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Biological markers of frailty

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Frailty and sarcopenia

Frailty as a geriatric syndrome clusters for its pathophysiological background different components as all syndromes do. Besides physical factors, psychological factors influence the phenotype of frailty. To diagnose and grade frailty, the criteria mostly used are those by Fried et al (1). They include five both objective and subjective factors, but no laboratory parameter and so strictly spoken no biomarker of frailty. The advantage of this approach is obvious, as it is easy to perform in different settings (community, hospital, longterm care), also in those lacking resources to take blood or other biomaterial. The disadvantage is clear too: Lack of the possibility to easily distinguish subtypes of the frailty syndrome, grading of frailty according to the extent of biochemical derangements and the difficulty to follow laboratory changes over time, thus helping to follow progression and/or to observe treatment effects.

The great interest in frailty surely comes from the fact, as it well describes the clinical impression when caring for older persons, that they lack the possibility to cope with both internal and external stressors as well as younger persons do. When searching for the pathophysiological background of frailty, there is a extensive overlap with sarcopenia. Recently, several consensus conferences on the definition of sarcopenia have been taken place. These definitions all include a decline in muscle mass in combination with a functional parameter (e.g. gait speed and/or handgrip strength) (2,3). In none of these definitions, biomarkers are described.

Proposed biomarkers of frailty

With regard to biomarkers of frailty, one can didactically distinguish between the deficit and excessive model of frailty. The deficit model mainly covers the decline of the different endocrine axes within the aging process. These are the menopause (estrogens), andropause (testosterone), adrenopause (cortisol), and the somatopause (growth hormone. In addition, the endogenously produced estrogen and testosterone precursor DHEA can also be mentioned here. Even declines, respectively low plasma levels have been described for all these hormonal axes and the functional decline as seen in the frailty syndrome, none of them shows a clear “dose-relationship” and substitutive interventional approaches have mainly been disappointing. Nevertheless, present concepts favour a multiple hormonal dysregulation leading to frailty. There is also an interplay between these hormonal axes and the increase in inflammatory parameters often seen in the frailty syndrome, sarcopenia and indeed in cachexia (see below).

The concept of “inflamm-aging” by Franceschi seems to also has an important impact on frailty. More specifically, interleukin-6, tumour necrosis factor alpha, C-creactive protein to name a few have been put into correlation to all the three entities described above. Studies have demonstrated an independent association of proinflammatory cytokines such as TNF-alpha and IL-1 and IL-6 with lower muscle strength, lower physical performance and a higher risk of disability in sarcopenic/frail persons (4). The degree of inflammatory load therefore appears to parallel the degree of frailty. This concept is the backbone for the excess model of frailty. Indeed, a certain threshold for interleukin-6 can is significantly paralleled by the degree of functional decline as seen in the frailty syndrome. Nevertheless, we still have not enough data to separate degrees of frailty (non-frail, prefrail, frail) in different settings of elderly persons. We also lack to distinguish by these inflammatory parameters prefrail persons who are also sarcopenic or cachectic. This is a pity as we would need such biomarkers and clear thresholds not just for diagnosis, but also to follow patients along the course of the frailty syndrome as well as to monitor possible therapeutic effects.

In addition, the monocyte/macrophage-derived immune activation marker neopterin is independently of IL-6 correlated with frailty. This points in the direction that also monocyte/macrophage-mediated immune activations are part of the frailty syndrome and may become a new avenue of research to tackle immune-related biomarkers of frailty.

As vitamin D is presently the probably most trendy hormone in geriatrics, its role as a biomarker in frailty should be shortly described. Low vitamin D levels are clearly related to functional muscle strength loss and falls as an indirect sign of sarcopenia. The correlation of a low vitamin D status as a single parameter for frailty risk is also described. Lower vitamin D levels in community-dwelling older persons are independently correlated with frailty, but do not predict a further progression in the following years. In summary, low vitamin D levels as a single biomarker only modestly predict progression of frailty, but vitamin D deficiency at a serum concentration <15 ng mL as a punctual measurement is paralleled by an around 4-fold increase in the odds of frailty.

Other biomarkers have been described in the frailty syndromes (e.g low haemoglobin), but these correlations still need to be substantiated by interventional trials.

Sarcopenia and cachexia

Having mentioned the close interplay with frailty and sarcopenia, there is also an important overlap to cachexia. Recent consensus conferences tried to dissect the differences between sarcopenia and cachexia. In this respect, the mostly used definition for cachexia incorporates biomarkers for the definition such as increased inflammatory markers (e.g. C-reactive protein, IL-6), anemia (Hb <12 g/dl), and low serum albumin (<3.2 g/dl) (5). Moreover, if we take this cachexia definition (5), it is interesting that they utilized three items of the Fried frailty criteria. These are: Decreased muscle strength, fatigue, and anorexia (weight loss in the Fried criteria).

Conclusions

Frailty as many other geriatric phenomena comprises a number of underlying causes and mechanisms. Factors involved are not just intrinsic changes themselves, but involve neuronal, humoral, and lifestyle factors. So, biomarkers for frailty would be important in the differential diagnosis of frailty and to follow-up such alterations for monitoring of progression or regression of symptoms of the syndrome, as well as to observe putative changes as a consequence of interventions to prevent, delay or regress frailty.

To date, no specific biomarker has been described. It seems more that a cocktail of both (hormonal) changes (deficit model of frailty) and increases in inflammatory markers (excess model of frailty) make up the clinical picture of this frequent Geriatric syndrome. It is to hope that future research will help to find clusters of biomarkers that help to distinguish different forms of frailty and their interaction especially with sarcopenia.

References

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