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Clinical laboratory findings in the elderly

O laboratório clínico na terceira idade

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key words	abstract
Clinical laboratory	The aging of Brazilian population is inevitable. Thus, this article reviews the main aspects related to the elderly population, taking into account the particularities and problems encountered in the clinical laboratory when serving this population group. We start with a brief review of the aging process physiology and then discuss the difficulties of pre-analytical (appropriateness of care), analytical (main issues for this age group sorted into body system categories) and post-analytical phases.
Elderly	
Geriatrics	
Physiology of aging	

resumo	unitermos
<i>O aumento da população idosa em nosso meio é fato incontestável. Assim, este artigo faz uma revisão dos principais aspectos referentes a essa população, sempre considerando as particularidades e os problemas observados no atendimento dessa faixa de população no laboratório clínico. Partimos de uma breve revisão sobre a fisiologia do envelhecimento para então percorrermos as dificuldades das fases pré-analítica (adequação do atendimento), analítica (principais problemas dessa faixa etária, divididos por sistemas orgânicos) e pós-analítica.</i>	<i>Laboratório clínico</i> <i>Terceira idade</i> <i>Geriatria</i> <i>Fisiologia do envelhecimento</i>

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Introduction

The aging process, or senescence, used here as a synonym, is a topic that is not thoroughly understood. Experimental studies using humans are subject to restrictions, and the literature offers models based on rodents and other organisms, such as the nematode *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, and the yeast *Saccharomyces cerevisiae*, whose biological characteristics, such as a short life span, a broadly sequenced genome, and a well-characterized biology, facilitate scientific research.

Biological aspects of aging

There are proposed theories to explain the aging process, and here we provide a brief discussion of each as well as a description of the expected changes in some organs. There are three proposed theories: evolutionary, molecular-cellular (cellular senescence), and systemic.

Evolutionary theory

Evolutionary theory presents several interesting facets, such as the low prevalence of death in early adulthood and the increasing prevalence in late adulthood. The maturity of reproductive function marks the beginning of aging, and the earlier the onset of reproductive capacity, the earlier the onset of the aging process^(22, 24).

Cellular senescence

Senescence can be expressed in two ways: stress-induced senescence resulting from molecular events and replicative senescence resulting from the loss of telomeres. Telomere shortening can be considered a molecular clock that signals replicative senescence.

Theories based on molecular and cellular mechanisms of aging are related to errors in protein synthesis that accumulate throughout life and mutations that arise due to exposure to the external environment, especially sub-lethal doses of radiation, which can induce changes that can promote death over the long term. The association with errors in DNA replication contributes to increasing the likelihood of this outcome⁽²³⁾.

The presence of free radicals predicts that regulatory mechanisms of production will become ineffective with age, and the accumulation of superoxide causes structural damage to cells, causing irreparable damage.

Systemic theory

The nervous, endocrine and immune systems play an important role in controlling the body's responses to external and internal stimuli. A lack of control in the performance of these systems will accelerate the aging process⁽²⁾.

From a neuroendocrine point of view, it is believed that aging results from changes that occur in the hypothalamic-pituitary-adrenal systems, which act as regulators. Changes that compromise the function of this axis, such as a low response to stimulation, contribute to an accelerated aging process.

Immunological changes are based on two premises: the decline of the functional capacity of the immune system and increased production of auto-antibodies. Immune senescence is thus characterized by reduced resistance to infections, the rise of neoplasia, and a reduction of the capacity for auto-recognition, which facilitates the occurrence of autoimmune diseases.

Cardiovascular system

Cardiac structural changes are marked by increased myocardial thickness, deposition of collagen tissue, and increased heart stiffness. Changes in arterial cell and renal perfusion are also identified. Coronary heart disease in elderly patients is two to three times higher than in patients younger than 65⁽⁵⁾.

Respiratory system

Conformational changes of the nose and of the costal cartilage, costo-vertebral joints, and lungs determine the senescence process characteristic of elderly patients. The main functional changes in the respiratory tract in elderly are:

- reduction of the chest wall;
- reduction of respiratory muscle strength;
- reduction of vital capacity;
- increased residual volume;
- increased arterial-alveolar oxygen gradient;
- reduction of pulmonary diffusion;
- hypoxia;
- hypercapnia.

Renal system

Renal blood flow tends to decrease by 50% due to a progressively decreasing rate of glomerular filtration.

Comorbidities, such as hypertension, diabetes, and previous episodes of pyelonephritis, may further influence the effects of senescence.

Nutritional and metabolic factors

There is a decrease in basal metabolism, a redistribution of body mass, and change in the digestive system. With increasing age, there is an increase in body fat and abdominal fat internalization. These phenomena are present in both males and females⁽¹⁹⁾.

As a result of obesity, diseases, such as hypertension and diabetes, increase in prevalence. An important metabolic factor is the occurrence of hyperelectrolytic disturbances, such as hyper- or hypo-natremia, which, when associated with other comorbidities, are associated with worse mortality and morbidity⁽¹⁰⁾.

Laboratory aspects

Pre-analytical factors

When a patient in this age group seeks health services, the first concern will be how to welcome the patient. Clinicians should also treat the physical facilities involved as a primary concern. Each unit should be equipped with devices that provide ease and comfort, ensuring the safety of the patients. It is important to remember that in this age group, difficulties with mobility, hearing, and vision are not uncommon. Clinics should be designed with these possible limitations in mind. The accessibility of the units should be developed to the fullest. Handrails and grips at appropriate heights should be available in corridors, collection rooms, and bathrooms. Furthermore, toilet bowls should be set at appropriate heights, and security handles should be provided.

The floor should be as uniform as possible, with ample provision of ramps and non-slip flooring, avoiding stairs and slopes.

The visual and auditory signals must be clear and prominent. Protocols should use large letters for easy viewing.

The process of sample collection should go beyond a collector well trained in the collection technique. A tourniquet should be applied to the minimum degree necessary, and extended use should be avoided. When a tourniquet is applied for more than three minutes, it can raise cholesterol by 5% and aspartat aminotranferase (AST) by almost 10%.

It is important to remember that patients of this age have to be treated with respect and care but not as children. Calmness and patience in this type of care are essential.

The clinical status of these patients may be extremely variable. Their state depends not only on the coexistence of multiple diseases, but also on aspects related to treatment of the patients past medical problems and to how the patient has been followed. Therefore, trying to set standards in terms of benchmarks and their consequences, such as communication or panic levels, becomes a complicated task.

These patients also present with polypharmacy. Drugs can interact with each other not only *in vivo*, but also *in vitro*. Insisting on obtaining information about the current drugs being used can solve many problems related to treatment.

Variations in clinical status are also affected by genetic factors and aspects of body composition. We know, for example, that levels of creatine kinase (CK) enzyme are generally higher in populations of African descent because individuals in these populations have more muscle mass. By contrast, white women have lower muscle mass. Substances produced by the muscles (such as CK and creatinine) may change⁽¹⁶⁾.

In turn, patients with a higher fat mass have increased levels of lipids, transaminases, insulin, glucose, and cortisol.

Menopause can alter the results of tests related to bone metabolism, and alkaline phosphatase may vary by up to 25%.

In summary, changes that are frequent in the elderly, such as changes in body composition and height loss, lead to a new homeostatic balance, which can vary in comparison to young adults.

Environmental factors also influence these patients and the results of their laboratory tests. Inpatients hospitalized for long periods or under inappropriate conditions should be evaluated carefully. Patients exposed to constant cold may have increased thyroid-stimulating hormone (TSH) and decreased thyroxine hormone (T4). Constant stress can alter corticotropin-releasing hormone (CRH), aldosterone, and renin. Additionally, stress can also lower thyroid hormones (TSH, triiodothyronine [T3], and T4).

In immobilized patients (forced postures), the plasma volume falls between 5% (on the first day) and 8% (on the sixth day). Calcium, urea, and T4 rise, while cortisol and metanephrine decrease.

Diet is also an important consideration because these patients often have chewing and swallowing problems and, therefore, opt for a diet with a higher proportion of

carbohydrates and fats. Malnutrition is common, and one study showed that up to half of admitted patients have low transferrin. The state of hydration must also be taken into consideration, and adequate hydration should be ensured.

The circadian rhythm can also change, and sleep disturbances are common. Cortisol, aldosterone (which depends on movement), TSH, metanephrines, and peptide C may be altered in the elderly.

Even healthy habits can affect test results. Exercise, for example, leads to higher protein turnover and increases the levels of circulating enzymes and stress hormones (cortisol, metanephrines, aldosterone, B-type natriuretic peptide [BNP]). However, it reduces cholesterol and triglycerides.

Changes in laboratory evaluation of physiological systems

Some changes are more prevalent in this population, and we will briefly discuss the clinical-laboratory correlations.

Endocrine changes

The most relevant changes are thyroid and metabolic syndromes. Thyroid function remains stable, despite the decrease in T3 due to reduced peripheral conversion of T4 into T3. T4 remains stable because reduced synthesis is offset by lower clearance.

There is an increase in the peripheral resistance of these hormones, and this resistance explains the fact that the TSH remains within the reference range.

Thyroid disorders are also common in this population. Hypothyroidism appears in 4% of the population, and it is present in subclinical form in 5%⁽⁴⁾. Approximately two thirds of the population in this age group tested positive for anti-thyroid antibodies^(12, 14).

Hyperthyroidism also presents with vague symptoms, such as cardiac abnormalities (tachycardia, atrial fibrillation, angina, congestive heart failure [CHF]), neurological abnormalities (weakness, emotional disorders), and gastrointestinal abnormalities⁽¹⁵⁾.

Hypothyroidism can also be frustrating to identify because the symptoms are not always clear to the doctor. It can present as debility, cold intolerance, constipation, dry skin, mental confusion, chronic anemia, or other autoimmune manifestations. The aspect of confusion can be difficult to differentiate from symptoms of dementia. Dementia resulting from hypothyroidism has been shown

to be an important cause of debility. Other serious illnesses can present similarly, and therefore, the laboratory plays an important role in diagnosis⁽¹²⁾.

Metabolic syndrome, which is well known in our country, should be considered based on the significant increase in its likelihood that is correlated with age⁽¹⁹⁾.

Assessment of renal function

Kidney function declines with age, falling about 1% per year. Renal plasma flow begins to decrease earlier than the glomerular filtration rate, which leads to a delay in clearance measures for assessing the extent of renal function⁽⁶⁾.

Creatinine remains stable because the production and excretion rates fall together, i.e., the loss of muscle mass (responsible for the production of creatinine) follows the reduction in excretion⁽¹⁾. Three factors directly influence the plasma concentration of creatinine: muscle mass, age, and diet. We know that an overload of animal protein in the diet can raise the levels of serum creatinine from 10% to 20%.

The route of excretion is glomerular filtration (for the greater part) and tubular secretion (for the lesser part). During renal insufficiency, tubular secretion becomes more significant, and purification may be overestimated by 50% to 200%. Creatinine purification is not related linearly with serum levels, so it is always important to remember that relatively "small" changes may indicate large decreases in renal function⁽⁷⁾.

Collection of the sample itself can be performed over a period of 12 to 24 hours or over shorter periods. Certain precautions should be taken, such as ensuring the accuracy of timing during collection, starting the test with a proper emptying of the bladder, providing adequate hydration, and preventing the loss of urine. Ideal hydration should be initiated with 20 ml/kg of body weight plus replacement.

In elderly patients, complications related to each of the items mentioned may be present, including difficulty for understanding the instructions for the collection, incomplete bladder emptying (residual urine), water restriction for medical reasons, and inability to control and collect urine (patients with urinary incontinence, for example).

The formulas most commonly used for estimation (Cockcroft-Gault and Modification of Diet in Renal Diseases [MDRD]) can be used with good accuracy, but purification of less than 60 ml/min is not recommended⁽⁸⁾. The use of cystatin C may be considered⁽¹¹⁾, although it is not yet in common use in our area.

Hematological features

Hematological problems are common in the elderly⁽¹⁷⁾. Bone marrow also undergoes characteristic changes over time. Values that would be considered appropriate in other age groups can take on a different clinical significance in the elderly⁽²⁰⁾. Leukocyte counts of approximately 10,000/mm³ may be normal for a youth, but in the elderly, this count may be highly indicative of infection⁽¹⁸⁾.

Anemia is a disease that is more prevalent in the elderly⁽⁹⁾. Its prevalence increases with age and other comorbidities. These include iron deficiency, chronic disease, bleeding, and injuries to the spinal cord⁽³⁾ (myelodysplasia and myeloproliferative disorders). A suggested strategy is to administer ferritin to differentiate between anemia caused by iron deficiency and that caused by chronic disease.

Lymphomas and myelomas are also important manifestations in this age group because their clinical manifestations are different from those observed in young adults⁽²⁵⁾. Anemia is a disease that is more prevalent in the elderly. Its prevalence increases with age and other comorbidities. These include deficiency, chronic disease, bleeding and injuries to the spinal cord (myelodysplasia and myeloproliferative disorders).

Markers of inflammatory activity

Inflammatory diseases are a common problem in older people. Thus, the evaluation of markers of these diseases involves some care regarding the interpretation of results⁽¹³⁾.

The tests are nonspecific, with high sensitivity, low specificity, low positive predictive value (PPV) and high negative predictive value (NPV). Therefore, negative results should be evaluated, and positive results should be carefully analyzed.

Common exams in clinical practice, such as antinuclear factor and thyroid antibody tests, also deserve attention. In an important study, Tan et al. showed that up to 3% of the population may have false-positives in high titers⁽²¹⁾.

Anti-thyroid antibodies, as well as other auto-antibodies, have an elevated incidence with increasing age.

Monitoring of therapeutic drugs

High or low values can be found in this range. Difficulty of absorption due to reductions in motility and the absorptive surface and differences in tissue distribution, with more body fat and less tissue perfusion, are factors involved in therapeutic drug levels. Additionally, metabolism is slower and excretion is impaired by reduced kidney and/or liver function^(18, 26).

Conclusion

Increases in the elderly population, especially those considered very old (over the age of eighty years), make it necessary to study this age group not only from the standpoint of institutional policies but also to address the various clinical and physiological factors that they are subject to.

It falls to the physician, regardless of specialty, to take into account that the diagnosis or treatment of elderly patients always depends on careful analysis of the disease and the physiological changes associated with age. No less important are aspects related to quality of life, such as functional changes, which are studied by evaluating the normal and instrumental activities of daily living. Finally, these patients also often suffer from co-morbidity caused by a combination of diseases.

As noted above, the physiological changes caused by aging interfere significantly with the function of organs and systems, which is reflected in the results obtained in laboratory tests. Thus, the correct interpretation of these tests depends, more directly than in young adults, on the analysis of the clinical, functional, and social characteristics of each patient.

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