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PROGRAMA: REINTEGRACIÓN FUNCIONAL DEL PACIENTE FRÁGIL. PREVENCIÓN Y TRATAMIENTO FARMACOLOGICO Y NO FARMACOLOGICO DE LA FRAGILIDAD

OBJETIVOS DE LA RED

Demographic predictions for 21st century (2012 EU Ageing Report) build a new scenario characterized by a modest increase in life expectancy, but a significant greater burden of disability, that will impact both in terms of healthcare specific demands and of sustainability of costs. Among the main features in the health status of the older population a high degree of heterogeneity, and an atypical and limited range of clinical manifestations of diseases are included.

Disability is the main consequence of the concurrence of three conditions in old people: the ageing process, life styles and health conditions. Although the health condition is one of the determinants of disability, the relationship is not linear and the nature of disability cannot be predicted solely from the clinical diagnosis (Guralnik et al., 2001; Maggi et al., 2004; Weiss, 2011). Furthermore, the predictive capacity of the health conditions for adverse outcomes (fatal/non-fatal) decreases as the age of

the population increases (Welch et al., 1996). Disability is usually preceded by a state characterized by a decreasing capacity to respond to demands, caused by diminishing functional reserve. This condition has been named frailty, a disorder that may precede by several years the development of disability (Fried et al., 2000) and other clinical outcomes. In contrast to chronic disease, the predictive capacity of frailty for adverse outcomes increases as the age of the population increases. The prevalence of frailty in people older than 65 is high, ranging from 7 to 16.3 %, increases with age (Fried, 2001; Bandeen-Roche et al., 2006; Garcia-Garcia et al., 2011), and it is the main risk factor for disability (Xue, 2011).

1.2 The concept of frailty

Frailty is a concept that encompasses changes associated with ageing, life styles, chronic diseases and the interactions among them (Bergman et al., 2007; Weiss, 2011). The concept of frailty has shifted towards the documentation of a more biological profile in recent times. The most accepted approach defines frailty as “an age-associated biological syndrome characterized by a decrease of the biological reserve and resistance to stress, due to a decline in several physiological systems, putting the individual in a special risk category when facing minor stressors and associated to poor outcomes (disability, death and hospitalization)” (Campbell & Buchner, 1997; Walston & Fried, 1999; Rockwood et al, 2000). Although these definitions stemmed from a biological conceptual framework, the practical approach to frailty is still based mainly on clinical BMs. The application of laboratory-based BMs remains quite limited.

1.3 The transition from non-frailty to frailty and disability

To detect frailty is of outstanding importance in preventing disability. When the frailty threshold has been surpassed and the disability has emerged, recovery from disability is unlikely (Ferrucci et al, 2002), especially as the age of the patient, the degree of disability or its duration increase (Fried & Guralnik, 1997). Although the usual evolution is to progress from non-frail to frail and disabled, a significant percentage of people improves in terms of functional status (Gill et al., 2006; Xue, 2011), with no clearly identified predictive factors of this evolution. In addition, the characteristics and the type of the interaction bewteen frailty and disease to promote disability is poorly understood as it is the efficacy of different treatments in terms of what, how, when and to whom.

However, some results from the Women´s Health and Aging Study II (WHAS II) suggest that some ill-defined characteristics associated with

muscle function could predict a differential risk (Xue et al., 2008). Although it is well known that the evolution from frailty to disability and its clinical consequences depends on several factors, including genetic and other biological factors (Bergman et al., 2007), their utility as BMs of frailty and of the risk to become frail, to develop disability and to respond to treatment, remains far from desirable for the day to day clinical practice. In fact, there are no studies addressing these issues.

1.4 The physiological and pathological framework of frailty

The most accepted physiological framework to explain frailty and its consequences was proposed by Walston and Fried (1999). Its fundamentals are sarcopenia and the energetic misbalance. They also established a feed-back between them: the so-called “frailty cycle”. This cycle stems from the physiological changes associated with ageing, producing an imbalance between anabolism and catabolism. This state embraces multiple systems and especially those related to hormonal changes and the development of a pro-inflammatory state: the decrease in sexual hormones (Iannuzzi-Sucich M et al, 2002), the dysfunction of GH-IGF-1 axis (Waters DL et al, 2003), insulin resistance (Barzilay et al., 2006), the increase in the ratio cortisol/DHEA-s (Walston & Fried 1999), testosterone deficit (Travison et al., 2007; Wu et al., 2010), the combination of several hormonal deficits (Cappola et al., 2010), increase in IL-6, IL-1 and TNF alpha circulating levels (Penninx et al., 2004), CRP and D-Dimer (Walston et al., 2002) and pro-inflammatory cytokines (Leng et al., 2002). These findings suggest that changes associated with sarcopenia and with the balance between production and use of energy may be among the most relevant factors associated with frailty: dysregulation of inflammatory cytokines and hormones, oxidative stress, nutrition, physical inactivity and mithochondrial dysfunction. In addition, the role of vascular disease (atherosclerosis) has been underscored by several authors (Strandberg & Pitkäla, 2007). The presence of clinical cardiovascular disease, but also subclinical cardiovascular disease has been shown to be associated to frailty, as it is the presence of other diseases like diabetes mellitus.

1.5 A step forward

During the last few years, there has been a progressive need to expand the concept of frailty from epidemiology to clinical practice. In this regard, several studies have been published showing the utility of the concept in improving the prognostic and predicting the risk in surgical patients

(Malani, 2009; Robinson et al., 2009) and in patients with cardiovascular disease (Afilallo et al., 2009). Although these are the group of older patients where the benefit has been clearly shown, other subgroups of patients (i.e the cancer patients, those at risk to visit emergency departments, etc.) seem to benefit from the diagnosis of frailty. However, as recently pointed out by two relevant studies, one of them coming from the group of LP Fried (Sternberg et al., 2011; Sanders et al., 2011), it is necessary to deep in the clinical profile and characteristics of frailty, as in its definition, to make this concept useful in the daily practice. In this regard several reports have shown improvements in some of the characteristics of the Fried´s criteria to best diagnose frailty. This is the case for the recent publication from one of the groups of the consortium (García-Garcia et al., 2011a) proposing a new frailty index that has shown a normal distribution in the older population and a good predictive capacity of the "biological age" of the participants.

Based on this framework a group of researchers are developing an EU Concerted Action (Frailty Operative Definition: Consensus Conference; FP7 2010 Health Program (Project number 261279) attempting to build a consensus around the operative/clinical definition of frailty and its components. Among its preliminary conclusions are the following:

1) There is a need to improve the validity of the existing definitions in order to demonstrate its clinical utility,

2) The combination of clinical (the components of the current definition) and laboratory BMs may be helpful,

3) There is a need to undertake research to identify new clusters of symptoms, signs and laboratory BMs to improve the ability to identify the risk of developing frailty in old people, its diagnosis and prognosis (i.e. its clinical consequences: death, hospitalization, permanent institutionalization and falls) and its response to treatments.

4) Finally, taking into account the importance of life style factors in the development of frailty, these findings need to be tested in populations with different life-styles and genetic backgrounds. Two recent papers show that in the European populations (Three-City Study) the predictive capability of the Fried´s criteria of frailty (obtained from Anglo-American populations) is lower than expected (Avila-Funes JA et al., 2008) and that adding some domains (cognition) to these criteria improve its predictive value for developing disability (Avila-Funes JA et al., 2009).

In this same regard it is necessary to test other approaches that allow to prevent or reverse frailty and frailty associated conditions, as to identify new routes and mechanisms with potential to become therapeutic targets. In summary, “Early detection of subclinical changes or deficits at the molecular, cellular, and or physiologic level is key to preventing or delaying the development of frailty” (Xue, 2011), and its consequences too. However, data evaluating the role of these substances in providing significant support to the clinical diagnosis of frailty or any of its associated risks are scarce, as it is the evidence supporting interventions that prevent, delay or reverse frailty, the mechanisms underlying the succes of these strategies and its prognostics biomarkers.