ward? (Multiple answers allowed)
   • Intensive or Subintensive Care
   • Acute-care ward
   • Long-term care ward
   • Outpatient clinic

9. Where is chest ultrasound performed?
   • At the bedside
   • In a separate room, devoted to ultrasound, inside the ward
   • In a separate room, devoted to ultrasound, outside the ward
   • Not applicable

10. For what clinical questions is chest ultrasound performed in your ward? (Multiple answers allowed)
    • Differential diagnosis of acute dyspnea/respiratory insufficiency
    • Volemic state evaluation (dry or wet?)
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- Diagnosis/follow-up of pleural effusions
- Diagnosis/follow-up of pneumonia
- Diagnosis/follow-up of acute heart failure
- Clinical monitoring of respiratory conditions diagnosed with other examinations
- Invasive procedures (thoracentesis, central venous line, pleural drainage)
- Evaluation of diaphragm motility
- Other (please specify______________________________)

11. With respect to traditional chest X-ray, how is chest ultrasound used in your ward practice?

- Ultrasound is performed as a substitute for chest X-ray
- Ultrasound is used to integrate chest X-ray irrespective of X-ray findings
- Ultrasound is used to integrate chest X-ray only if X-ray yields negative or uncertain results, or results that are not in accordance with the clinical presentation
- Other (please specify______________________________)

12. When is chest ultrasound performed on acute patients in your ward’s clinical practice? (Multiple answers allowed)

- In combination with the physical examination, at the moment of the first evaluation
- In case of urgency
- Following a scheduled program
- For monitoring inflammatory and circulatory conditions, without a specified schedule
- Chest ultrasound is not performed on acute patients
13. Is chest ultrasound integrated with bedside transthoracic echocardiography in your ward’s practice?
   - YES
   - NO

14. Is chest ultrasound integrated with ultrasound evaluation of diaphragmatic motility in your clinical practice?
   - YES
   - NO

15. Based on your personal experience, do you feel that chest ultrasound improves the diagnostic pathway of older patients with dyspnea or other acute respiratory symptoms, as compared to X-ray?
   - In every situation
   - Only if chest X-ray results negative
   - Only in selected situations
   - Never

16. How much frequently do chest ultrasound findings change the clinical management of geriatric patients admitted to your ward?
   - Very often
   - Only in some selected cases
   - Rarely
   - Never

17. Do you feel that the use of chest ultrasound has contributed to decrease the number of chest Computed Tomography prescriptions in your ward?
   - YES
   - NO
   - NOT ABLE TO JUDGE
Atherosclerosis impacts the link between hepatocyte growth factor and cognition

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INTRODUCTION

Hepatocyte growth factor (HGF) is a heparin-binding polypeptide (728 amino acids) that regulates the growth, migration, and morphogenesis of various cells. An increased serum level of HGF has been reported in patients with hypertension, peripheral arteriosclerosis and carotid atherosclerosis. Ankle-brachial index (ABI) is considered as a marker of atherosclerosis. We hypothesized that hypertension or atherosclerosis with hypertension could alter the relation between HGF serum level and cognitive function.

Aim. To study HGF and cognitive function in hypertensives with and without atherosclerosis versus healthy controls.

Methods. This case-control study included ninety elderly subjects attending outpatient primary care geriatric clinics. They were subdivided into 3 groups; Group A (30 normotensives with normal Ankle-brachial index (ABI) as controls, group B (30 hypertensives with normal ABI) and group C (30 hypertensives with abnormal ABI) as cases. Cognitive function was assessed by Rowland Universal Dementia Assessment Scale (RUDAS).

Results. Group C had worse score in RUDAS than controls (P = 0.01). HGF was negatively correlated with ABI in group C (p = 0.007). HGF was positively associated with RUDAS score, in group A (p < 0.001), in group B; after further adjustment for systolic blood pressure (SBP) (p = 0.024) and in group C; after adjustment for ABI (p = 0.031) or ABI and SBP (p = 0.05).

Conclusions. The potential beneficial link between HGF serum concentration and cognition was met in normotensive subjects with normal ABI. However, this link is halted in the presence of hypertension or atherosclerosis as assessed by ABI. Alternatively, the raised HGF serum level may be an epiphenomenon of atherosclerosis.

Key words: ankle-brachial index, atherosclerosis, cognition, hepatocyte growth factor, hypertension
Atherosclerotic vascular disease affects large- and medium-sized arteries of most circulatory beds and it is the leading cause of death and disability in developed countries. Lower-extremity atherosclerosis, peripheral arterial disease (PAD), is a significant public health problem.

There is a controversy about the association between HGF serum level and cognition. Although some consider HGF as a new targeted therapy in dementia, others found that it is associated with cognitive dysfunction, with reports about increased HGF levels in the cerebrospinal fluid (CSF) of patients with AD. Similarly, others found that HGF serum level is associated with the presence of cardiovascular disease (CVD) risk factors. Recently, literature has increased interest in evaluating the link between dementia and serum HGF. Zhu et al found that magnetic resonance imaging (MRI) markers of small vessel disease (SVD) rather than large vessel disease were associated with higher serum HGF, among those with cognitive impairment not demented or Alzheimer's disease.

As previous literature reported the presence of SVD in normal elderly and diabetics, along with the supposed cross talk between large and small arteries in hypertensives, the current work aimed to explore the link between HGF serum level and cognition in hypertensive elderly with abnormal ankle-brachial index (ABI), as a known marker of atherosclerosis, and hypertensive elderly with normal ABI versus controls, among non-diabetic subjects.

As atherosclerosis, which is of a major link to hypertension, is linked to vascular dementia, we hypothesized that hypertension or atherosclerosis with hypertension could alter the relation between HGF serum level and cognitive function.

MATERIALS AND METHODS

A case-control study was conducted among elderly subjects, aged ≥ 60 years, attending outpatient primary care geriatric clinic. Ninety eligible elderly patients were consecutively included and were subdivided into 3 groups. Group A included 30 normotensive subjects with normal ABI as controls, group B included 30 hypertensive subjects with normal ABI as cases and group C included 30 hypertensive subjects with abnormal ABI as cases. The data were collected from January 2017 to June 2017. Those with diabetes mellitus, severe liver or renal dysfunction or cancer were excluded from the study because serum levels of HGF are well known to be influenced by these diseases.

Subjects were excluded if they had severe sensory or cognitive impairment which could interfere with the assessment or refused to participate. The minimum sample size was based upon the odd ratio for the association between ABI and cognitive test performance in elderly. Using Epi-info program, version 3.5.1, power 1-B 80%, and confidence interval of 95%, the minimum number was 16 for cases and 16 for controls.

COGNITIVE FUNCTION

It was assessed by The Rowland Universal Dementia Assessment Scale (RUDAS). The RUDAS is a cognitive assessment tool that was created for culturally and linguistically diverse populations. The RUDAS is a 6-item questionnaire that assesses multiple cognitive domains and can be administered in less than 10 minutes. In the original validation study of RUDAS, both the interrater and test-retest reliabilities of the test were very high. Compared with the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), the RUDAS was found to have a sensitivity of 89% and a specificity of 98%. Performance on the RUDAS was not affected by years of education or the preferred language.

DIAGNOSIS OF HYPERTENSION

Blood pressure was measured using a standard mercury sphygmomanometer in the right arm, in supine position after rest for 5 minutes. Systolic and diastolic blood pressure was recorded as the mean of two measurements. The diagnosis of hypertension was based upon known history of hypertension diagnosis and its treatment or it was based upon the cutoff values stated by the National heart foundation of Australia, systolic ≥ 140 mmhg and/ or diastolic ≥ 90 mmhg, on two separate occasions, at least one week apart.

MEASUREMENT OF ANKLE-BRACHIAL INDEX

The ABI is an objective non-invasive reproducible measure that reflects PAD severity, and ABI is considered as a marker of atherosclerosis in the Cardiovascular Health Study, Cardiovascular Heart Study Collaborative Research Group. ABI was assessed by hand-held vascular Doppler, BT-200, HI-dop. Steps were applied according to known references, with abnormal ABI < 0.9.

LABORATORY DATA

Sampling

Five milliliters of fasting venous blood were collected under complete aseptic precautions in plain test tubes.
The serum was separated by centrifugation (1000x g for 15 minutes) and was divided into two aliquots. One was designated for the immediate assay of fasting lipid profile. The other aliquot was stored at -20ºC for subsequent assay of HGF. Hemolysed samples were discarded. Repeated freezing and thawing were avoided.

**Analytical Methods**

Serum fasting lipid profile [total cholesterol, triglycerides (TG) and high-density lipoprotein-cholesterol (HDLC)] was measured using Synchron CX-9 autoanalyser (Beckman Instruments Inc.; Scientific Instruments Division, Fillerton, CA 92634, 3100, USA). Low density lipoprotein-cholesterol (LDL-C) value was calculated according to Friedewald equation. HGF assay was done using the commercially available enzyme-linked immunosorbent assay (ELISA) kit, supplied by Elabscience Company (Building 4, Room 401, Guandong Science and Technology Industry Park, Wuhan, P.R.C.).

**Statistical Method**

SPSS version 16 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Qualitative data were expressed in the form of number and percentage and were compared using Chi-Square test. Quantitative data were expressed in the form of mean ± SD for parametric data or median and interquartile range for non-parametric data and were compared using ANOVA test (with least significant difference as post-hoc test), after log transformation of non-parametric data. Distribution normality was assessed using a z test for skewness.

Generalized linear model was used to study the significance of serum HGF level as a predictor of cognitive function, linear distributional assumption was used, in each group, after adjustment for the possible confounding variables.

**Results**

Using ANOVA, there was no significant difference between the 3 groups in age (p = 0.98).

Serum HGF concentration was higher in group C (hypertensives with abnormal ABI) compared with group A (controls) or B (hypertensives with normal ABI) (p < 0.001 and 0.025 consecutively), and serum HGF concentration was higher in group B than group A (p = 0.028) (Tab. I).

Group C had worse RUDAS score than controls (P = 0.01), with no significant difference between group B and C in RUDAS score (p = 0.22) (Tab. I).

<table>
<thead>
<tr>
<th>Table I. Comparing characteristic data between the 3 groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A (controls)</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Males (n, %)</td>
</tr>
<tr>
<td>Education years*</td>
</tr>
<tr>
<td>Smoking Index*</td>
</tr>
<tr>
<td>IHD</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>SBP (mmhg)</td>
</tr>
<tr>
<td>DBP (mmhg)</td>
</tr>
<tr>
<td>BMI*</td>
</tr>
<tr>
<td>WC (cm)</td>
</tr>
<tr>
<td>GDS-15 score*</td>
</tr>
<tr>
<td>T chol. (mg/dl)</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
</tr>
<tr>
<td>ABI*</td>
</tr>
<tr>
<td>RUDAS score</td>
</tr>
<tr>
<td>HGF (pg/ml)*</td>
</tr>
</tbody>
</table>

ABI: Ankle-Brachial Index; BMI: Body Mass Index; DBP: Diastolic Blood Pressure; GDS-15: Geriatric Depression Scale-15 items; HDLC: High Density Lipoprotein-cholesterol; HGF: Hepatocyte Growth Factor; IHD: ischemic heart disease; LDL-C: Low Density Lipoprotein-cholesterol; RUDAS: Rowland Universal Dementia Assessment SCALE, SBP: Systolic Blood Pressure; T chol.: Total cholesterol; TG: Triglycerides; WC: waist circumference; * data were expressed as median (interquartile range) for non-parametric quantitative data; P1, P2 and P3: P values for post-hoc analysis; P1: Group A vs Group B; P2: Group A vs Group C; P3: Group B vs Group C.
By Pearson correlation, serum HGF concentration was positively correlated with RUDAS score only in group A ($p = 0.035, r = 0.4$). HGF concentration was negatively correlated with ABI, in group C ($p = 0.007, r = -0.49$), and it was positively correlated with systolic blood pressure (SBP), in group B ($p = 0.045, r = 0.37$). In group C, HGF was positively correlated with SBP, after adjustment for ABI. Serum HGF concentration was not correlated with lipid profile.

Generalized linear model, in each group, revealed the followings; in group A, serum HGF concentration was positively associated with RUDAS score ($p < 0.001$). In group B, serum HGF concentration was positively associated with RUDAS score only after further adjustment for SBP ($p = 0.024$). In group C, serum HGF concentration was positively associated with RUDAS score only after adjustment for ABI or ABI and SBP ($p = 0.031$ and 0.05 consecutively) (Tab. II). After further adjustment for lipid profile, the significant association between HGF and RUDAS score was found only in controls ($p = 0.017, OR = 1.004$ and CI = 1.001-1.006).

Furthermore, adjustment for gender, body mass index, ischemic heart disease and lipids doesn’t affect the significant association between HGF and RUDAS score in controls ($p = 0.017, OR = 1.004$ and CI = 1.001-1.006).

**DISCUSSION**

The current data explored that HGF was higher in hypertensives with/or without abnormal ABI than controls, and hypertensives with abnormal ABI had higher HGF than hypertensives with normal ABI. Therefore, HGF might mediate the pathology of hypertension ± atherosclerosis. Alternatively, the raised HGF serum level may be an epiphenomenon of hypertension ± atherosclerosis.

This is in accordance with Yoshitomi et al. 27 who found that patients with PAD showed higher serum HGF concentrations than controls. Similarly, Nakamura et al. 28 explored that serum HGF concentration in hypertensive subjects without any complication was higher than normotensive subjects ($p < 0.001$). Furthermore, serum HGF concentration in hypertensive patients with complications was significantly higher than those without complication or normotensive subjects.

Recently, Bell et al. 29 proved the positive association

| Table II. Predictors/associates of RUDAS score, in each group. |
|---------------------|-----|-----|-----|-----|-----|
| **Groups** | **Parameter** | **B** | **Sig.** | **O.R.** | **95% Confidence Interval for O.R.** |
| **Controls** | | | | | |
| • Step 1: | HGF | 3.172 | < 0.001 | 23.846 | 8.276-68.712 |
| • Step 2: | HGF | 3.537 | < 0.001 | 34.370 | 10.409-113.484 |
| | ABI | 14.494 | 0.017 | 1.971E6 | 12.747-3.04E11 |
| • Step 3: | HGF | 4.281 | < 0.001 | 72.288 | 21.288-245.475 |
| | ABI | 7.880 | 0.204 | | |
| | SBP | 0.110 | < 0.001 | 1.116 | 1.074-1.160 |
| **Hypertensive with normal ABI** | | | | | |
| • Step 1: | HGF | 0.512 | 0.246 | | |
| • Step 2: | HGF | 0.564 | 0.206 | | |
| | ABI | 7.405 | 0.411 | | |
| • Step 3: | HGF | 1.081 | 0.024 | 2.948 | 1.155-7.526 |
| | ABI | 6.561 | 0.467 | | |
| | SBP | -0.037 | 0.003 | 0.964 | 0.941-0.988 |
| **Hypertensive with abnormal ABI** | | | | | |
| • Step 1: | HGF | 0.099 | 0.782 | 1.104 | 0.550-2.216 |
| | ABI | 0.878 | 0.031 | 2.407 | 1.084-5.342 |
| • Step 2: | ABI | 6.694 | < 0.001 | 807.519 | 29.081-22423.449 |
| | HGF | 0.789 | 0.05 | 2.201 | 0.989-4.900 |
| • Step 3: | ABI | 5.936 | 0.001 | 378.581 | 12.984-11038.819 |
| | SBP | -0.038 | 0.009 | 0.963 | 0.935-0.991 |

ABI: Ankle-Brachial Index; HGF: Hepatocyte Growth Factor; RUDAS: Rowland Universal Dementia Assessment Scale; SBP: Systolic Blood Pressure; step 1: HGF was used in regression alone; step 2: adjusted regression for ABI; step 3: adjusted regression for ABI and systolic blood pressure.
between higher circulating HGF levels at baseline and the progression of atherosclerosis, as defined by coronary artery calcium and carotid plaques, among participants aged 45-84 years. Additionally, Decker et al. reported positive relation between changes in HGF levels and clinical coronary heart disease; rather than subclinical atherosclerosis, as defined by coronary artery calcium.

The positive association between SBP and HGF serum level, in the current work, was in accordance with Nakamura et al. The current results explored that serum HGF concentration was negatively associated with ABI, as a marker of atherosclerosis. This might be explained by Taher et al. who declared that the migration of vascular smooth muscle cells (VSMCs) to the intima is the main event in neo-intima formation and atherogenesis. They found that Met, the receptor for HGF, is expressed on VSMCs derived from the intima of atherosclerotic plaques. Furthermore, HGF promoted VSMC migration across fibronectin-coated filters. Their findings suggested a role for the HGF in the pathogenesis of atherosclerosis and restenosis.

Although some previous evidence found a possible role for serum HGF concentration for the treatment of PAD, through angiogenesis and improved necrosis in rat ischemic limbs, these positive results were not the same for humans in two multicenter, double blind, placebo controlled clinical trials by Powell et al. and Shigematsu et al.

In the current study, serum HGF concentration was positively associated with cognitive performance, in controls. These data are supported by previous experimental studies which revealed improvement in neurodegenerative diseases by HGF. The beneficial effect of HGF could be explained by Takeuchi et al. who found that injection of A-beta peptide decreases the blood-vessel density which improved after HGF expression. A decrease in cerebral blood flow is observed in Alzheimer disease patients. These findings are also attributed to the anti-apoptotic effect of HGF on endothelium via Bcl-2 induction, Bcl-2 is an inhibitor of apoptosis.

On the other hand, previous studies found increased HGF levels in the CSF of patients with AD, however other cardiovascular risk factors were not considered. Recently, Zhu et al. linked MRI markers of SVD, rather than large vessel disease, to higher serum HGF levels, among those with cognitive impairment not demented or Alzheimer’s disease subjects, even after controlling for cardiovascular risk factors. Zhu et al. excluded vascular dementia and stated that the precise mechanism for small rather than large vessel disease is unclear.

Hypertensives with abnormal ABI had worse RUDAS score than controls, and in cases, serum HGF concentration was positively associated with RUDAS score, only after further adjustment for SBP and ABI. These findings suggest the negative impact of hypertension and atherosclerosis on the positive association between HGF serum concentration and cognitive function. After further adjustment for lipid profile, the significant association between HGF and RUDAS score was found only in controls. Although of the presence of traditional knowledge about the deleterious effect of lipids upon cognition, this is not a well established risk in recent intervention studies, even some studies linked higher levels of cholesterol, triglyceride and LDL in older adults to a lower risk for vascular dementia and better cognitive performance.

CONCLUSIONS

The potential beneficial link between serum HGF concentration and cognitive function could be met in normotensive subjects with normal ABI. However, this link is halted in the presence of hypertension or atherosclerosis, as assessed by ABI, which was negatively associated with serum HGF concentration. Alternatively, the raised HGF serum level may be an epiphenomenon of atherosclerosis.

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Delirium accompanies kidney dysfunction in hospitalized elderly patients

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INTRODUCTION

Delirium, defined as an acute mental status with altered level of consciousness, is a common geriatric syndrome and a typical complication in hospitalized elderly patients. We aimed to assess the occurrence of delirium and the possible relationship with renal impairment.

Methods. Patients aged over 65 years admitted consecutively to a Geriatric Unit, were screened for a first diagnosis of delirium. Delirium was evaluated using the validated Assessment Test for Delirium and Cognitive Impairment (4AT).

Results. Final analysis included 311 patients (182 women, 129 men). Mean eGFR was 62.44 ± 28.84 mL/min/1.73 m². Prevalence of Cognitive impairment or delirium was 5.4, 84.8 e 9.8% for 0, 1-3 and ≥ 4 4AT scores. At univariate analysis, prevalence of clear delirium was increased with the worsening of CKD, being 3.7% in stage IIIb up to 68% in stage IV-V (p < 0.001). At multivariable logistic analysis, adjusted for gender and smoking habit, higher eGFR levels were associated with a reduced risk for the presence of delirium (OR = 0.86 95% CI 0.82-0.91, p < 0.001) and for developing possible cognitive impairment (OR = 0.87 95% CI 0.83-0.90, p < 0.001).

Discussion. Mild to moderate delirium is a pervasive condition among geriatric patients with manifested renal function impairment.

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of previous cognitive disorders, represent other acknowledged predisposing factors 4.

Chronic kidney disease (CKD) is another hallmark of geriatric populations that may increase the risk of acute neurological sequelae. Besides vascular complications, elderly individuals with CKD are highly prone to develop cognitive dysfunction and encephalopathy due to a series of factors including inflammation, uremic toxins, oxidative stress and an altered permeability of the blood brain barrier 5. Early identification of neurological conditions is of foremost importance in this population setting, in order to establish proper therapeutic management and to avoid irreversible clinical impact at later stages.

In our study, we aimed to assess the incidence and severity of acute cognitive impairment in a series of individuals hospitalized in a geriatric division and to explore the possible relationship with the severity of chronic renal impairment and other risk factors.

METHODS

Individuals aged over 65 years hospitalized between March and July 2018 in the Geriatric Unit of “Pugliese-Ciaccio” General City Hospital of Catanzaro (Italy) were screened for the presence of cognitive impairment using the Assessment Test for Delirium and Cognitive Impairment (4AT), a validated short test for patients admitted to acute and rehabilitation hospital wards 6,7.

A score of ≥ 4 indicates delirium and/or cognitive impairment, 1-3 possible cognitive impairment, 0 neither delirium nor cognitive impairment. Severity of CKD was assessed by estimated Glomerular Filtration Rate (eGFR) computed according to CKD-EPI formula. Since the urine protein excretion value was not routinely collected, the KDOQI staging was used to define the CKD stage: I-II, IIIa, IIIb, IV and V if eGFR was > 60, 60-45, 30-44, 15-29, < 15 mL/min/1.73 m². Prevalence of delirium (score ≥ 4) was calculated in the overall cohort and for CKD stage.

Blood samples were taken in the morning before any food intake and traditional biochemical parameters were measured at baseline in all subjects, following standard methods in the routine clinical laboratory (Tab. I). Blood pressure was measured three times and the average value was considered for data analysis. Exclusion criteria were the following: patients with no verbal communication (for pathological reasons or unable to speak or communicate in Italian for lack of interpreters), severe hearing or learning disability or in a state of unconsciousness according to a score of ≤ 4 or less at the Richmond Agitation and Sedation Scale (RASS) 9. Informed consent from patients or their legal proxies was obtained.

ETHICAL APPROVAL

This study adhered to the principles of the Declaration of Helsinki. Ethical approval was granted by “Pugliese-Ciaccio” General City Hospital of Catanzaro (Italy). All participants gave informed consent.

STATISTICAL ANALYSIS

Continuous variables were reported as either mean ± standard deviation (SD) or median and interquartile (IQR) range, based on their distribution. Comparison among 4AT score categories was assessed by one-way ANOVA or Kruskall-Wallis test. Categorical variables were analyzed using Chi-square test. We built a multivariable logistic regression model using a backward elimination process beginning with a full model where clinical variables with a plausible effect on the onset of delirium have been included. Presence of delirium at basal visit was the dependent variable of the logistic model. A variable was removed if its p-value was > 0.15. Amore stringent cutoff was not used to avoid eliminating potentially important predictor variables 10. Multicollinearity was assessed with variance inflation factors, which is a measure of the degree to which a single predictor variable can be expressed as a linear combination of the remaining predictor variables; values greater than 10 are cause for concern 11.

As sensitivity, we performed an ordinal logistic regression under a proportional odds model to evaluate the predictors of changing score 4AT categories 12. This approach simultaneously models two cumulative logits that corresponds to using 4AT cut points at 1 and 3, written as \( \log[\text{Pr}(RI \geq 1)/\text{Pr}(RI < 1)] \) and \( \log[\text{Pr}(RI > 3)/\text{Pr}(RI \leq 3)] \), respectively. Under this proportional odds model, one coefficient is estimated for each predictor in the model. The coefficient represents the effect of a one-unit increase in the predictor variable on the logit (log odds), which is assumed to be the same for both logits. A score test was used to verify the proportional odds assumption in the final 13. First order interaction effects between covariates for the presence of delirium were also tested from the model. A two-tailed \( p \) value < 0.05 was considered significant for all analyses. Data were analyzed using STATA version 14 (Stata Corp. College Station, TX, USA).

RESULTS

We studied 311 geriatric patients (182 women, 129 men). Subjects had a mean age of 81.4 ± 6.9 yrs (ranging from 66 to 100 yrs). Demographics and clinical characteristics of patients are depicted in Table I. Overall population was characterized by a mean eGFR of 62.44 ± 28.84 mL/min/1.73 m², with 51.4% and...
48.6% of patients falling above and below the eGFR cut-off of 60 mL/min/1.73 m², respectively. Prevalence of current smokers was moderate and amounted to 14.1% of the entire population. Overall lipid profile was normal with total cholesterol and LDL-cholesterol, being 144 ± 48 and 77 ± 37 mg/dL, respectively. Patients at hospital admission were intensively treated, being the mean number of drugs per patient 8.1 ± 2.9. From admission to hospital discharge, treatments were increased in 39%, reduced in 22.5% and unchanged in 38.6% of patients. Delirium and cognitive deficiency were fully absent in only 5.47% of the study cohort. Conversely, 84.89% had a 4AT score of 1-3, suggesting a mild cognitive impairment, and 9.64% had a score of ≥4, indicating clear delirium. Moving from the normal range to clear delirium according to the 4AT score, frequency of smokers, levels of serum potassium and uric acid, were significantly increased (p < 0.001, 0.007 and 0.013, respectively). A similar trend, although not significant, was shown for ages that ranged from 79.1 ± 8.1 years in absence of delirium to 83.6 ± 6.8 years in the clear delirium category. Conversely, impairment of kidney function, as assessed by eGFR values, was significantly increased from lower to higher 4AT score categories (p < 0.001).

As depicted in Figure 1, prevalence of cognitive impairment was higher in mild-moderate CKD stages (I to IIIa) than in advanced stages, whereas the prevalence of clear delirium increased from 3.7% for stage IIIb to 66.7% and 69.2% for stage IV and V, respectively. This trend was overall significant (p < 0.001).

At multivariable adjusted analyses (Tabs. II, III), male gender and patients with preserved kidney function were less likely to have delirium (OR = 0.14 and 0.86 respectively). On the other hand, current smokers showed a 10-fold increased risk for the presence of clear delirium (p = 0.008). Similar results were found, by restricting analysis to patients with eGFR < 60 mL/min/1.73 m² (Tab. III). VIF (Variance Inflation Factors) was < 10, the threshold of concern for multicollinearity. In Table II, VIF was 1.86, 1.66 and 1.19 for gender, eGFR and smoking habit, suggesting that considering these variables as independent predictors in the multivariable model was appropriate. At ordered logistic regression (Fig. 2), that considered the predictors of changing 4AT score categories as endpoints, eGFR persisted as an independent risk factor (OR = 0.87 95% CI 0.83-0.90, p < 0.001). This means that a reduction in eGFR levels is independently associated with the presence of cognitive impairment as compared to normal category and with the presence of delirium as well. Score test for proportional odds was not significant (p = 0.135), thus suggesting that modeling an ordered logistic regression from these data was appropriate. No interactions

### Table I. Baseline characteristics of patients overall and by 4AT delirium categories.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 311)</th>
<th>Score 4AT</th>
<th></th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n = 17)</td>
<td>1-3 (n = 264)</td>
<td>4  (n = 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>81.4 ± 6.9</td>
<td>79.1 ± 8.1</td>
<td>81.3 ± 6.8</td>
<td>83.6 ± 6.8</td>
<td>0.079</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>41.5</td>
<td>52.9</td>
<td>42.0</td>
<td>30.0</td>
<td>0.275</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>14.1</td>
<td>5.9</td>
<td>11.0</td>
<td>46.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index, Kg/m²</td>
<td>25.7 ± 4.1</td>
<td>25.0 ± 4.4</td>
<td>25.7 ± 4.1</td>
<td>25.9 ± 3.8</td>
<td>0.779</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>62.4 ± 28.8</td>
<td>118.1 ± 15.8</td>
<td>63.5 ± 23.8</td>
<td>21.7 ± 9.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>8.8 ± 0.8</td>
<td>8.7 ± 0.7</td>
<td>8.8 ± 0.8</td>
<td>8.7 ± 0.9</td>
<td>0.634</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>144 ± 48</td>
<td>139 ± 38</td>
<td>145 ± 48</td>
<td>135 ± 56</td>
<td>0.699</td>
</tr>
<tr>
<td>HDL Cholesterol, mg/dL</td>
<td>40 ± 16</td>
<td>51 ± 17</td>
<td>39 ± 16</td>
<td>41 ± 17</td>
<td>0.368</td>
</tr>
<tr>
<td>LDL Cholesterol, mg/dL</td>
<td>77 ± 37</td>
<td>65 ± 13</td>
<td>80 ± 36</td>
<td>59 ± 43</td>
<td>0.147</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>110 ± 56</td>
<td>82 ± 35</td>
<td>109 ± 54</td>
<td>124 ± 78</td>
<td>0.195</td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>138.6 ± 5.6</td>
<td>136.8 ± 5.4</td>
<td>138.9 ± 5.7</td>
<td>137.5 ± 4.7</td>
<td>0.194</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.1 ± 0.8</td>
<td>4.0 ± 0.7</td>
<td>4.1 ± 0.7</td>
<td>4.6 ± 0.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>6.35 ± 2.31</td>
<td>4.43 ± 1.84</td>
<td>6.35 ± 2.27</td>
<td>7.08 ± 2.51</td>
<td>0.013</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.1 ± 2.2</td>
<td>10.8 ± 2.4</td>
<td>11.2 ± 2.2</td>
<td>10.9 ± 2.4</td>
<td>0.651</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.1 ± 1.2</td>
<td>2.6 ± 1.5</td>
<td>3.1 ± 1.2</td>
<td>3.0 ± 1.4</td>
<td>0.295</td>
</tr>
<tr>
<td>CPK, UI/L</td>
<td>53 (34-100)</td>
<td>60 (42-62)</td>
<td>49 [33-89]</td>
<td>67 (41-235)</td>
<td>0.200</td>
</tr>
<tr>
<td>Increasing treatment*, n</td>
<td>38.9</td>
<td>41.2</td>
<td>40.2</td>
<td>26.7</td>
<td>0.138</td>
</tr>
<tr>
<td>Reducing treatment*, n</td>
<td>22.5</td>
<td>11.8</td>
<td>21.2</td>
<td>40.0</td>
<td>0.138</td>
</tr>
<tr>
<td>drugs, n</td>
<td>8.1 ± 2.9</td>
<td>7.1 ± 3.7</td>
<td>8.1 ± 2.8</td>
<td>8.9 ± 2.7</td>
<td>0.113</td>
</tr>
</tbody>
</table>

BMI: Body mass index; eGFR: estimated Glomerular Filtration Rate; drugs refers to the all types of drugs used; p value refers to p for trend between RI risk categories; CPK: creatine kinase; *: change in treatment between admission and discharge from the Hospital.
Delirium accompanies kidney dysfunction in hospitalized elderly patients

between covariates have been found in multivariable models.

**DISCUSSION**

To the best of our knowledge, this is one of the first reports aiming at assessing the relationship between reduced kidney function and the risk of delirium occurrence in a large sample of hospitalized geriatric patients. The findings reported here indicate that mild to moderate delirium was highly pervasive in this study cohort, becoming exceedingly prevalent in patients with severe renal insufficiency. In a recent large German study on patients followed in general practices by family physicians, the prevalence of renal insufficiency in subjects with delirium, assessed by ICD-10, was 18.2% \(^{14}\). Interestingly, in our study the prevalence was notably higher than that reported in the German study. This could be explained by the worse risk profile of our cohort, which was represented by hospitalized patients. The presence of delirium was screened

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**Table II.** Multivariable logistic regression for determinants of the presence of delirium in all patients.

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (vs female)</td>
<td>-2.01</td>
<td>0.14</td>
<td>0.02-0.76</td>
<td>0.023</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m(^2)</td>
<td>-0.15</td>
<td>0.86</td>
<td>0.82-0.91</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking habit, yes vs no</td>
<td>2.35</td>
<td>10.48</td>
<td>1.85-59.21</td>
<td>0.008</td>
</tr>
</tbody>
</table>

OR: Odds Ratio; CI: Confidence Intervals; eGFR: estimated Glomerular Filtration Rate

**Table III.** Multivariable logistic regression for determinants of the presence of delirium in patients with eGFR < 60 mL/min/1.73m\(^2\).

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (vs female)</td>
<td>-1.99</td>
<td>0.14</td>
<td>0.02-0.77</td>
<td>0.024</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m(^2)</td>
<td>-0.14</td>
<td>0.87</td>
<td>0.82-0.91</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking habit, yes vs no</td>
<td>2.33</td>
<td>10.32</td>
<td>1.84-57.96</td>
<td>0.008</td>
</tr>
</tbody>
</table>

OR: Odds Ratio; CI: Confidence Intervals; eGFR: estimated Glomerular Filtration Rate.

Figure 1. Prevalence of 4AT score categories for delirium/cognitive impairment by CKD stage.
with the Assessment Test for Delirium and Cognitive Impairment (4AT), a recently validated, brief and easy to use tool for diagnosis. This tool does not require specific clinical experience or training and has been revealed to be successful in previous studies, in order to minimize the risk of under-detection and misdiagnosis. In our population, reduction of kidney function was associated with an increasing score of 4AT. A diagnosis of clear delirium (score = 4) was confirmed at stages IV and V in about 68% of patients. Conversely, in early stages of CKD (I-IIa, IIIb) the vast majority of patients scored between 1 and 3. These findings confirm that cognitive dysfunction accompanies renal function impairment in a strong and independent manner.

In patients with advanced renal failure needing chronic dialysis, the occurrence of a delirium episode, based on psychiatric symptoms, is relatively more frequent, particularly afterlong periods of substitutive dialysis therapy. Patients on dialysis often manifest with psychological traits of cyclothymia, with continuous changes in state of mind and energy that are rarely as severe as to be considered maniac depressive episodes; however, these symptoms are often sufficient to influence the patient’s quality of life. The mood oscillations are sudden and can be short- or long-term, spanning from joy, to sadness, to irritability with rare moments of cheerfulness. It has been shown, although not completely clarified, that non-dialysis CKD patients are at increased risk for development of cognitive impairment and delirium. The main recognized factors, associated with delirium in CKD patients, are represented by polypharmacy and accelerated cerebrovascular disease. CKD patients are likely susceptible to polypharmacy due to the reduced clearance of commonly prescribed drugs. However, when we added as additional sensitivity analysis, the number of drugs prescribed overall and during hospitalization to the multivariable model (Tab. II), results were confirmed (data not shown). Thus, eGFR decline has been confirmed as a powerful risk factor for delirium, and it is plausible that underlying metabolic disorders, commonly present in CKD, can contribute to the development of this condition. In accordance with other studies, cigarette smoking was related to the occurrence of delirium and represents a potentially modifiable risk factor. Abrupt nicotine withdrawal due to hospitalization has been called into question as a triggering factor for delirium due to an imbalance in neurotransmitters, such as the acetylcholine cascade. In addition to the correlation of smoke with delirium occurrence, smoking habit is an independent risk factor for incident CKD.

Indeed, several previous studies have shown the deleterious nephrotoxic effect of smoking habit. Cigarette
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smoking acts by reducing the nitric oxide availability and endothelial cell-dependent vasodilation, which lead to an enhanced oxidative stress, glomerulosclerosis and renal tubular atrophy. Furthermore, cigarette smoke contains glycotoxins, which induce advance glycation end products and thus directly promote pathological vascular changes.

Our study has some limitations that need to be mentioned. Firstly, the cross-sectional and observational nature of the study does not allow to draw definitive conclusions on the exact causal relationship between renal impairment and delirium occurrence. Secondly, the absence of a follow-up observation did not allow us to analyze in the long-term the possible relationship between the worsening renal function and the occurrence of delirium episodes.

We can speculate that cognitive impairment related to uremia might be the milieu that triggers the manifestation of delirium episodes with neurodegenerative or cerebrovascular mechanisms. Accumulation of uremic toxins results in a neurodegenerative process, causing an alteration of the neural transmission activity. More than 100 retained compounds have been detected as accumulating in CKD patients of which few substances have been clearly identified. In our analysis, we found increased uric acid to be directly correlated with the 4AT score and inversely with eGFR. Uric acid has been largely acknowledged as a promotor of proinflammatory cytokine expression and secretion, as well as a key-factor of atherosclerosis and endothelial dysfunction. Hemodynamic impairment of the vascular axis in CKD causes a direct effect on cerebral endothelium with augmented inflammation and oxidative stress. These factors lead to disruption of the blood-brain barrier with altered cellular water transport that may, in turn, elicit cognitive brain dysfunction and abnormal response to drugs.

In conclusions, in a large cohort of hospitalized geriatric patients, we have found that cognitive impairment is highly prevalent and independently correlated with the severity of renal insufficiency. Simple assessment tests, like the 4AT score, might be advocated to screen geriatric patients with CKD for subclinical forms of cognitive dysfunction. Further studies are required to extend these findings in other cohorts, as well as to clarify the causal factors that may underpin this association.

References


Management of epilepsy in elderly

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INTRODUCTION

The prevalence of seizures and epilepsy in the elderly is generally underestimated. Epileptic seizures are not a rare occurrence in the elderly and their prevalence increases with age. The clinical manifestations of seizures, the aetiology, the treatment and the psychosocial impact of the epilepsy diagnosis may differ in the elderly. Differential diagnosis with episodes of unconsciousness and/or fall or other non-epileptic manifestations is often difficult. The presence of comorbidities, the polypharmatherapy and the age-related pharmacokinetic changes can represent a problem for the treatment of epilepsy in the elderly, with a higher risk of adverse effects and potentially inappropriate drug interactions. Epileptic seizures in the elderly can have semiological characteristics similar to those of other age groups. On the other hand, the richness of the electroclinical syndromes of childhood and adolescence is not found in the elderly, and, in particular, idiopathic generalized epilepsies are rarely expressed at this age. Symptomatic seizures related to acute structural injury or metabolic causes are particularly frequent. Therapy management of the elderly with an epileptic seizure should concern not only neurologists, but also general practitioners, geriatricians, and cardiologists, therefore involving a wide range of clinical specialties. This review aims to summarize the management of epilepsy in the elderly, reporting also differences in epidemiology, electroclinical features, aetiology and diagnostic procedures.

Key words: epilepsy, seizure, older, antiepileptic drugs
aetiology, the treatment and the psychosocial impact of the epilepsy diagnosis may differ in the elderly. Differential diagnosis with episodes of unconsciousness and/or fall or other non-epileptic manifestations is often difficult. The presence of comorbidities, the polypharmatherapy and the age-related pharmacokinetic changes can represent a problem for the treatment of epilepsy in the elderly, with a higher risk of adverse effects and potentially inappropriate drug interactions. Elderlies are more vulnerable to the sequelae of seizures due to physical and psychological trauma, with loss of confidence in autonomy and reduced degree of independence. The concurrence of osteoporosis multiplies the risk of fractures. Fears of seizures and falls can confine an elder at home, or in armchair. Due to seizures, or fear of seizures, the elderly are often excluded and marginalized by the activities. The driving license revocation can greatly limit autonomy and quality of life. Finally, older people have mortality rates 2 or 3 times higher than the general population.

For all these reasons, the management of the elderly with epilepsy should concern not only to neurologists, but also general practitioners, geriatricians, and cardiologists, therefore involving a wide range of clinical specialties. With the worldwide-distributed increase of the elderly population, the problem has also assumed a considerable economic importance, with a growing weight for health care expenditure.

EPIEDEMOLOGY

From the Hauser’ study on the Rochester population, it is possible to evaluate how the incidence of epilepsy, substantially stable between the second and fifth decades of life with 30-40 cases/100,000 persons/year, starts to grow up from the age of 60's, reaching an incidence of around 150 cases/100,000 persons/year in the 80 years old subjects. As expected, the main contribution to increasing epilepsy incidence is given by focal seizures (over 100 cases/100,000 persons/year at 80 years), in relation to the typical aetiology from injury rather than the generalized attacks (around 40 cases/100,000 persons/year at the same age). Hersdorffer et al. investigated the cumulative incidence and probability of a person to develop epilepsy over lifetime (lifetime risk) starting from the current age. The authors calculated that one person out of 26 (1/21 males and 1/28 females) will develop epilepsy during his/her lifetime. This parameter is useful both for clinical and health planning purposes because it allows to predict the weight of the disease in the community. However, the rapid growth in the world of the elderly population, the different prevalence of several diseases expressing with seizures in different countries, the difficulty in collecting data, and the various methodologies used, make it difficult to accurately estimate the incidence of Epilepsy in the elderly, possibly explaining discrete dissimilarities found in other epidemiological studies. It is however evident that epileptic seizures and epilepsy represent a frequent problem of considerable importance in this age of life. Therefore, rather than proceeding on the difficult field of epidemiology, it is more useful to recall some definitions that will occur below (Tab. I).

ELECTROCLINICAL FEATURES OF SEIZURES

Epileptic seizures in elderly can have semiological characteristics similar to those in other age groups. On the other hand, the richness of the electroclinical syndromes of childhood and adolescence is not found in the elderly, and in particular idiopathic generalized epilepsies are very rarely expressed at this age. In relation to age-specific aetiologies, the contribution of different seizures types (clear prevalence of partial, simple or complex seizures, with or without secondary generalization) and of epileptic syndromes (greater prevalence of symptomatic epilepsies than idiopathic ones), and acute symptomatic seizures related to structural injuries or metabolic causes are particularly frequent. It is also necessary to point out some milestones:

- the post-ictal status can be particularly prolonged, and a post-ictal hemiparesis (Todd's paralysis) is frequently found, sometimes raising the issue with a differential diagnosis of stroke;
- some types of seizures are peculiar of the elderly, such as confusional states with periodical lateralized epileptiform discharges (PLEDs) and transient epileptic amnesia (TEA);
- status epilepticus is particularly frequent in the elderly, often marking the onset of epilepsy or in the context of acute symptomatic seizures, and is burdened by frequent mortality. Myoclonic seizures following cardiac arrest and cardio-respiratory resuscitation are characterized by poor prognosis, with over 90% of death or persistent vegetative status. Non-convulsive status epilepticus must be considered in the differential diagnosis of confusional disorders in elderly;
- the contribution of intercritical EEG in diagnosis is generally less relevant than in the Epilepsies of childhood-adolescence-youth. Ictal recordings, on the other hand, are crucial, allowing the recognition of confusional disorders associated with PLEDs and non-convulsive status epilepticus that would otherwise be difficult to diagnose.

AETIOLOGY OF SEIZURES AND EPILEPSY IN ELDERLY

The high incidence and prevalence of seizures in the elderly are related to the high frequency of diseases
representing risk factors for epilepsy (cerebrovascular, degenerative diseases, cancers, traumas; metabolic disorders etc). Furthermore, case-control studies suggest that aging itself may have an epileptogenic effect. In the Lühdorf et al. study, the most frequent cause was represented by stroke (32%) followed by cancers (14%); a significant portion was attributable to consumption of alcohol or drugs. Finally, about a quarter of cases remains of unknown reason, and, despite the improvement in neuroradiological investigations, the percentage of events without evidence of Central Nervous System (CNS) structural lesions remains high. However, even considering that it is the most frequent source of CNS damage, stroke very frequently causes seizures and epilepsy in the elderly. Seizures can occur at the time of stroke, even be an early clinical manifestation of cerebrovascular disease (acute symptomatic seizures), or they can appear later. Risk of epilepsy increases up to 20 times in the first year after a stroke. Epilepsy is most likely to occur if the stroke involves the cortex, if it is extensive or multiple, hemorrhagic and accompanied by acute symptomatic seizures. The association of epileptic seizures with cerebrovascular disease appears to be bidirectional, so that the appearance of an epilepsy in elderly is accompanied by an approximately three-fold increase in risk of a subsequent stroke. Therefore the appearance of seizures in an elderly requires a careful search for a possible underlying vasculopathy, the identification of possible risk factors and a preventive therapy. Both epilepsy and hypertension are frequent, chronic diseases that can coexist in the same individual. Hypertension may be a cause of seizures and epilepsy through direct or indirect mechanisms. Large-artery stroke, small vessel disease and posterior reversible leukoencephalopathy syndrome are hypertension-related brain lesions able to determine epilepsy by indirect mechanisms. However, hypertension is a predictor of late-onset epilepsy also independently from vascular damage, and renin-angiotensin system might play a central role in the direct interaction between hypertension and epilepsy. In addition, posterior reversible encephalopathy syndrome (PRES) is an acute condition, often caused by hypertensive crisis, associated with the occurrence of acute symptomatic seizures.

Epileptic seizures are a frequent occurrence in the history of a patient with dementia, in particular with a risk up to 10 times greater in Alzheimer disease (AD) patients. Seizures can appear at every stage of the disease, but especially in the advanced phases. AD and other neurodegenerative diseases constitute the cause of 10-20% of all epilepsies of the elderly. Duration, severity and age of dementia onset are risk

<table>
<thead>
<tr>
<th>Terms</th>
<th>Definition</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epileptic seizure</td>
<td>Transient occurrence of signs and/or symptoms due to an abnormal and excessively synchronized discharge of a neuronal population</td>
<td>It is not synonymous of Epilepsy!</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Condition characterized by a persistent tendency to generate epileptic seizures</td>
<td>Epidemiological studies are based on the presence of at least 2 chronologically distinct unprovoked seizures</td>
</tr>
<tr>
<td>Epilepsy in the elderly</td>
<td>Epilepsy that occurs after the age of 65.</td>
<td>To be distinguished from a pre-existing epilepsy for many years in an elderly patient, “aged” epilepsy</td>
</tr>
<tr>
<td>Acute symptomatic seizures</td>
<td>Seizures chronologically correlated with an event that alters the metabolic or structural homeostasis of neuronal function</td>
<td>An acute symptomatic seizure is not in itself a predictor of the onset of epilepsy</td>
</tr>
<tr>
<td>Immediate or very early seizures</td>
<td>Attacks that occur within seconds or minutes of acute brain damage</td>
<td></td>
</tr>
<tr>
<td>Early seizures</td>
<td>Seizures occurring within the first week of the acute event</td>
<td>Some authors extend the period up to 1 month from the acute event</td>
</tr>
<tr>
<td>Late seizures</td>
<td>Seizures that appear more than a week after an acute event</td>
<td></td>
</tr>
<tr>
<td>Remote symptomatic epilepsy</td>
<td>Epilepsy residual to a previous brain damage</td>
<td></td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>Condition characterized by prolonged or repeated seizures for at least 30 minutes</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>Abrupt, transient and complete loss of consciousness, associated with inability to maintain postural tone, with rapid and spontaneous recovery. The responsible pathophysiological mechanism is cerebral hypoperfusion</td>
<td></td>
</tr>
</tbody>
</table>
factors for the development of epilepsy, while there are
insufficient data regarding the possibility of developing
dementia in patients with epilepsy. Some authors
suggest that subclinical epileptiform activity in patients
with Alzheimer’s disease, detected by extended
neurophysiological monitoring, can also lead to
accelerated cognitive decline.

Head trauma is common in elderly, and its consequences
are often severe. Epilepsy lasting to head injury is
a frequent occurrence, particularly if parenchyma
contusion, subdural hematoma, skull fracture and
prolonged coma occurred. Between 10 and 30% of seizures in the elderly are related
to both primary and secondary CNS cancers. Seizures
are often the revealing symptom of the cancer. Generally,
epilepsy associated with a brain cancer is more frequent
in primary and slow-growing brain tumors.

Acute metabolic disorders and infections can cause
acute symptomatic seizures. Up to 19% of patients
with non-ketotic hyperglycaemia develop somatomotor
focal seizures, often reflexes and sometimes an
epilepsia partialis continua, often resistant to the classic antiepileptic drugs, with phenytoin that can worsen
the symptoms by inhibiting the release of insulin.
Obstructive sleep apnoea syndrome can lower the
seizure threshold in elderly patients with epilepsy.

Many drugs can be responsible for seizures. Different
classes of drugs can induce acute symptomatic
epileptic seizures (Tab. II), often as a consequence
of an increased exposure caused by a reduced
clearance, a frequent occurrence in elderly, although
the correlation between drug intake and attack onset
is not explained in all cases from the mechanism of
action, and the causal relationship is not always
demonstrable.

### Diagnostic Procedure and Differential Diagnosis

Diagnosis of epilepsy in the elderly requires special
care. At this age, in fact, numerous other disturbances
of other nature are very frequent, in particular syncopal
episodes. The risk of diagnostic errors or delays is
high. Elderly often live alone and there are no witnesses
to the attacks. There may be cognitive disorders
or other conditions that hinder the collection of the
anamnesis; falls and incontinence can sometimes be
erroneously related to the attacks. Table III shows some
conditions that can lend to diagnostic errors, and the
role of instrumental exams is indicated.

A detailed medical history is necessary, possibly
supplemented by the testimony of witnesses, a
detailed history of the use of drugs or alcohol intake,
a general clinical and metabolic balance; a cardiology
study, possibly with a dynamic ECG, or with stimulation
manoeuvres, is often essential. The usually lesional
etiology of seizures requires an accurate neurological
examination of the patient and neuroradiological
examinations. Nevertheless, sometimes it is not
possible to obtain assurance that a critical episode was

Table II. Classes of drugs reported as possible causes of seizures (from LICE - SIMG Guidelines, https://www.lice.it/LICE_ita/documenti_LICE-SIMG/pdf/FARMACI_AE_e_INTERAZIONI.pdf).

<table>
<thead>
<tr>
<th>Class of drugs</th>
<th>Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiate analgesics</td>
<td>Tramadol, morphine, pentazocine</td>
</tr>
<tr>
<td>Anti-asthmatics</td>
<td>Theophylline, salbutamol</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Cephalosporins, fluoroquinolones, erythromycin, penicillins, gentamicin</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Tricyclics, SSR1, bupropion, mianserin, trazodone, venlafaxine</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Chloroquine, mefloquine</td>
</tr>
<tr>
<td>Antineoplastics</td>
<td>Busulfan, cisplatin, chlorambucil, methotrexate, vinblastine, vincristine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol, chlorpromazine, fluphenazine</td>
</tr>
<tr>
<td></td>
<td>clozapine, olanzapine, risperidone</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Chlorphenamine, diphenhydramine</td>
</tr>
<tr>
<td>Antivirals</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Digoxin, beta-blockers (metoprolol, propranolol), quinidine, disopyramide, mexiletine</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam</td>
</tr>
<tr>
<td>Drugs of abuse</td>
<td>All, in particular ethanol and cocaine</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Azathioprine, corticosteroids, cyclosporine, interferon-α, tacrolimus</td>
</tr>
<tr>
<td>Hypoglycemic agents</td>
<td>Chlorpropamide, glipizide, insulin</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Amphetamines, ephedrine, phenylephrine</td>
</tr>
<tr>
<td>Others</td>
<td>Baclofen, cimetidine, cycloserine, dantrolene, desmopressin, disulfiram, domperidone, erythropoietin, fampridine, flumazenil, probenecid</td>
</tr>
</tbody>
</table>

NSAIDs: Non-steroidal anti-inflammatory drugs.
Management of epilepsy in elderly

Management of epilepsy in elderly

of epileptic nature, and it must be limited to observation over time (*wait and see*).

The EEG assessment must take into account the possibility of physiological changes in elderly and the possible presence of unusual variants without pathological significance. Prolonged monitoring, both outpatient and video-EEG, is a tool of considerable diagnostic value, still underused in the elderly. The possibility of easily acquiring “domestic” films with the help of devices now commonly used can often provide a decisive contribution to the differential diagnosis of critical episodes.

### Table III. Differential diagnosis of epileptic seizures in the elderly.

<table>
<thead>
<tr>
<th>Terms</th>
<th>Definition</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>Abrupt, transient and complete loss of consciousness associated with loss of postural tone caused by a sudden failure in cerebral perfusion, with rapid and spontaneous recovery</td>
<td>It may be related to cardiac causes (asystole, arrhythmias, structural heart diseases such as aortic stenosis), autonomic control deficits (orthostatic hypotension), nervous reflexes (vasovagal syncope, carotid sinus disease). Syncope involves loss of consciousness and fall with possible traumas, similar to generalized seizures. Subtle myoclonic seizures or brief tonic contractions are possible if the cerebral hypoperfusion is protracted; there is frequently incontinence. The differential diagnosis with a generalized epileptic seizure is based on the accurate collection of history (prodromes, conditions and modalities of onset, presence or absence of post-critical confusion, etc.), ECG and Holter-ECG, and arterial pressure (orthostatic changes) evaluation. In selected cases the study of the vegetative nervous system and the Tilt-test are indicated.</td>
</tr>
<tr>
<td>Transient ischemic attacks (TIA)</td>
<td>Focal neurological deficit of short duration (not exceeding 24 h), reversible, from ischemia in the carotid or vertebral-basilar territory</td>
<td>Paralysis after a hemispheric seizure (Todd’s palsy) can complicate the differential diagnosis. Physical examination, EEG and neuroradiological examinations can contribute to the diagnosis.</td>
</tr>
<tr>
<td>Recurrent falls</td>
<td>Unexpected or apparently inexplicable falls are frequent in the elderly, correlated with multiple possible causes</td>
<td>They require a careful anamnesis, in particular for the possible concomitance of disorders of consciousness, and an accurate neurological examination. Consider the possibility of drop-attacks, sudden episodes of fall, with a conserved conscience, related to sudden loss of postural tone, in the absence of signs of posterior circulation dysfunction. They typically especially occur in middle-aged women who fall unexpectedly walking and only rarely standing, often with difficulty in getting up.</td>
</tr>
<tr>
<td>Transient global amnesia (TGA)</td>
<td>Prolonged episodes (hours) of anterograde amnesia in the absence of altered consciousness or confusion</td>
<td>During the episode the autobiographical memory is preserved, but the patient is unable to reap new memories. The contribution of a witness is therefore essential for the diagnosis. Exclude the use of benzodiazepines or alcohol ingestion! Rarely semilogically overlapping episodes are of epileptic nature (Transient Epileptic Amnesia, TEA). Diagnostic criteria are a generally shorter duration of critical episodes, the tendency to repeat, the coexistence of other clinical symptoms and epileptic abnormalities on EEG. According to some A. it represents a specific epileptic syndrome in the elderly patient.</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>Particularly frequent in the elderly are the confusional awakenings, the behavioral disorder of the REM sleep (“REM behavior disorder”, RBD), the nocturnal myoclonus and the restless legs syndrome</td>
<td>RBD is a parasomnia of REM sleep characterized by violent motor behaviors; when awakened the subjects are aware of the fact that they were having vivid dreams. RBD is due to impairment of normal pathophysiological mechanisms that block muscle activity in REM sleep.</td>
</tr>
<tr>
<td>Non-epileptic psychogenic episodes</td>
<td>Non-epileptic critical episodes on psychogenic basis can occur at any age and in both sexes</td>
<td>Often for the differential diagnosis – particularly delicate when real epileptic seizures coexist – a video-EEG examination is necessary. The acquisition of a “domestic” movie can also be of great importance.</td>
</tr>
</tbody>
</table>

TREATMENT OF EPILEPTIC SEIZURES IN THE ELDERLY

The choice and management of therapy with antiepileptic drugs is a particularly delicate topic in the elderly 2,21,23. The main problems can be summarized as follows:

1. as a physiological consequence of the aging process, there is an increased sensitivity to drugs:
   - even if changes in liver function cannot be demonstrated, the overall metabolic activity is altered with aging 24,25;
   - similarly, there is an overall reduction in renal function with a decline in glomerular filtration, a decrease in tubular secretory function, a decrease in renal blood flow;
   - changes in body composition, and in particular a reduction in total body water which, together with the reduced drug-protein binding caused by the reduced production of hepatic albumin, can also significantly reduce the volume of distribution of strongly water-soluble and strongly bound drugs such as gentamicin, digoxin, and theophylline. In such cases, the loading dose should be reduced;
   - changes in neurotransmitters and brain receptors, such as decreased choline-acetyltransferase, acetylcholine and serotonin receptors, enzymes involved in the synthesis of GABA/glutamic acid, dopamine levels, also associated with changes in receptor affinity and signal transduction mechanisms.

2. the elderly population is frequently exposed to polytherapy (antidepressants, antipsychotics, tranquilizers, hormones, anticoagulants, cardiology drugs, anti-hypertensives, etc), with the possibility of pharmacokinetic and pharmacodynamic interactions, not always perfectly predictable. Faught et al. 26 have recently evaluated the risk of pharmacokinetic interactions between Anti-epileptic drugs (AEDs) and other molecules, and the factors associated with changes in receptor affinity and signal transduction mechanisms.

General strategies should foresee 23:
- monotherapy. If this still represents the gold standard in epileptology, it is a priority in the elderly;
- to simplify all therapies as far as possible;
- to know the pharmacokinetic mechanisms of the different drugs used, the possible interactions, and to pay attention to their prediction. Many of the new AEDs are probably less involved in pharmacokinetic interactions and may therefore represent a more appropriate choice in the elderly 26;
- to monitor, when appropriate, plasma levels of AEDs, in order to prevent their toxicity;
- often the information reported by the manufacturers on the drug doses and speed of titration are not appropriate for the elderly, which presents a marked variability, often not predictable, of drug pharmacokinetics and pharmacodynamics. The advice is to start with low doses, and to proceed with slow and gradual increases (start low and go slow).

The choice of the most appropriate drug is a complex problem, and many parameters need to be taken in consideration, including both the characteristics of epilepsy and of the patient as well. Nowadays, about 25 AEDs are available; a list of current AEDs and their suggested mechanism of action is reported in Table IV 27.

Regarding the specific drug choice, it is easier to indicate those that should be avoided than to give indications based on reliable evidence for recommendation. About adverse effects on the CNS, and possibly on other organs, anti-epileptic depressants such as phenobarbital and benzodiazepines should be avoided; the pharmacokinetic interactions, and the high binding to plasma proteins make the use of phenytoin not very advisable.

Wide spectrum of effectiveness, good tolerability, modest pharmacokinetic interactions and the possibility of rapid titration make valproate one of the possible therapeutic options. In view of the frequency of partial seizures in the elderly, carbamazepine (CBZ) is a particularly used drug, however with caution and slow titration due to possible idiosyncratic effects, possible interactions (eg, with anticoagulants) and for the possibility of skin rashes; therefore the more favourable kinetics, the reduced potential of enzyme induction and the better tolerability of oxcarbazepine (OXC) seem to suggest the latter as one of the first-line drugs in the elderly. OXC also requires special attention to the risk of hyponatremia, which is more frequent than with CBZ, a risk to which the elderly population is particularly exposed, particularly if taking diuretic therapy.

Relatively few randomized controlled trials specifically designed for the elderly population are available, and essentially they involve some new antiepileptic drugs. One study compared lamotrigine (LTG) and CBZ, demonstrating approximately similar efficacy but greater tolerability of LTG, which was therefore proposed as a possible first choice 28. Moreover, the differences are reduced or cancelled if the comparison was made with the CBZ controlled release rather than with the standard formulation. Another randomized double-blind study compared LTG, gabapentin and CBZ. Once again, the efficacy was approximately equal, with better tolerability for lamotrigine 29.
A double-blind pilot study demonstrated the efficacy of topiramate in the elderly already at 50 mg/day, suggesting the use of medium-low doses, in particular in monotherapy, in this age group; however, the possible negative impact of this drug on cognitive functions must be kept in mind. Open-label studies also support the use of LTG, OXC, levetiracetam (LEV), zonisamide and lacosamide in the elderly. However the impact of epilepsy and its treatment on cognitive functions, behaviour and mood, and, more in general, on the elderly quality of life, often already compromised, is a topic of considerable importance that should be adequately investigated with specifically designed studies. Recently new AEDs have entered the market. Two of these, brivaracetam and eslicarbazepine (ESL) represent the evolution of the previous drugs LEV and OXC, with possible advantages in terms of efficacy, tolerability, pharmacokinetics and compliance.

Moreover, ESL seems to positively affect serum lipid profile, in contrast to the negative impact observed with older carboxamides. Another drug, perampanel (PER), presents a new mechanism of action, since it is a non-competitive highly selective AMPA receptor antagonist. Subgroup analyses derived from controlled studies, and, subsequently, real life studies support the indication of these drugs in the population aged 65 or over.

CONCLUSIONS

Epileptic seizures and epilepsy in the elderly represent, and will represent even more in the future, a significant medical, social and economic problem. The differential diagnosis is not always simple and requires more than ever a careful anamnesis and, in relation to the usually lesional aetiology, a prudent use of instrumental examinations. The frequency of epilepsy, and the high risk of mortality or disability that accompany this condition require a rapid and effective treatment of this neurological emergency. Acute symptomatic seizures require rapid recognition and treatment of the underlying pathology.

Epilepsy in the elderly generally responds positively to drug treatment. However the choice of the drug is conditioned by several factors characteristic of the elderly, including the modified metabolic conditions and sensitivity to antiepileptics, the higher exposure to neurological adverse effects, the frequent comorbidity and the concomitant polytherapy. Some controlled trials seem to favour the use of specific new generation antiepileptic drugs as first choice. In any case, therapy simplification (monotherapy, drugs with simple kinetics) and caution (low doses, very gradual increase, attention to adverse effects and possible drug interactions, repercussions on cognitive performance) must be general criteria to adopt. Last but not least, correct decision making should always include a thorough assessment of the patient's individual frailty, with particular attention to the impact of the drug treatments on the quality of life of the elderly.
information and adequate support for the patient are important. The involvement of general practitioners and geriatricians, and of course the family and caregiver, is essential in the effective management of this condition.

Bibliografia


The contributions of physical activity and fitness for the optimal health and wellness of the elderly people

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Elderly people often have typical age-related changes that may influence their way of life, for instance; hearing loss, impaired vision, joint pain, hypertension, coronary disease, diabetes, osteoporosis, cognitive impairment and so on. Being physically active helps one with coping better in older years. This review discusses the contribution of physical activity and fitness for the optimal health and wellness of older people. The types of physical activity are discussed, the benefits of physical activities are highlighted and the role of physical activity in the prevention of falls is also reviewed. Specifications for physical activity for the elderly people are highlighted, and importantly, safety considerations for physical activity for the elderly people are provided. In conclusion, physical activities have advantages for the prevention and management of many health-related conditions faced by an elderly person; as such, even limited or moderate physical activity is better than none.

Key words: preventive care, exercise, falls, cardiovascular disease, optimal health

INTRODUCTION

Most elderly people have age-related changes that may influence their way of life, for example; hearing loss, impaired vision, joint pain, hypertension, coronary disease, diabetes, osteoporosis, cognitive impairment and so on; being physically active helps with coping better in older years. Physical activity is characterized as any substantial activity which makes use of the skeletal muscles that require energy use. Physical activity incorporates all exercise performed during the 24 hour period, both formal exercise and day to day activities. This activity need not be organized, tedious or planned to get health benefits, and may incorporate activities, for example, strolling to the nearby shop, cleaning, working, walking, and so on. In elderly people of 65 years or more, examples of physical activity include; strolling, planting, climbing, swimming; transportation (e.g. strolling or cycling), family errands, playing, diversions, sports or arranged exercise. Importantly, physical activity is essential for an adult's health because it improves muscle quality, and good muscle tone gives an elderly person the ability to do daily activities around the home. Also, physical activity diminishes the rate of falls and enhances posture. The more one spends exercising, the more the advantages, as such, any degree of physical activity is better than none. Hence, this review examines the role and importance of physical activities in the prevention
The contributions of physical activity and fitness for the optimal health and wellness of the elderly people

METHODS OF REVIEW

This review focuses on the benefits of physical activity and fitness for the optimal health and wellness of the elderly people. An extensive literature review was performed in Google, Springer link and PubMed databases. Publications from major international health institutions, such as the World Health Organization, were also searched to retrieve relevant information. The year of publication was not a factor, as the author wished to include all relevant information. Careful screening was done to ensure that pertinent data were included in this review. Subsequently, all references of all studies included in this review were carefully examined.

TYPES OF PHYSICAL ACTIVITY

There are four basic types of physical activity. They are; Aerobic, Resistance or Muscle-strengthening, Bone-Strengthening and Stretching. Elderly people will get the most advantages from physical activity by taking an interest in every one of the four types. For the best health results, it is essential that older people participate in new methods of physical activity every week 5 (Fig. 1).

1 Aerobic activities. Oxygen consuming (or cardiovascular perseverance) exercises require consistent use of big muscles in the body for 10 minutes. Lively strolling, moving, running, bicycling, dancing, jumping and swimming are good examples. Vigorous activity enhances cardio-respiratory rate, blood pressure and blood lipid reduction. Also, vigorous physical activity enhances physical and mental health 6.

2 Muscle-strengthening or resistance activities. Resistance activities or muscle-strengthening exercises include making use of resistance activities or exercises to help build muscle mass in the body, and to increase muscle quality. Weight training, digging in the garden and climbing stairs are examples of muscle-strengthening exercises. When combined with bone-strengthening activities, these exercises lessen falls and helps in the optimal functioning for daily activities. Furthermore, bone-strengthening activity enhances portability, lessens the risk of falls, and enhances mobility 7. Tai chi significantly enhances balance and decrease falls in elderly people 8.

3 Bone-strengthening activities. Bone-strengthening activities help in the balancing of the body. They are basic exercises that can be performed in the home, for example, remaining on one leg unsupported, jumping with a rope, walking and lifting weights. Importantly, improvement in balancing diminishes the occurrence of joint inflammation, and prevents osteoporotic cracks in elderly people 7.

4 Stretching activities. Stretching activities improves flexibility, and the ability to move the joints. Body flexibility reduces as one ages 10. Stretching activities includes touching of toes, doing side stretches. Also, yoga is another example of stretching activities, washing of dishes and family home chores, (for example, sweeping, washing and planting) are examples of flexibility exercises as well 11.

Figure 1. Examples of activities guide for the elderly people. Self developed.
elderly patients, and improves functional capacity, quality of life and adherence to the Mediterranean diet 15. Also, resistance activities are effective to reduce blood pressure (peripheral and central) in middle-aged and older adults with at least elevated blood pressure at baseline 14. In addition, a study ‘Exercise Intervention on Functional Decline in Very Elderly Patients during Acute Hospitalization’ revealed that the exercise intervention proved to be safe and effective to reverse the functional decline associated with acute hospitalization in elderly patients 15. Furthermore, physical activity helps in the prevention of cardiovascular diseases which are associated with death, like chronic ischaemic heart disease, pulmonary heart disease, arrhythmias, heart failure, cerebrovascular events, aneurysm and peripheral vascular diseases 16. Even low doses of physical activity are protective for health and reduce by 22% the risk of premature death 17. Furthermore, physical activity is an important therapeutic tool for patients with cardiovascular diseases, hypertension, type 2 diabetes, cancer, chronic obstructive pulmonary disease (COPD), as an appropriate dosage of physical activity reduces the risk of recurrence and disease progression, improves the control of clinical parameters and increases the quality of life 17. People with COPD may benefit from engagement in low levels of physical activity, particularly walking and structured exercise 18. Exercise training may be an effective strategy to promote metabolic health, and also increase brain-derived neurotrophic factor (BDNF); a protein favoring neuroplasticity, thereby helping in learning and memory improvements in an elderly people, and also improvements in diabetes risk factors 19. Likewise, preconditioning exercise reduces brain damage and neuronal apoptosis 20. Furthermore, bone fractures and breakage risk can be prevented and reduced among elderly women through engagement in physical activity and reduction in sedentary lifestyle 21. There is an association between physical activity and reduced risk of depression, as elderly people engaging in physical activity can reduce their risk of depression and anxiety 22. Further evidence of benefit is provided by the dose-response relationship; high-intensity physical activity has more obvious cardiovascular benefits than those of moderate-intensity physical activity 23. A study on the effect of 6 months of aerobic training on adipokines as breast cancer risk factors in postmenopausal women revealed that exercise programs can be considered as an effective behavioral modification in breast cancer prevention 25. Also, for improved functional ability in elderly people with dementia, a person-centered exercise approach, delivered by an expert is effective 26.

THE ROLE OF PHYSICAL ACTIVITY IN THE PREVENTION OF FALLS

Falls are common in older people aged 65 years and above, and are the main causes of injuries in this age group; as around 33% of elderly individuals of more than 65 years fall every year, and half of those in their eighties fall once per year 27,28. It is estimated that 82% of hospital admissions for adults over 75 years are falls-related, and falls frequently happen while an elderly individual is doing common activities in the home 28,29. The rate of falls increases drastically with age 28,29. Importantly, most falls are preventable, and physical activity has a vital role in lessening the danger and rate of falls in elderly people. A multifaceted intervention which includes exercise reduces the rate of falls in elderly people 30. A study on the Interventions to Prevent Falls in Older Adults revealed that exercise is associated with fewer people experiencing a fall and a reduced number of injurious falls in average- and high-risk older adults 31. Furthermore, a multifactorial tailored approach (which included physical exercise) for treating dizziness (a risk factor for falls in elderly people) was effective in reducing dizziness handicap in community-living people aged 50 years and older 32. Exercise decreases the risk of falls among elderly people with Alzheimer’s disease using antihypertensive and psychotropic drugs 33. Furthermore, a study on the effect of Exercise and Cognitive Training on fall and Fall-Related Factors in Older Adults with Mild Cognitive Impairment revealed that, exercise, and combined exercise and cognitive training improve specific factors associated with falls such as gait speed, cognitive function, and balance in adults with mild cognitive impairment 34. Also, exercise as a single intervention prevents falls in community-dwelling elderly people; therefore, an exercise programme that improves balance, and are of a higher dose have larger effects on the prevention of falls 35. In addition, Lafiska, a form of exercise in Indonesia, improves balance and health status in the elderly people, and is a viable exercise option in the prevention of falls in older adults with independent mobility, as well as older adults using assistive devices, for example, a walking stick 36. Also, a study on the effects of Tai Chi Chuan, a form of exercise originating in Asia and ‘Brisk Walking Exercise on Balance Ability in Elderly Women’ revealed that 12 and 16 weeks of Tai Chi Chuan and brisk walking respectively were essential to improve balance (which is a major factor in risk of fall) with eyes closed among the women aged 60-70 years. Exercise can either be done alone or in groups, although, group exercise is the best as older adults who participate in group exercise receives additional benefits related to falls prevention compared with those who exercise alone 37,38.
The contributions of physical activity and fitness for the optimal health and wellness of the elderly people

SPECIFICATIONS FOR PHYSICAL ACTIVITY IN THE ELDERLY PEOPLE

As indicated by the World health organization:

• elderly people and adults should do 150 minutes of aerobic physical activity consistently, or do no less than 75 minutes of vigorous-intensity aerobic physical activity consistently, or a proportionate mixture of moderate- and vigorous-intensity activity;
• aerobic activity should be performed for 10 minutes;
• for extra medical advantages, elderly people should expand their moderate-intensity aerobic physical activity to 300 minutes every week, or participate in 150 minutes of vigorous-intensity aerobic physical activity every week, or a proportionate mixture of moderate-and vigorous-intensity activity;
• elderly individuals with poor mobility should perform physical activity to improve balance and avert falls in at least three days of the week;
• muscle-strengthening exercises, which include the use of significant muscles in the body, should be done on at least two days in the week;
• at the point when elderly people cannot do the prescribed measures of physical activity because of health conditions, they should be as physically active as their abilities and health conditions permit.

SAFETY CONSIDERATIONS IN PHYSICAL ACTIVITY FOR THE ELDERLY PEOPLE

There are risks related to elderly people taking part in significant numbers of physical activities, because not all physical activities can be performed safely by an elderly person. Proper screening and ongoing management by a health professional or physical activity specialist is required for high-effect and serious exercises to guarantee that an elderly person stays safe. In spite of the advantages of physical activity, physical activity may disturb and aggravate some prior health conditions, for example, angina, joint inflammation, osteoporosis, extreme hypertension and previous wounds. To prevent a health condition from being aggravated while an elderly person is partaking in a specific activity, a reasonable degree of physical activity can be performed with endorsement from the individual’s general practitioner (GP), physiotherapist or clinical exercise physiologist. If an elderly person has persistent illnesses, geriatric conditions or disability, or has been inactive for a long time, the person needs to be checked by their GP, physiotherapist or clinical exercise physiologist before one can attempt an activity program or strenuous physical activity (Fig. 2).

Although, it is safe for elderly individuals with co-morbidities or disability to take part in physical activity, it is best to begin with lower-intensity activities and progressively advance onto moderate or higher-impact activities. Furthermore, elderly people should stop physical activity if their breathing becomes difficult or if they feel woozy or develop any chest tightness or pain. Also, elderly individuals with disability should defer high impact or weight-bearing aerobic exercises until the point when they have undertaken sufficient balance and strength training. A straightforward test to check whether an elderly individual is ready to undertake moderate-intensity aerobic or higher-impact activities is to get the individual to get up from a seat, remain with their eyes closed, open one eye, and afterward stroll across the room. If the elderly person experiences issues with this activity, they need to work on resistance and balance training before attempting aerobic or higher-impact exercises.

CONCLUSIONS

The importance of Physical activity are many as it diminishes the risk of various non-communicable and chronic health conditions, which includes heart disease, hypertension, type 2 diabetes, colon, post-menopausal breast and endometrial cancers, stroke, osteoporosis, osteoarthritis, depression, falls and disability in the elderly people. From the extant review, it is therefore concluded that physical activities have numerous advantages for the prevention and management of many health-related conditions been faced by the elderly people. Hence, it is imperative for every elderly person to always engage in physical activities to obtain optimal health and wellbeing in their old age, as limited or moderate physical activity is better for health and wellness of older people than none. Furthermore, it is important for elderly people to always talk to their health care provider if they have any prior health condition or they feel unease before, during and after any physical activity sessions to guaranty health safety.

ACKNOWLEDGEMENTS

Great thanks are given to unknown reviewers for valuable comments. Furthermore, I thank all my colleagues who over the time have contributed to the ideas discussed in this article.

DEDICATION

The article is dedicated to all the elderly people around the world.
References


The contributions of physical activity and fitness for the optimal health and wellness of the elderly people


Atrial fibrillation: all the elderly go hospitalized? A minireview

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Atrial fibrillation (AF) is a very common in clinical practice. The prevalence of AF is high after the age of 65 years. Patients with AF have a worse quality of life than healthy controls. However, concomitant higher hemorrhagic risks, severe cognitive and functional impairment may at least partly explain under-prescription of oral anticoagulants in the elderly.

EPIDEMIOLOGY

Patients with Atrial fibrillation (AF) are at greater risk for thromboembolic events, hospitalization, heart failure and death ¹⁻³. Clinical risk factors for AF are reported in Table I. The prevalence of AF is high after the age of 65 years and it is 1.5 times more frequent in men than women ⁴⁻⁶. For example, the prevalence rate in males 75-79 aged is doubled compared to males aged 65-69 years and more than 5 times greater than males 55-59 years old ⁶. However, in the European Union by 2030, about 120,000-215,000 newly diagnosed patients per year are estimated ⁷.

TYPES

Traditionally there are five types of Atrial fibrillation ⁷:
- first diagnosed atrial fibrillation. Atrial fibrillation that has not yet been diagnosed, not taking into account the duration of the arrhythmia, the presence and severity of symptoms;
- paroxysmal atrial fibrillation. Atrial fibrillation ends spontaneously in the first 48 hours in most cases. Some AF can last up to 7 days. An episode of AF with a cardioversion within seven days should still be considered paroxysmal;

Table I. Clinical risk factors for atrial fibrillation.

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Advanced age</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Rheumatic and non-rheumatic valvular disease</td>
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<tr>
<td>Myocardial infarction</td>
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</table>
• persistent atrial fibrillation. Atrial fibrillation that lasts more than 7 days. Also episodes where there is a cardioversion with both drugs and dc-shock after 7 days or more;
• long-standing persistent atrial fibrillation. Continuous AF that lasts for ≥ 1 year when you decide to use rhythm control;
• permanent atrial fibrillation. Atrial fibrillation that is accepted by the patient (and physician).

SIGNS AND SYMPTOMS

Patients with AF have a worse quality of life than healthy controls. They develop a range of symptoms ranging from lethargy, palpitations, dyspnea, chest pain, difficulty sleeping and psychosocial distress. In Emergency department it’s not uncommon to find patients with signs of congestive heart failure (as pulmonary edema, peripheral edema, ascites) or with signs of embolism (ischemic attack transient, or stroke) 7.

MANAGEMENT

In the Emergency Department in the evaluation of AF play a fundamental role, a history and physical examination, specific laboratory and cardiological tests.

HISTORY AND PHYSICAL EXAMINATION

Not all patients with AF are symptomatic, so the history and physical examination must focus on a few key points 8:
• description of symptoms, focusing on the severity and qualitative characteristics of the symptoms;
• possible precipitating causes;
• the presence of associated pathologies such as, cardiovascular or cerebrovascular diseases, diabetes, hypertension, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, alcohol and hyperthyroidism, which can be potentially reversible, causes;
• cardiopulmonary and neurological examination is essential because they can highlight the presence of complications such as congestive heart failure or stroke.

EKG

The electrocardiogram, (EKG), (class IB) is necessary to make the diagnosis. AF has the following electrocardiographic characteristics 7:
• the RR intervals follow no repetitive pattern;
• there are no distinct P waves.

ECHOCARDIOGRAPHY

A transthoracic echocardiography (classed IC) is another crucial exam to do because it is important to know:
• the size of the atria. In fact, large atria could orient to a long-term AF and lean towards a more conservative therapeutic strategy;
• structural anomalies. In particular, it can guide vs the use of rhythm control drugs (as amiodarone) rather than others (as flecainide and propafenone).

Certainly transthoracic echocardiography has a very low sensitivity to recognize the presence of atrial thrombi. In this case it is necessary to carry out a trans esophageal echocardiography 7-8.

BASELINE LABORATORY TESTING

Baseline tests test include 7:
• thyroid evaluation. In particular, hyperthyroidism is present in less than 5% of patients with AF. Generally we should have in all the patients with AF a TSH and free T4 (9-10);
• complete blood count;
• serum creatinine;
• analysis for proteinuria;
• test for diabetes mellitus;
• test to study possible risk factors and concomitant diseases.

CLUSTER DISEASE

Hypertension and coronary heart disease are the most common diseases found in patients with AF in developed countries. The rheumatic disease, still very present in developing countries, is very much associated with the incidence of AF. Cluster diseases associated to AF are reported in Table II.

HYPERTENSIVE DISEASE

Hypertension is the most common disorder present in patients with AF. Also due to the high frequency of hypertension in the general population, the history of hypertension increased the risk of developing AF about 1.42 fold 11.

<table>
<thead>
<tr>
<th>Table II. Cluster Diseases associated to atrial fibrillation.</th>
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<tbody>
<tr>
<td>Hypertensive disease</td>
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<tr>
<td>Coronary disease</td>
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<tr>
<td>Valvular heart disease</td>
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<tr>
<td>Heart failure (HF)</td>
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<tr>
<td>Venous thromboembolic disease</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Obstructive sleep apnea syndrome</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Diabetes</td>
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<td>Chronic kidney disease</td>
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</table>
CORONARY DISEASE
Atrial fibrillation occurs in 6-10% of patients with acute myocardial infarction. These patients also have a poorer prognosis, and have a mortality increase at 30 days and 1 year 12.

VALVULAR HEART DISEASE
Almost any valvular lesion that leads to significant stenosis or regurgitation is associated with the development of AF. In a review of 89 patients with mitral valve prolapse and 360 with flail leaflets, the rate of development of AF was about 5% per year 13. Atrial fibrillation is an infrequent (about 1%) in patients with aortic valvular diseases. Left atria and age are the most important parameters to determine the occurrence of AF in patients with rheumatic heart disease 13,14.

HEART FAILURE (HF)
Atrial fibrillation and heart failure (HF) often occur together and each of the two can predispose to the other. Atrial fibrillation is found in more than one half of individuals with HF. These data are particularly interesting, because knowing that one third of people with AF can develop Heart Failure; it's possible to start a prevention of HF and prevention of stroke 15.

VENOUS THROMBOEMBOLIC DISEASE
The risk of Atrial fibrillation is increased in patients with Deep Vein Thromboembolism or Pulmonary thromboembolism. The mechanism is not known, but is probably due to the increase in pulmonary vascular resistance and to the right post cardiac loading that cause a right atrial strain. Pulmonary thromboembolism is more frequently associated with AF than Deep Vein Thromboembolism 16.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE
In patients with chronic obstructive pulmonary disease it has been shown that the reduction of FEV1 correlates with an increase in the incidence of AF 17.

OBSERVATIVE SLEEP APNEA SYNDROME
There is a possible causal relationship between obstructive sleep apnea syndrome (OSAS) and AF. A history of hypoxemia and hypercapnia may lead to an increase in circulating catecholamine that may predispose to AF. In addition, the presence of numerous increased inflammation factors in patients with OSAS may predispose to AF 18.

OBESITY
Obese individuals (as body mass index [BMI] > 30 kg/m²) are significantly more likely to develop AF than those with a normal BMI (< 25 kg/m²). In the Framingham Heart Study, every unit increase in BMI was associated with about 5% an increase in risk 19.

DIABETES
In the Framingham Heart Study (over 4700 individuals without valvular heart disease), the presence of diabetes was associated with a significantly increased risk for the development of AF 20.

CHRONIC KIDNEY DISEASE
Chronic kidney disease (CKD) increases the risk of the development of AF. In patients with CKD there are several reasons to develop AF. They tend to have higher pressure values and an overload of fluids that can lead to ventricular hypertrophy, atrial stretch, and fibrosis. In addition CKD patients have an up-regulated renin-angiotensin-aldosterone (RAA) system that can cause remodeling of the heart chambers and predispose to AF 21.

TREATMENT
A key point for the management of AF for the healthcare providers is to know if is new or old onset AF.

RATE VS RHYTHM CONTROL
Rate control is indicated in hemodynamically stable patients with AF more than 48 hours, in which immediate cardioversion cannot be performed. The rationale for rate control is to avoid hemodynamic instability, improve symptoms and avoid tachycardia-mediated cardiomyopathy. There are two frequency targets 22:
• < 80 beats/min at rest and < 110 beats/min under stress;
• < 110 beats/min.
It is not clear what the best strategy is, but above all in the initial phases, more delicate management can be accepted 7. In the presence of structural heart disease, it is recommended amiodarone (loading dose: 5-7 mg/kg over 1-2 hours; and follow-up dose 50 mg/hour to maximum of 1.0 g over 24 hours). Amiodarone has an efficacy comparable to the drugs of the class Ic (as flecainide, 1.5-2 mg/kg over 10 min iv or propafenone, 1.5-2 mg/ kg over 10 min) in the return to sinus rhythm in the first 24 hours. The drugs of the class Ic show a more rapid onset of action, with some effects already after 1-2 hours after administration 24,25. It is crucial avoid these drugs (class Ic) in the presence of structural heart diseases. Rhythm control can be obtained with two methods:
• pharmacological or electrical cardioversion.

PHARMACOLOGICAL CARDIOVERSION
The drugs used in the rhythm control (class IB) are reported in Table III. A disadvantage of pharmacological cardioversion is that the patient must be observed for at least 50% of the half-life, so as to check the pro-arrhythmic effects of these drugs 7,23.
The management of the AF with rhythm control offers no advantages compared to the rate control or rather can be aggravated by numerous side effects. 

**Electrical Cardioversion**

In hemodynamically unstable patients, an emergency electrical cardioversion is indicated. It has a success rate ranging from 67-94%, remains a very safe technique and the most effective in ending AF. It is necessary to obtain sedation analgesia with drugs, such as Fentanyl, Midazolam, or Propofol. The risks of this procedure are related to sedation, as skin burns and pro-arrhythmias, which are very rare since the shock is synchronized with the QRS.

**Prevention of Embolization**

Various trials and meta-analyses have shown how the use of an antithrombotic therapy reduces the onset of stroke. For the choice to make or not an anticoagulant therapy it is necessary to be guided by the CHADS-VASc score. In particular, oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHADS-VASc score of 2 or more, and of 3 or more for all female with AF (class IA).

The drugs of choice are:
- warfarin;
- direct thrombin inhibitors as dabigatran;
- inhibitors of factor Xa (as rivaroxaban, apixaban, edoxaban);

The oral anticoagulant (NOACs) seem to have better clinical benefits and a better safety profile with regard to bleeding, than warfarin, in particularly in the elderly and the frailty elderly. Although the use of NOACs is associated with a reduction in bleeding, about 2.1-3.6% of major bleeding is found. To this regard, two specific antidotes were approved by the FDA, as idarucizumab for dabigatran, and alpha-andexanet for apixaban e rivaroxaban. In addition, non-specific prohaemostatic agents have also been used, as prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (APCC). For the management of life-threatening bleeding or bleeding in critical organs, or major bleeding that do not respond to supportive therapies, it is recommended to use antidotes or non-specific prohemostatic agents, while in other bleeding is not recommended. In fact in other bleeding are recommended:
- withdrawal of NOACs and other drugs that interfere with coagulation (as antplatelet);
- direct compression of the bleeding site;
- volume resuscitation and transfusion.

For patients with mucosal bleeding (epistaxis and uterine bleeding) anti-fibrinolytic therapy is recommended. In cases of suspected overdose, oral activated charcoal may be useful to reduce absorption if it occurred in the last hours.

**NOACS in Elderly**

Female patients with AF are older, with more frequent cognitive and functional impairment, and higher rate of comorbidity than males. The risk of stroke is known to increase with increasing age. Aspirin is still used in patients over 75 years of age, because considered more convenient. Numerous trials (as BAFTA trial and AVERROES trial) demonstrated how warfarin and NOACs are more effective and safety than aspirin. In patients over 90 years of age, warfarin and NOACs are more effective in reducing stroke, and NOACs are more effective in reducing intracranial hemorrhage (ICH) than warfarin. The best drugs for the prevention of embolization in elderly patients remain the NOACs, even if only 16.1% of very elderly population receives the NOACs.

**Prevention of Embolization in CKD**

Numerous studies have been carried out on patients with CKD and AF, especially regarding the issue of prevention of embolization. CKD alone is a risk factor for stroke and prothrombotic states. In moderate CKD, is recommended both warfarin and reduced dose of NOACs (as reported in Table IV). In the case of end stage renal disease and hemodialysis patients there are no very decisive studies. The NOACs have a greater renal metabolism compared to warfarin. In particular, dabigatran almost completely metabolized via the kidney (80%) and apixaban instead only a small part (25%). The FDA authorized the use of apixaban and rivaroxaban in these patients. The AHA/ ACC/HRS recommended warfarin in this type of patients even if numerous studies are still necessary. In patients with chronic kidney disease, the use of low molecular weight heparin (LMWH), as enoxaparin, remains quite safe, even...
Table IV. The NOACs in patients with CKD moderate.

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Dabigatran (110 mg bis in die)</td>
<td>110 mg twice daily</td>
</tr>
<tr>
<td>Apixaban (2.5 mg bis in die)</td>
<td>2.5 mg twice daily</td>
</tr>
<tr>
<td>Rivaroxaban (15 mg once daily)</td>
<td>15 mg once daily</td>
</tr>
<tr>
<td>Edoxaban (30 mg once daily)</td>
<td>30 mg once daily</td>
</tr>
</tbody>
</table>

in those patients with glomerular filtration rate below 30 ml/min/1.73 m², with a dosage of 1 mg/kg once daily 44.

INDICATIONS FOR HOSPITALIZATION

Most of the new-onset AF agents are not hospitalized. Possible indications for hospitalization of patients with new-onset AF are reported 45:

- patients considering ablation. Especially if very symptomatic associated with elevated ventricular response or haemodynamically unstable;
- patients with severe bradycardia post cardioversion;
- treatment of other concomitant pathologies of AF (as exacerbation of chronic obstructive pulmonary disease, thyrotoxicosis, infections, pulmonary embolism, coronary syndrome);
- treatment of elderly patients. In fact, in these patients embolic events are more easily found and very often have numerous comorbidities 46;
- start of a chronic rhythm control therapy;
- management of heart failure and hypertension after control of the rhythm or the control rate.

CONCLUSIONS

Prevention of thromboembolic risk in elderly with AF is an imperative clinical need. However, concomitant higher hemorrhagic risk and other characteristics that were more frequent in elderly patients (as severe cognitive, CKD, morbidity and functional impairment) may at least partly explain the under-prescription of oral anticoagulants in these patients.

References


Infra-hissian Wenckebach phenomenon. A case report, with some reflection about slow conduction

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We describe a case of Wenckebach periodicity in the distal conduction system. Our observation strengthens the concept that Wenckebach type block in surface ECG may reflect block in infra-hissian tissues, especially if there is a wide QRS complex in the conducted beats.

Key words: Wenckebach, slow conduction, AV block

CASE REPORT

A 80-years old woman with hypertension, mild chronic renal failure, in chronic treatment with digitalis, nifedipine, ramipril, furosemide, was admitted for a recent history (few days) of sudden fainting (without syncope), lasting a few seconds, often with dyspnea at the same time. On admission, she was asymptomatic; physical examination was consistent with aortic valve pathology, and revealed occasionally missing pulse. The blood pressure was 180/70 mmHg. There was not evidence of heart failure. Echocardiogram showed calcific aortic valve disease, with mild stenosis and moderate regurgitation; an hypertrophic, not dilated, left ventricle was evident, with good systolic function. Laboratory data showed a mild-moderate renal failure, with 2.2 mg/dl of creatinine level. A good reason for digitalis therapy was totally missing, however the serum level of the drug was inside acceptable range (1.02 ng/ml). The electrocardiogram (ECG) showed presence of sinusual rhythm at frequency of 78 b/min, with intraventricular conduction characterized by...
right bundle branch block. In addition, the PR interval was prolonged, with type 1 second degree AV block (Wenckebach phenomenon), and 3:2 and 4:3 AV ratios (Fig. 1). The patient was quickly subjected to electrophysiological studies, in order to define the level of block.

The endocavitary electrical activity derived at His level during Wenckebach periodicity showed normal AH interval, while HV interval, within normal range at the start of sequence, manifest a progressive lengthened, until H wave is not followed by a V wave (Fig. 2). Thus, the block level was found below the His bundle. Furthermore, during electrophysiological study, the intraventricular conduction of the first P wave that follow the blocked P wave, showed always (together with right bundle branch block) a typical phase 4 posterior left hemiblock, a further sign that a critical disease of the distal conduction was present (Fig. 3). The patient was advised to undergo permanent pace maker implantation, and the procedure was soon performed without any problem.

**DISCUSSION**

Syncope or pre-syncope, a relevant clinical problem especially in the geriatric population, can be defined as “neuromediated”, “cardiac”, “drug-induced”, “multifactorial” or “unexplained” 3. Although neuromediated syncope is the most frequent, cardiac syncope has a far worse prognosis, accompanied by high mortality 3. In this context, the bradyarrhythmic mechanism, linked to sinus node disease or distal conduction disorders, occupies a preponderant role. It is important to recognize in time a sick sinus syndrome or a widespread distal disease of the conduction system in order to implement the related therapeutic measures before serious adverse events. Simple concepts of the physiology and a sufficient knowledge of the electrocardiogram can help clinicians even in clinic-electrocardiographic contexts that are not easy to interpret. Conduction velocity in cardiac tissues is determined primarily by membrane excitability (ie, the magnitude and kinetics of depolarizing currents) and by the degree of intercellular gap junctional coupling 4-6. In the AV node, both reduced excitability (conduction is based predominantly

![Figure 1. ECG at the admission (see text).](image-url)
on the L-type Ca2-channels) and reduced gap junctional coupling are the major mechanisms of very slow conduction. Furthermore, it is well established that in the AV node nonuniform anisotropy contributes to discontinuous, slow conduction in the direction transverse to myocardial fibers. Finally, slow conduction and/or block is also influenced by the presence of structural inhomogeneities within AV node tissue. Such inhomogeneity can create an electrical source-to-load mismatch, a misbalance between the current provided by a smaller mass of tissue (source) and the current necessary to bring to threshold a larger mass of tissue downstream (load).

Although in normal state these mechanism of slow/decremental conduction are almost restricted in AV nodal and surroundings tissues, under a lot of functional and structural derangement they may act also in the common myocardial working fibers and/or in distal conduction pathways creating the conditions for slow conduction, block and reentry.

Since a slow/decremental conduction are usually typical of AV node, a periodic AV conduction disturbance where a P block was heralded by progressive increment of PR tract, is usually referred as a manifestation of AV nodal block. This peculiar behaviour was first described by Wenckebach long before the invention of the ECG. He described it as a form of conduction disturbance characterized by a progressive lengthening of the interval between the “a” and the “c” waves of the jugular pulse, terminating in a dropped “c” wave. But Wenckebach periodicity is not synonymous of AV nodal block! Only if there is a narrow QRS complex in the conducted beats the likely of nodal block is very high, because a type I block in the His bundle is very rare. However, in a type I second-degree AV block with a wide QRS (> 120 msec), the distal site of block is not rare. Often, this conduction disturbance indicates diffuse disease of the His-purkinje system, with a poor prognosis that is believed to be the same as for type 2 second-degree AV block (in most patients, even asymptomatic, a permanent pace maker should be considered). The diagnosis of type 1 infrahisian block require usually invasive His bundle recording, but some aspects on surface ECG (for instance intermittent phase 4 left posterior hemiblock, as in our case) may render the electrophysiological investigation actually redundant.

In conclusion, our case strengthens the concept that Wenckebach type block in surface ECG may reflect...
block in infra-hissian tissue, especially if there is a wide QRS complex in the conducted beats.

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Figure 3. The same findings of the Figure 2, at 100 mm/sec paper speed.
The use of non-invasive ventilation to treat acute respiratory failure in long term care setting: clinical experience in elderly patient

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Background. Nowadays older patients with acute respiratory failure (ARF) leading to a severe respiratory acidosis are frequently ventilated using a non-invasive approach in intensive care unit (ICU). Current guidelines suggest that patients with more severe acidosis should be managed in a higher dependency area. However, the use of non-invasive ventilation (NIV) is effective and safe in treating ARF in general wards in elderly.

Case report. A 82 years old male patient was admitted to a long term care facility due to a severe chronic obstructive pulmonary disease (COPD). Three days after the admission, he suffered of severe acute exacerbation of COPD leading to hypercapnic coma. NIV in Bi-PAP mode and standard medical therapy was started, taking into consideration the do-not-intubate order of the patient. His state of consciousness improved after 48 hours of NIV with decreasing of PaCO2 values and the patient was progressively weaned from the ventilator.

Conclusions. NIV should be considered a successful approach even in unusual setting of long term facility. The choice of use NIV should be taken by multidisciplinary medical staff in a setting where nurses and medical team are trained in NIV protocol, in order to reduce ICU admission, intubation rates and mortality.

Key words: elderly, non-invasive ventilation, hypercapnic coma, long term care facility

CASE DESCRIPTION AND DISCUSSION

Here we report the case of a 82-years old male in hypercapnic coma treated successfully with non-invasive ventilation (NIV) in a long-term care facility. The patient was admitted because of a severe chronic obstructive pulmonary disease (COPD). In the two previous years, due to acute exacerbation of COPD he suffered of several severe episodes of acute respiratory failure (ARF) that required NIV and in one case tracheal intubation in Intensive Care Unit (ICU). His medical history included mild cognitive impairment without behavioral symptoms (Mini mental status examination: 25/30), ischemic heart disease, arterial hypertension, and benign hypertrophy prostate.
At the admission in the long-term unit, the patient was alert, responsive and partially oriented. His Glasgow Coma Score (GCS) was 15. His arterial blood gases (ABG) tests are reported in Table I. On the third day, there was a rapidly worsening of his respiratory status. ABG showed slight respiratory acidosis (pH = 7.33) with severe hypercapnia (pCO$_2$ = 92 mmHg). NIV via facial mask was started using Bi-PAP mode: IPAP was 20 mmH$_2$O and EPAP was 6 mmH$_2$O. The time of inspiration was 1.5 sec, respiratory rate was set at 16 breath/min and FiO$_2$ was adjusted to maintain a SaO$_2$ > 90%. After one hour of ventilation, ABG revealed a slight improvement in pH and pCO$_2$. IPAP level was raised at 22 mmH$_2$O and standard medical therapy was started, including steroids iv and empirical antibiotic therapy with ceftriaxone.

The patient showed a moderate rejection to NIV due principally to facial mask discomfort and it was not possible to maintain proper ventilation. He became progressively agitated and confused, but no specific treatment was taken into consideration because of the lack of experience in sedation during NIV. His state of consciousness progressively worsened, until coma. His GCS was 5, with a severe respiratory acidosis (pH = 7.23) and hypercapnia (PaCO$_2$ = 131 mmHg) at ABG. At this moment, invasive treatment should be started, but his relatives had refused intubation, respecting the patient's will. In front of this do-not-intubate (DNI) order, NIV was continued although the comatose state and after 48 hours of NIV his state of consciousness improved with decreasing of PaCO$_2$ values. Regular pressure relief and skin-protective strategies were adopted to reduce patient’s discomfort and improve NIV’s effectiveness. The blood gas parameter remained acceptable and stable over time and the patient was progressively weaned from the ventilator.

Our aim is to support the possibility to apply NIV with success in a non-intensive setting. Nowadays older patients with ARF leading to a severe respiratory acidosis are frequently ventilated using a non-invasive approach in ICU. However, the use of NIV on general wards has been investigated and in literature it is reported that NIV is effective and safe in treating ARF in a non-ICU setting in elderly followed by a multidisciplinary staff with appropriate experience. Although current guidelines suggest that patients with more severe acidosis should be managed in a higher dependency area, this case demonstrates that NIV should be considered a successful approach even in long term facility. In this setting the familiarity with the non invasive technique could define its success and the medical staff and nurses should be trained in NIV protocol to achieve the goal. In this contest, it could be possible to reduce ICU admission, intubation rates and mortality.

Furthermore, in presence of poor toleration to ventilation and comatose state, patients should be considered for intubation in ICU setting. However, the decision to stop or continue NIV is not based on an objective physiological variable, but only on the patient's will and a review underlined the importance of NIV as the primary treatment when intubation is not wanted by the patient.

In this case of hypercapnic coma, the choice to continue NIV was supported by previous reports demonstrating that cautious application of NIV can be attempted in comatose patient by an experienced team. This case report showed that old patient affected by ARF and with DNI order could be treated successfully with NIV in an unusual setting of long term care facility, avoiding ICU admissions. The choice of NIV should be considered by a multidisciplinary medical staff in a setting where nurses and medical team are trained in NIV protocol.

References


