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Optimizing Hyaluronic Acid

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Highlights

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Discovering Thoughts, Inventing Future

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Optimizing Hyaluronic Acid: A Comprehensive Review of Rheological Insights for Clinical Practice

By Fernanda Lacerda de Almeida Romanó Peixoto, Isabela Espasandin, Paulo Henrique Bastos, Juliana do Carmo Públio & Antony de Paula Barbosa

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Optimizing Hyaluronic Acid: A Comprehensive Review of Rheological Insights for Clinical Practice

Fernanda Lacerda de Almeida Romanó Peixoto [α], Isabela Espasandin [σ], Paulo Henrique Bastos [ρ], Juliana do Carmo Públio [ω] & Antony de Paula Barbosa [¥]

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Keywords: cohesiveness, extrusion force, hyaluronic acid, rheology, skin quality improvement, swelling degree, facial aging, dermal fillers, aesthetic procedures, injection techniques.

I. Introduction

Increased understanding of facial aging has led to the introduction of several products for aesthetic use. Hyaluronic acid (HA) - based fillers have expanded in proportion to knowledge in availability and manufacturer diversity.

HA fillers currently account for about 80% of all fillers used for rejuvenation and volume correction [1]. These products have low complication rates, good durability, are relatively inexpensive, may be broken or degraded through a mechanism of enzymatic action (lysis) by injection of hyaluronidase[1, 4, 6].

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HA is a natural linear polysaccharide of high viscosity and high molecular weight, found in the extracellular matrix, vitreous humor, and cartilage [4, 13, 17]. Its total amount in a 70 kg individual is approximately 15 g, and its average turnover rate is 5 g/d. Approximately, 50% of its amount in the human body is concentrated in the skin and has a half-life of 24-48 hours. The natural process of degradation involves mainly two mechanisms: enzymatic degradation and degradation by free radical action [4,13].

Molecule of HA consists of alternating units of N-acetyl-D-glucosamine and glucuronic acid. This molecule is part of almost every tissue in vertebrates. Chemically, it is a hydrophilic macromolecule with -COOH and -OH functional groups (hydroxyl and carbosyl group). Its solubility in water is high, and it forms highly viscous solutions. In physiological conditions, the carboxyl group (-COOH) interacts with sodium ion (Na+) [4], attracting water molecules, so it is considered a hygroscopic molecule, so cross-connections formed the reticulation of the molecule, expanding according to its absorption of water. From this phenomenon the viscoelasticity occurs [28].

The functional group -OH (hydroxyl) is linked to the GLCNac anomeric carbon that donates a proton (H+) to -OH from the GLCA anomeric carbon (C1), and thus the C1 OH is now positively loaded oxygen and oxygen C3 is negatively charged, he attacks carbon C1 and releases H2O, thus forming the HA disaccharide (Figure 1. HA is a linear macromolecule composed of repeating disaccharide units) [29].

Such solutions show unique viscoelastic properties. It is synthesized by a class of integral membrane proteins known as HA synthases, which lengthen HA by repeated addition of glucuronic acid and N-acetyl-d-glucosamine groups to the growing sugar (Figure 1. HA is a linear macromolecule composed of repeating disaccharide units). They can form intramolecular hydrogen bonding, which leads to three-dimensional structures. HA can trap water within its structure and can form gels, which inside the body can provide flexibility to the animal tissue and lubrication the set of bundles surrounded by dense connective tissue, in muscular tissues. Its role in the body is strictly connected with its properties, it plays an important role in ECM (extracellular matrix) by several specific and non-specific interactions.

The role of HA usually depends on its molecular weight. For example, low weight HA is essential in healing and scar formation, whereas high molecular weight HA may support tissue integrity [20]. It can be used in tissue repair because it is able to promote mesenchymal and epithelial cell migration and differentiation. It is also helpful for the growth of epithelial tissue cells, eosinophil, macrophages, and a few animal tissues cells [20, 27]. Biological properties make it very good material for tissue engineering [20].

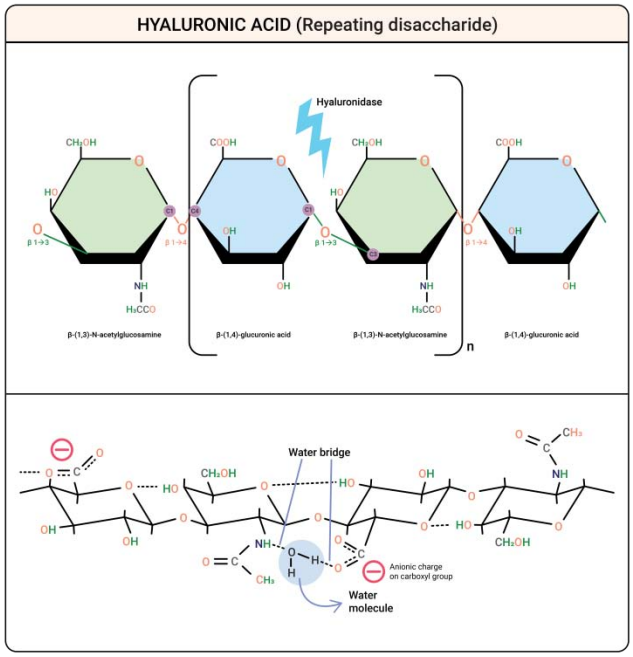


Figure 1: HA is a linear macromolecule composed of repeating disaccharide units. Each disaccharide unit consists of two sugar molecules: glucuronic acid (C1) and N-acetylglucosamine (C3 and C4), represented in brackets. The chemical bonds between units are called glycosidic bonds, which occur between carbon 1 (C1) of one unit and carbon 4 (C4) of the next unit. The molecular structure of HA is highly hydrophilic, meaning it has a natural affinity for water. This is because of the functional hydroxyl groups (-OH) and carboxyl groups (-COOH), which are highly polar, meaning they have an unequal distribution of electrical charge, with a partial positive charge on hydrogen and a partial negative charge on oxygen and carbon. Water is also a polar molecule, with an uneven distribution of electrical charge due to its H2O structure. The hydrogen atoms in the water molecule have a partial positive charge, while the oxygen atom has a partial negative charge. This polarity causes water molecules to interact attractively with HA molecules. Hyaluronidase is an enzyme naturally present in the human body that breaks glycosidic bonds in HA. It acts by cleaving the β(1→4) bonds between disaccharide units, converting HA from its viscous, high-molecular-weight form into lower-molecular-weight fragments.

a) *The structure of the skin and forces acting on HA fillers*

The skin has many vital functions, including protection against external physical, chemical and biological aggressors, as well as preventing the body from excessive water loss and a role in thermoregulation [15]. The integumentary system is formed by the skin and its derived structures, divided in three layers: the epidermis, the dermis, and the subcutaneous tissue. These layers are referred to as an epidermis of stratified squamous epithelium, a basement membrane zone (BMZ) and a fibrous neurovascular dermis which supports on a hypodermis or subcutaneous fat [16].

At the outermost level, the epidermis is mainly composed of sheets of keratinocytes (Figure 2. Skin Structure and Appendages) but also contains non-epithelial cells, including antigen-presenting dendritic Langerhans cells as well as melanocytes and Merkel cells[16, 21]. Reinforcing the epidermis is to the dermis, that accommodates the vascular, neural, lymphatic and adnexa of the skin (Figure 2. Skin Structure and Appendages) [21].

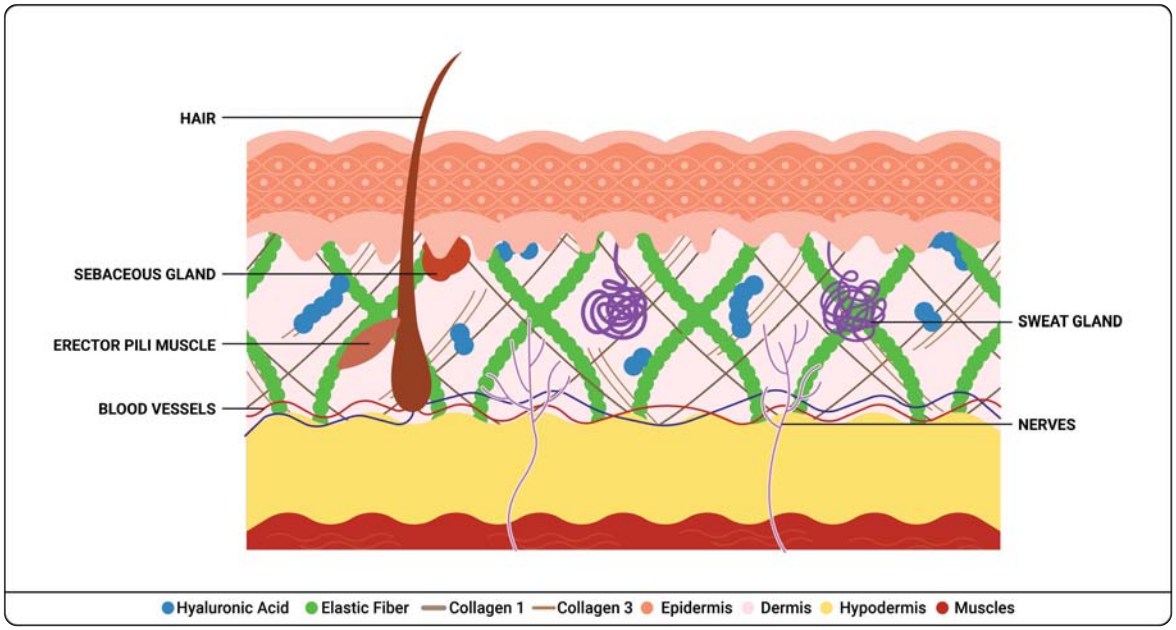


Figure 2: Skin Structure and Appendages: Epidermis: it is the outermost layer of the skin, composed of several layers of epithelial cells. It provides a protective barrier against environmental factors and pathogens. Dermis: it is the layer beneath the epidermis and consists of connective tissue. It contains blood vessels, lymphatics, nerves, and various structures like hair follicles, sweat glands, and sebaceous (oil) glands. Collagen and elastin fibers in the dermis provide strength and elasticity to the skin, still HA free provides hydration, wound healing, nutrient transport, protection, volume and elasticity. Subcutaneous Tissue (Hypodermis): this tissue lies below the dermis and is mainly composed of fat cells (adipocytes).It acts as an insulator and provides cushioning and energy storage.

The middle layer, the dermis, is connective tissue itself which are the cells and the fibers that compose them. Such cells are: fibroblasts, fibrocytes, macrophages, lymphocytes, plasmocytes, mast cells and adipose cells. Its papillary layer is the most superficial and thin, made up of loose connective tissue. The reticular layer, deepest and thicker, consists of dense non-patterned connective tissue. The primary cell type is the fibroblast, which produces matrix extracellular structural proteins, glycosaminoglycans (which hydrate the tissue due to the high-water binding capacity of hyaluronic acid), collagen and elastin fibers (Figure 2. Skin Structure and Appendages). Both contain many fibers and elastic, responsible, in part, for the elasticity of the skin. In addition to blood and lymphatic vessels and nerves, the following structures are also found in the dermis: hair, sebaceous and sweat glands [21].

The hypodermis is situated within the subcutaneous tissue, primarily composed of loose connective tissue. It plays a crucial role in facilitating the smooth movement of the skin over the underlying structures. Depending on an individual's nutritional status and overall health, this layer may exhibit varying amounts of adipose tissue. Their consists of small clusters of fat cells known as adipocytes (Figure 2. Skin Structure and Appendages). The thickness of the subcutaneous layer can vary significantly depending on the specific anatomical location of the body [21].

The Superficial Muscle Aponeurotic System (SMAS) connects the facial muscles to the dermis and aims to transmit, distribute and amplify the activity of all facial muscles. True ligaments are easily identifiable structures that connect the skin to the underlying periosteum (the membrane that covers the outer surface of the bone). And false retention ligaments are more diffuse condensations of fibrous tissue that connect the superficial and deep fascia to the skin [30]. In muscle tissues, HA can retain water, which provides lubrication to the dense connective tissue (Epimysium, Perimysium, and Endomysium) that surrounds its fibers.

After injection, the fillers are subjected to compression, shear, stretching, torsion by muscle movements, weight of soft tissue, pressure on external surfaces (e.g., face while sleeping), and gravitational force. All these forces modify the shape, distribution, time and the degree of correction of the filled defect (figure 5. This schematic representation illustrates the relationship between cohesiveness and viscosity in an HA gel, emphasizing their effects on the gel's behavior and shape when injected into the dermis and figure 6. Schematic representation of the cohesion and viscosity of an HA gel reveals a pivotal correlation). The gel's fluidity is greatly enhanced by its low viscosity and low cohesiveness, which results in a lack of unity. On the other hand, a gel that has low viscosity but high cohesiveness maintains its structural integrity while still remaining fluid. This balance also influences the level of force necessary to extrude the gel through a syringe and needle. When examining a filler with high viscosity and strong cohesiveness, it manifests as a denser and more

cohesive gel, demanding greater force for extrusion. Conversely, in the absence of cohesiveness, the gel fails to maintain its unity after being injected into the dermis. In summary, the delicate balance between viscosity and cohesiveness significantly influences both the physical properties of the gel and its performance during injection, shaping the final outcome in dermal applications) [1,11].

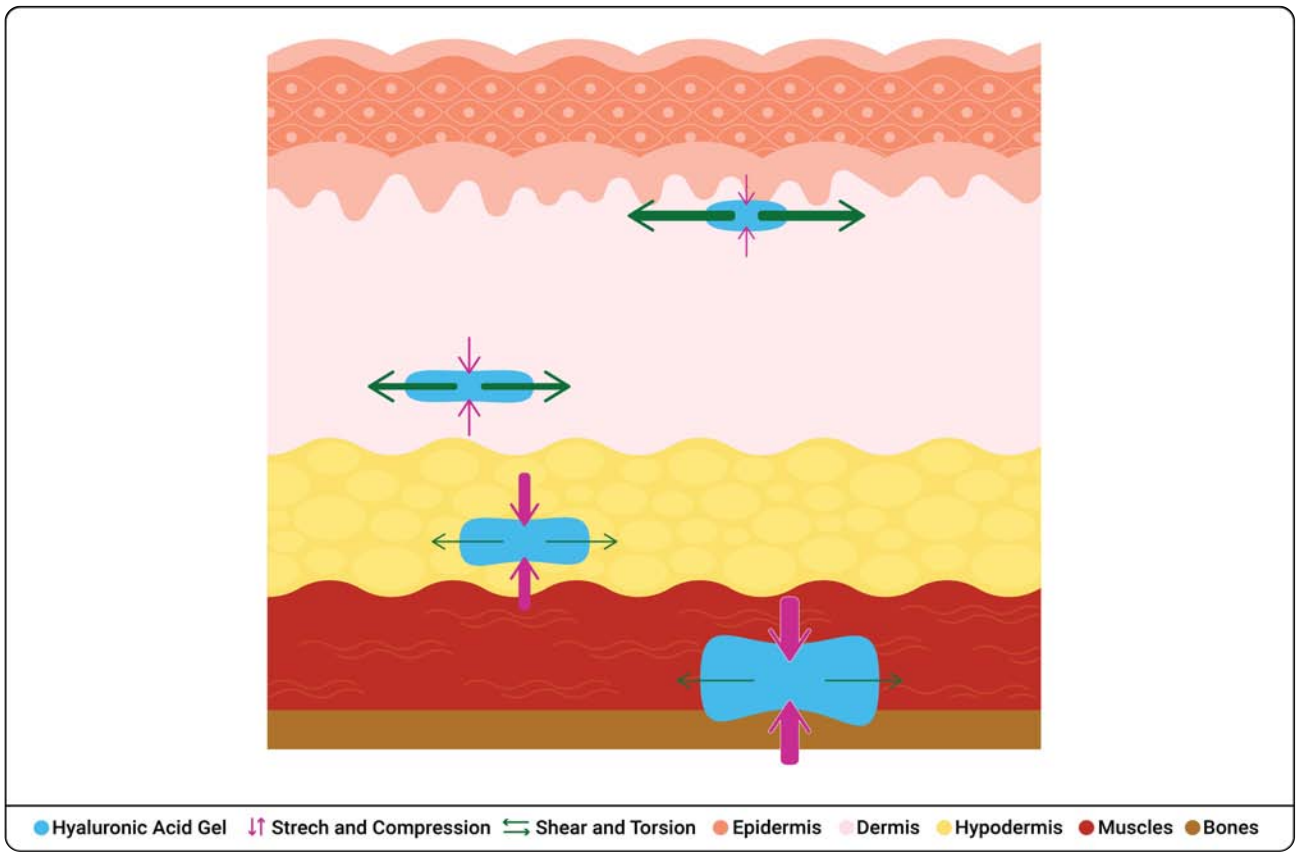


Figure 3: Dynamic forces of the HA in different planes of the dermis. Superficial Dermis: when it is injected into the superficial dermis, it remains close to the skin's surface. The forces acting on it are primarily associated with facial expressions and muscle movements. It in this plane can help address fine lines and superficial wrinkles, providing subtle volume enhancement. Mid-Dermis: injecting it into this plane allows it to interact with collagen and elastin fibers, which provide structural support. Forces in this plane involve both muscle movement and the skin's natural tension. It placed here can help restore volume, correct moderate wrinkles, and enhance facial contours. Deep Dermis or Subcutaneous Tissue: it injections in the deep dermis or subcutaneous tissue reach areas with more robust support structures, including fat compartments and ligaments. The forces acting on it in this plane relate to the underlying bone structure and the pull of facial muscles. It is suitable for addressing deeper wrinkles, volume loss, and providing structural support for facial features.

Considering the previous statement, depending on the region of the face where the HA is implanted, it will be submitted to 2 types of forces, each one causing a product deformation in a different plane. The first, in a horizontal plane parallel to the skin surface, is the shear or torsion force. The second, which is the compression/stretching force, is applied in a vertical plane perpendicular to the surface. Mechanical facial strains involve a combination of these 2 types of forces, and depending on the region in concern, one type of strain may be predominant (Figure 3. Dynamic forces of the HA in different planes of the dermis) [13, 14]. To what extent these forces act on the product depends on several factors, such as the plane of injection (i.e., superficial versus deep) and anatomical location. Although the indications and instructions for use by the manufacturer are important, the skills required to create an aesthetic effect is dependent on the accuracy of the person performing the facial analysis and performing the filler [19].

b) The Rheology versus its applications

Rheology is a section of mechanics which studies the deformation and flow of matter, particularly in light of its limits of resistance to deformation. Introducing this concept is important to understand the application of HA from the perspective of this property, as will be listed and explained below.

Understanding the rheological and biophysical fundamentals will result in clinical implications that facilitate the appropriate choice for Orofacial harmonization treatments [1,2,10]. For example, the HA filler applied when the aim is to restore volume has different rheological characteristics from those indicated for the treatment of fine skin lines. Therefore, the fillers indicated for each aim and area will have different properties.

Several studies can provide insights into material behavior under different temperature stresses. Therefore, the study of a new formulation requires multiple steps to demonstrate safety, efficacy and stability to ensure consumer protection and satisfaction. During formulation of fillers, use and storage time, exposure to possible external factors such as physical damage, microbiological and chemical influences can.

These features influence the integration between the HA and the surrounding soft tissues and they determine the filler's ability to modify the anatomical layer volume, based on this statement, clinical planning can show different HA for different anatomical areas and even the same areas with different goals.

The objective of this study is to carry out a review on the rheology of HA fillers, characterizing and understanding the mechanical and viscoelastic properties of this polysaccharide in various contexts, including its concentration, temperature, and the presence of other components. This research will facilitate enhanced utilization of the product across a range of applications within tissue engineering and aesthetics area, leading to more effective and personalized clinical applications. As we delve deeper into understanding hyaluronic acid and its role in facial harmonization, the subsequent sections of this article will explore various aspects, starting with the manufacturing technology, followed by an examination of its physical-chemical properties and will culminate in a detailed exploration of its rheological features. These sections collectively shed light on the multifaceted aspects of HA-based fillers and their applications in clinical practice.

II. Manufacturing Technology

HA is made naturally in the human body, has a half-free radical action. For this reason, the HA used as a filler needs to be modified through a process called crosslinking. HA fillers differ in their manufacturing technologies, formulations, additives, and clinical indications [2]. The HA used for the manufacture of fillers is mainly produced with biotechnology, from the fermentation of microorganisms, such as the genus of Streptococcus aerobic bacteria. This is biocompatible with the human body, as the structure of HA is highly conserved in different species [8].

Bacterial fermentation produces non-crosslinked HA of varying lengths. HA chains must undergo a stabilization process to avoid rapid enzymatic and oxidative HA 9 adapted resorption [1, 4, 8]. To achieve this goal, the HA polymerization is enhanced by a crosslinking process that adds a molecule, called BDDE (1,4-butanediol diglycidyl ether) linking the polymer chains to each other [1,4, 17,18] (Figure 3. Dynamic forces of the HA in different planes of the dermis). BDDE is the crosslinking agent with the lowest toxicity, its amount is limited by the FDA (Food and Drug Administration) to a residual level of unreacted BDDE <2 parts per million (ppm) [1]. BDPE, which stands for "1,4-butanediol di-(propan-2,3-diolyl)ether," is derivatives formed throuth of nucleophiles during the cross-linking process the epoxide groups of BDDE. This results in the formation of a three-dimensional network that prevents rapid dissolution to improve the mechanical and physical properties. This processes, crosslinking significantly reduces the rate at which the body metabolizes the filler, prolonging its presence in the treated area. This results in longer-lasting effects and improved structural support. Additionally, crosslinked fillers are better equipped to resist degradation, maintaining their shape and volume over time. Crosslinked HA has been used for over 15 years and it is well tolerated. It has structural properties similar to native tissue, excellent biocompatibility and good integration [2, 1]]. Over time, unreacted BDDE is degraded through hydrolysis [4].

Crosslinked HA has structural properties similar to native tissue, excellent biocompatibility and good integration. In areas where long-lasting results are desired, such as the midface or temples, fillers with higher cross-linking are preferred [4].

Hyaluronidase naturally occurs in various organs (such as the testis, spleen, skin, eyes, liver, kidneys, uterus, and placenta) and body fluids (tears, blood, and semen). There are six known types of hyaluronidase (hyaluronidase 1–4, PH-20, and HYALP1). Hyaluronidase 1, encoded by the HYAL1 gene, is prevalent in major organs

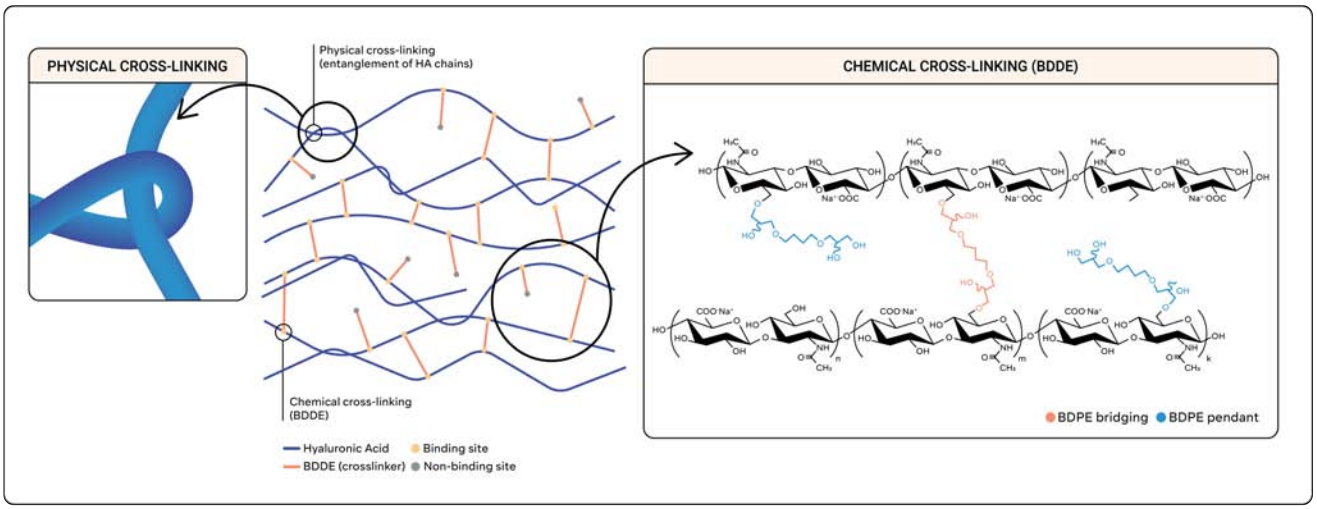


Figure 4: This schematic representation illustrates the differences between natural, cross-linked HA and the process of physical crosslinking. Natural HA: represented by the blue line as a linear molecule composed of repeating disaccharide units. Cross-Linked HA: represented by the blue line connected by the orange, at higher magnification, in which there are additional, BDDE ou BDPE connecting bonds between HA chains. These bonds, often formed through chemical processes, create a network or matrix. Crosslinking enhances the stability and longevity of HA fillers when used for cosmetic purposes. The degree of cross-linking can vary, influencing the gel's cohesiveness and resistance to degradation. Physical Crosslinking: is a technique that allows for HA modification without the use of chemical agents, such as changes in temperature, pH, or the application of external forces to induce cross-linking.

However, the natural linear form of HA molecules is susceptible to rapid degradation by hyaluronidase, rendering it unsuitable as a filler due to its inadequate consistency and short half-life. To overcome this limitation, it is essential to modify the physical properties of HA to increase its resistance to in vivo degradation [7]. In practice, dermal HA is composed of both unmodified HA (without crosslink) and crosslinked HA (with crosslink), forming a polymeric network that achieves the desired durability and stability [6,7].

Unlike the linear polymer, the crosslinked network is able to swell in aqueous media without dissolving, it behaves rheologically as a gel-like material, shows a viscosity that decreases with shear rate under flow conditions, and it is less sensitive to degradation by hyaluronidase. It thus gives the injected HA gel hydration, projection (filler effect), injectability, and a longer tissue permanence than linear HA[18].

Production methods are used to alter the molecular technologies available on the market with their respective manufacturers, indications for use, type of filler marketed, and HA concentration (mg/ml) [11,19]. The technology manufacturing too will influence in the action of the natural hyaluronidase, to action order for it to dissolve a HA filler, it must be able to access the intramolecular bonds. Interfer in this access include the number of crosslinks and the concentration of HA. The more crosslinking, the more difficult it is for hyaluronidase to access its binding inside the HA filler. For this reason, fillers with high crosslinking require a long time to dissolve with by this enzyme action. In addition, the higher the concentration of HA, the slower it will be dissolved by hyaluronidase [22].

It is important to remember that the hyaluronic acid gel will always be degraded by the action of the hyaluronidase enzyme, and it is important to pay attention to the amount of hyaluronic acid injected versus the dose of hyaluronidase, which can directly determine the final degradation time of the product (dose-dependent responses).Its use has safety implications in the context of HA filler procedures. It serves as an important tool in managing filler-related complications, such as overcorrection or vascular occlusion. However, its use must be carefully considered and administered by trained professionals to minimize potential risks, including allergic reactions or tissue damage [23].

Manufacturing parameters such as high temperatures and strong acidic and alkali pH are sensitive for the HA chains. Indeed, the usual manufacturing conditions (heat, alkali pH, and sterilization) are prone to degrade HA gels and release low-Mw soluble HA (sHA) [11]. Therefore, it is necessary to explain the manufacturing processes available. XpresHAn technology, which has varying degrees of crosslinking to provide different levels of flexibility and support while maintaining natural movement in areas of dynamic expression. The NASHA technology (Non Animal Stabilized Hyaluronic Acid) produces firmer gels based on molecular entanglements and small amounts of chemical crosslinking, with controlled particle sizes at

different levels. The OBT technology (Optimal Balance Technology) is based on four different levels of crosslinking, producing gels from very soft to intermediately firm, providing different levels of tissue support [24]. Vycross technology, which combines low-molecular weight and high-molecular weight HA to improve the crosslinking efficiency of the HA chains. Preserved Network technology, designed with reduced synthetic crosslinking due to preserved natural HA polymers [25]. Cohesive polydensified matrix (CPM) HA is also characterized by a higher mean molecular weight of non–cross-linked (soluble) HA than in other currently available products, the variable cross-linking is intended to confer resilience and retention of structural integrity [26].

Table 1: Classification of dermal fillers according to manufacturers, manufacturing technology, HA concentration, product type and indications [11,19].

Manufacturer	Manufacturing Technology	Concentration (mg/mL)	Type	Indication
Galderma	NASHA™	20	Restylane® Skinboosters™ Vital	Fine lines. Superficial dermis
Galderma	NASHA™	16	Restylane® Skinboosters™ Vital Light	
Allergan	Vycross™	12	Juvederm® Volite™	
Allergan	Vycross™	15	Juvederm® Volbella™	
Teoxane	Preserved Network	15	TEOSYAL® RHA 1	
Merz	CPM™	20	Belotero® Soft	
Galderma	NASHA™	20	Restylane® Lido	Fine and medium lines, lips; Superficial to mid dermis
Galderma	OBT™/ XpresHAn™ Technology	20	Restylane® Refyne™	
Galderma	OBT™/ XpresHAn™ Technology	20	Restylane® Defyne™	
Galderma	OBT™/ XpresHAn™ Technology	20	Restylane® Volyme™	
Allergan	Vycross™	17.5	Juvederm® Volift™	
Teoxane	Preserved Network	23	TEOSYAL® RHA 2	
Teoxane	Preserved Network	23	TEOSYAL® RHA 3	
Merz	CPM™	22.5	Belotero® Balance	
Galderma	NASHA™	20	Restylane® Lyft™ Lido	Volume (restoration, sculpting)- subcutaneous and supraperiosteal
Allergan	Vycross®	20	Juvederm® Voluma™	
Teoxane	Preserved Network	23	TEOSYAL® RHA 4	
Merz	CPM™	26	Belotero® Volume	
Merz	CPM™	25.5	Belotero® Intense	

III. Physical-chemical Properties

In the context of clinical orofacial harmonization procedures, understanding the composition and concentration of hyaluronic acid (HA) in dermal fillers is of paramount importance. Manufacturers often provide the total HA concentration in the gel, but they usually do not distinguish between the amount of insoluble crosslinked HA and soluble non-cross-linked HA within the biopolymer. The soluble portion of HA is intentionally included to optimize the filler's viscosity, making it easier to inject through a needle. It's worth noting that this soluble HA is readily metabolized by the body. As a result, the total concentration stated for commercially available fillers should be viewed as more of a reference value rather than an absolute measurement [1].

Soluble HA enhances the filler's viscosity, which makes it more fluid and easier to extrude through a needle during the injection process. This improved injectability allows for smoother and more precise placement of the filler in the target area. Also contributes to the initial volume of the filler, allowing it to provide immediate results in terms of volume enhancement and wrinkle reduction[1, 33, 34].

However, the presence of it also has implications for the longevity of the filler, because is easily metabolized by the body, which means that over time, may gradually break down and lose its volume-enhancing effects and this can vary from person to person but typically occurs over several months[14].

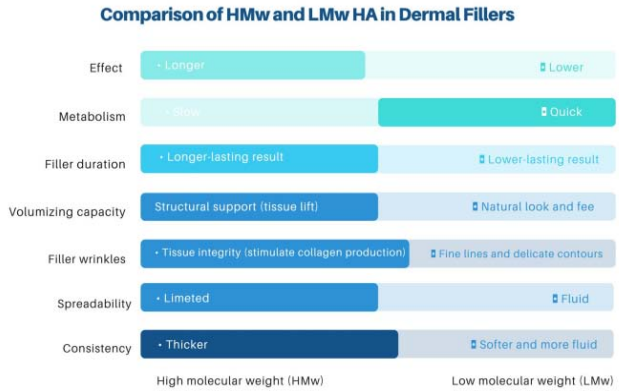
The ideal concentration of hyaluronic acid (HA) is 20mg/mL or higher. This concentration enables significant volume expansion when the filler is injected into the target tissue, resulting in a prolonged effect that enhances its structural integrity. Furthermore, it retards the rate at which the body metabolizes the filler. This concentration should demonstrate a viscosity that strikes a balance between ease injection for delivering

adequate support and structure to the treated area of the face [1, 7].

Therefore, this concentration it presents better cost-effectiveness, because can achieve the desired results with smaller volumes, patients may require less product, and clinicians can achieve their treatment goals with fewer syringes of filler. Then it offers a balance between ease of injection, longevity of results, and cost-effectiveness [1, 7].

In clinical practice, dermal fillers primarily consist of high molecular weight HA (HMw). These fillers exhibit unique viscoelastic and biophysical properties based on their chemical compositions, including HA concentration, Mw of HA, and the specific crosslinker used in their formulation. The molecular weight of HA plays a pivotal role in providing structural and physicochemical integrity to the filler, and it directly influences its viscosity, in addition can influence how it behaves in various facial areas during injection [33]. HMw and Low molecular weight HA represent two distinct options in dermal fillers. HMw HA offers several advantages, including its tendency to provide longer-lasting results when compared to LMw fillers. It is metabolized more slowly by the body, contributing to its durability. Also offers robust structural support, effectively addressing deeper wrinkles and areas with volume loss and diminished tissue integrity. Additionally, it can promote tissue integrity by stimulating collagen production. On the other hand, LMw HA provides a more natural appearance and offers a softer and more fluid texture, making it particularly suitable for areas with fine lines and delicate contours. Furthermore, it facilitates easier injection and yields quicker results [34, 34].

Both also have disadvantages, as HMw HA fillers look less natural in the treated area due to their thicker consistency and have limited spreadability. While LMw HA fillers are less durable, they provide limited structural support and are metabolized more quickly. Therefore, the choice between HMw and LMw AH fillers depends on the patient's specific aesthetic goals and treatment area (graphic 1) [33, 34].



Graph 1: This chart illustrates the advantages and disadvantages of using HMW-HA and LMW-HA in dermal fillers across various characteristics. The comparison covers factors such as effect, metabolism, filler duration, volumizing capacity, wrinkles filler, spreadability and consistency of the gel. HMW-HA offers extended longevity and robust structural support but may be less suitable for fine corrections. LMW-HA, on the other hand, excels in ease of spreading, making it ideal for fine lines and precise results. However, it tends to have a shorter duration and may require more frequent touch-up sessions.

This understanding of HA characteristics and concentration is crucial for clinicians aiming to achieve optimal results in facial harmonization and other aesthetic procedures.

IV. Rheological Features

Rheology, a subfield of physical chemistry, delves into the study of how different materials respond to deformation and flow, whether they are solid, semi-solid, or liquid. It examines the ability of matter to maintain its shape, which is a defining characteristic of solids, and this property is known as stiffness. Stiffness is evaluated using elasticity, which measures a material's resistance to deformation. Hooke's law establishes a mathematical relationship between the elastic strength, stress applied, and deformation induced in a material. This understanding of rheology is fundamental in exploring how substances deform and flow [1, 2].

To analyze a gel for injection into the skin layers the most main features are viscosity (η), complex modulus (G*), elastic modulus (G'), tan delta - δ (G''), cross-linking, concentration and the swelling factor (the absorption factor) [2,6,7,19].

Fluids are shapeless, thus they are unable to resist deformation. They have an intrinsic and specific feature: viscosity (η). It can be defined as the ability of a fluid to resist flow [1,3]. This tells the pressure required to determine the flow of a fluid (for example: water and honey) [1].

Viscosity is a measure of a fluid's resistance to flow. It determines how easily a substance flows or moves when subjected to an applied force. Liquids with high viscosity are thick and flow slowly, while those with low viscosity are thin and flow more easily. Viscosity is influenced by factors such as temperature and the internal friction of the fluid's molecules [12].

The viscosity of a dermal filler is related to the concentration of non-crosslinked and crosslinked HA, the degree of crosslinking, the molecular weight distribution, the average particle size of the gel, and the manufacturing process. It is crucial that hydrogels have low viscosity at high shear (100 s-1), so that they can be extruded through a small-caliber needle. High viscosity under low shear is in fact comparable to the condition of the hydrogel after injection or when resting in the package [12]. If the viscosity is too high, the injection of the fillers becomes difficult to apply. Adding free HA reduces the viscosity, because hydration effect increases the overall viscosity of the filler, making it thicker and more gel-like, it trap water within its structure, lead to the formation of gels, enhances its volumizing capacity can influence the texture and consistency of the filler. However, professionals lack information on the amount of free HA present in the product (i.e. soluble and insoluble fractions). The total concentration of commercially available HA is a reference value, so this parameter is not absolute for assessing the filler's performance[13].

From a clinical perspective, it is crucial for these fillers to demonstrate low viscosity when subjected to high shear forces. This characteristic enables smooth extrusion through a fine-gauge needle during the injection process, ensuring precise and controlled injection in target tisues. This, in turn, reduces discomfort for the patient during the injection and facilitates even distribution of the filler. Achieving even distribution is essential for achieving natural-looking results, particularly in delicate facial areas.

Conversely, high viscosity under low shear conditions is like the state of the hydrogel within the product vial or after injection into the target area. This condition, after injection ensures that the filler maintains its shape and position over time, it provides structural support and volume, helping to lift and restore sagging or deflated areas of the face and minimized migration. Lower viscosity is often preferred, especially in areas with fine lines or where precise distribution is necessary, such as the lips or tear troughs. It allows for smoother and more controlled injection[13].

Complex viscosity is a crucial parameter that assesses the gel's capacity to withstand shear forces within a tissue following injection. In addition, the elastic modulus, another significant factor, gauges the hydrogel's inherent stiffness and its interactions with the surrounding environment. These parameters collectively influence the hydrogel's ability to effectively withstand the tensile forces exerted on it following injection, primarily arising from the dynamic movements of facial muscles [2,6].

These last two parameters directly impact a gel's ability to endure the shear and tensile forces experienced within facial tissues post-injection.

The measure of the total energy needed to deform a material using shear stress is complex modulus, which indicates the overall resistance to deformation of a material, regardless of whether that deformation is recoverable (elastic) or non-recoverable (viscous). This measure is favorite to quantify the gel hardness, being it is a good indicator of projections in clinical applied, in which the stiffness or hardness of the HA filler has direct relation: the higher the magnitude of the complex modulus, the stiffer the material [30].

The complex modulus combines both elastic and viscous responses of a material to deformation. It is used to characterize a material's overall resistance to deformation, considering both its ability to return to its original shape (elastic behavior) and its tendency to flow or deform irreversibly (viscous behavior) when subjected to stress. It is particularly important in the study of materials' response to dynamic forces and shear stress. It is represented as a complex number, often in the form $G^* = G' + G''$, where G' represents the elastic modulus and G'' represents the viscous modulus[30].

The complex modulus, referred to as G*, is a comprehensive measure that takes into account both the elastic modulus (G') and viscosity modulus (G''). It's crucial to highlight that the filler material should strike a delicate equilibrium between its ability to be pliable, enabling it to flow smoothly through the needle, and its structural robustness, ensuring it retains its intended shape once it's injected into the soft tissues. The injection procedure itself comprises several distinct phases, starting with the material's passage through the needle and culminating in its seamless integration into the adjacent soft tissues. Therefore this filler needs to possess adequate malleability to navigate the needle without resistance while maintaining structural integrity to provide the desired cosmetic enhancement. This balance ensures a successful and aesthetically pleasing outcome. For precise sculpting in areas like the nose or jawline, higher G* values are beneficial, allowing for better control during injection [30].

Typically, the clinical choice of G' is guided by the extent of correction needed and the treatment plan in place. In cases where a deeper injection plan is warranted to provide robust support for achieving a higher degree of correction, it is advisable to opt for hydrogels with a higher (firmer) G*. These firmer hydrogels excel in their corrective capacity when it comes to deep deposition and the creation of elevations or projections, especially in areas like the malar cheek, chin, and jaw, where they can be strategically placed against the bone for enhanced projection. In such

scenarios, they exhibit superior compressive strength, effectively countering the intrinsic forces within the deeper tissue planes [19].

On the other hand, if the injection plan involves shallower planes with less pronounced corrections, hydrogels with a lower G* (softer) can be a suitable choice. However, it's worth noting that these softer products can also be employed in deeper planes to achieve clinical effects when necessary. Additionally, they can be layered atop higher G* products to attain the desired outcome [19].

Elasticity, in the context of materials and mechanics, refers to the property of a substance to return to its original shape and size after it has been deformed or stretched[1, 7].

Elastic modulus (E) is the ratio between Stress (σ) and Strain (ε), in other words, it is the stress applied to the material over the strain that induced it. To better understand the concept of stress, if an external compressive force is applied in a solid its molecules are pushed together, and they accumulate a repulsive force. The internal pressure, determined by the repulsive force, is the stress. Therefore, stress is the internal pressure that material is subject to when external forces are applied and this is a measure of how much the dimension of an object has changed [1]. In simpler terms, it quantifies how a material responds to an applied force and how much it deforms under that force. Practitioners need to consider how these materials respond to the forces applied during the injection process and how they behave within the target tissues (Figure 7 Material Properties: Elasticity, Viscosity, and Viscoelasticity)[1, 7].

Elastic modulus (G') is a measure of the stored energy in a material in which shear deformation has been employed. In other words, it can be thought of as the proportion of the total stiffness (the complex modulus - G*) of a material that is attributable to elastic deformation. It represents the fraction of energy G' stored during deformation which can be used to recover its original shape when the deformation is removed. Combined, G' and G" define the complex modulus, or G*, which represents gel is resistant to deformation [1,7,10]. With higher G*, the material is stronger and less deformable (Figure 3. Dynamic forces of the HA in different planes of the dermis and Figure 5. This schematic representation illustrates the relationship between cohesiveness and viscosity in an HA gel, emphasizing their effects on the gel's behavior and shape when injected into the dermis) [1].

Viscous modulus (G") represents the amount of energy that is absorbed by a substance when it experiences deformation [1,7]. A gel with a higher G" value is more viscous or thicker, which means it demands a greater amount of force to be extruded through a needle [7]. For example, if we have two gels, one with a low G" and another with a high G", and we attempt to push them through a needle, the gel with the higher G" will resist the flow more strongly and require more force to pass through the needle compared to the one with the lower G". This is because the higher G" indicates a greater ability of the gel to absorb and dissipate energy when subjected to strain, resulting in increased resistance to flow.

For professional, a higher G' value indicates that the material is stronger and less prone to deformation. A gel with a higher G" indicate heightened resistance is a result of the higher G", signifying the gel's greater ability to absorb and dissipate energy when subjected to strain. They must be aware of these G" values as they directly impact the ease and precision of material delivery during procedures (Figure5. This schematic representation illustrates the relationship between cohesiveness and viscosity in an HA gel, emphasizing their effects on the gel's behavior and shape when injected into the dermis.).

Tan delta (δ) is the measure of the elasticity versus viscosity balance in the gel, and it is defined by G" and G' ratio. Gels characterized by a high (d), with values close to one, are predominantly viscous (e.g. honey), while those characterized by a low (d), with values close to zero, are predominantly elastic (e.g. gelatine) [7].

Swelling Factor (hydration capability) occurs due to the insoluble HA and the cross-linking degree can impair the penetration and binding of the water molecule[1]. The expansion after injection adds the volumeizing effect [1, 7] and, if excessive, it may lead to unwanted effects such as becoming palpable and edema [1, 3]. In vivo swelling depends on the structure of the surrounding tissue, its fluid balance and pH value [5].

The closer to the equilibrium state of hydration (saturation) of a gel the smaller the swelling will be after injection. If below equilibrium (unsaturated), it will easily absorb water from the surrounding fluid until it reaches equilibrium. This feature varies from product to product and it depends on the hyaluronic acid concentration and the physical constraints imposed by the cross-linking. Usually, the higher the cross-linking and the G*, the lower the swelling factor [19].

This hydration capability is significant because it contributes to the volume-enhancing effect of the filler after injection. However, excessive swelling can result in unwanted side effects, including palpable lumps and edema. In vivo, the extent of swelling following injection is influenced by several factors. These include the structure of the surrounding tissue, the local fluid balance and the pH value of the environment. In cases where the gel is below equilibrium (unsaturated), it will readily absorb water from the surrounding fluid until it reaches the equilibrium state. This property is crucial in areas like the cheeks or nasolabial folds, in which can

quickly restore volume in the cheeks, offering an instant rejuvenating effect [19].

Typically, a higher degree of cross-linking and a higher value of G* (complex modulus) result in a lower Swelling Factor. This means that products with strong cross-linking and higher G* values tend to exhibit less swelling after injection, which can be advantageous in clinical applications where precise control over volume enhancement and reduced risk of side effects are desired[25].

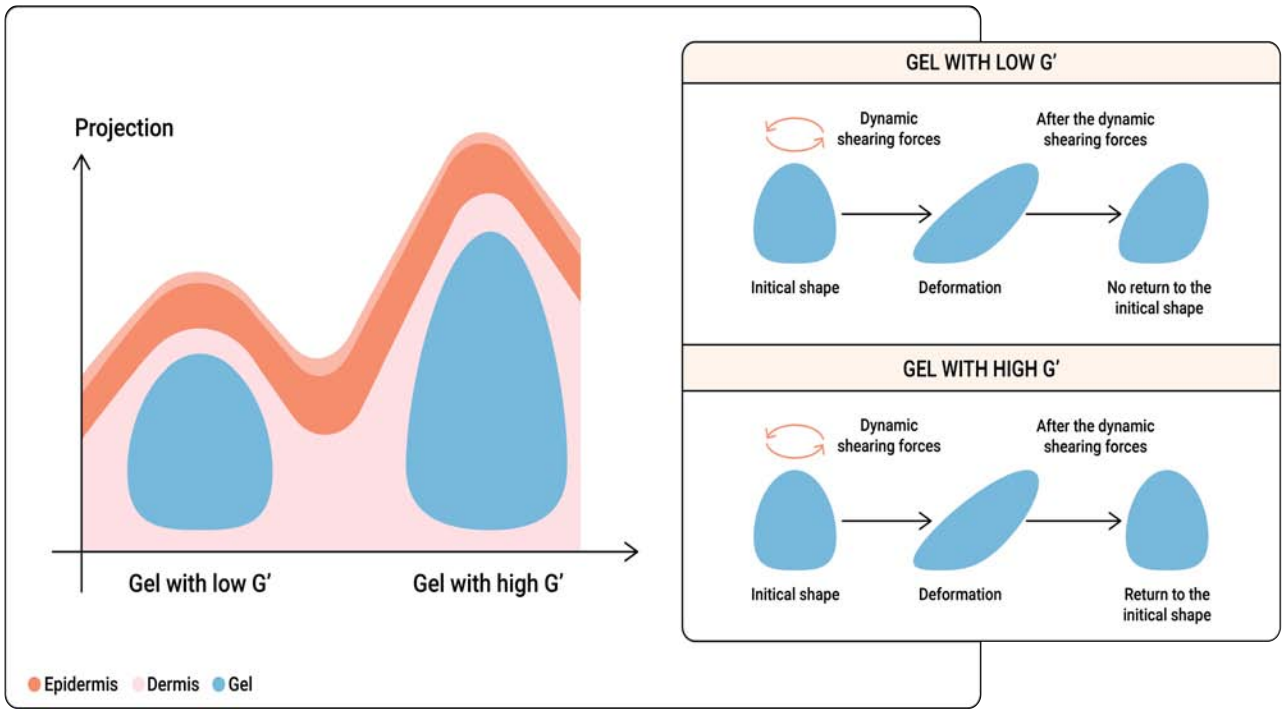


Figure 5: This schematic representation illustrates the relationship between cohesiveness and viscosity in an HA gel, emphasizing their effects on the gel's behavior and shape when injected into the dermis. A highly cohesive gel is represented with robust intermolecular connections, forming a structured network. In the dermis, cohesiveness ensures that the gel maintains its shape, doesn't excessively spread, and provides structural support, as the draw. The increased dermal projection can be observed in the graph. When viscosity is higher, the gel appears as thicker, while lower viscosity results in a more fluid consistency. Therefore plays a significant role in how the gel flows during injection and its ability to conform to dermal contours.

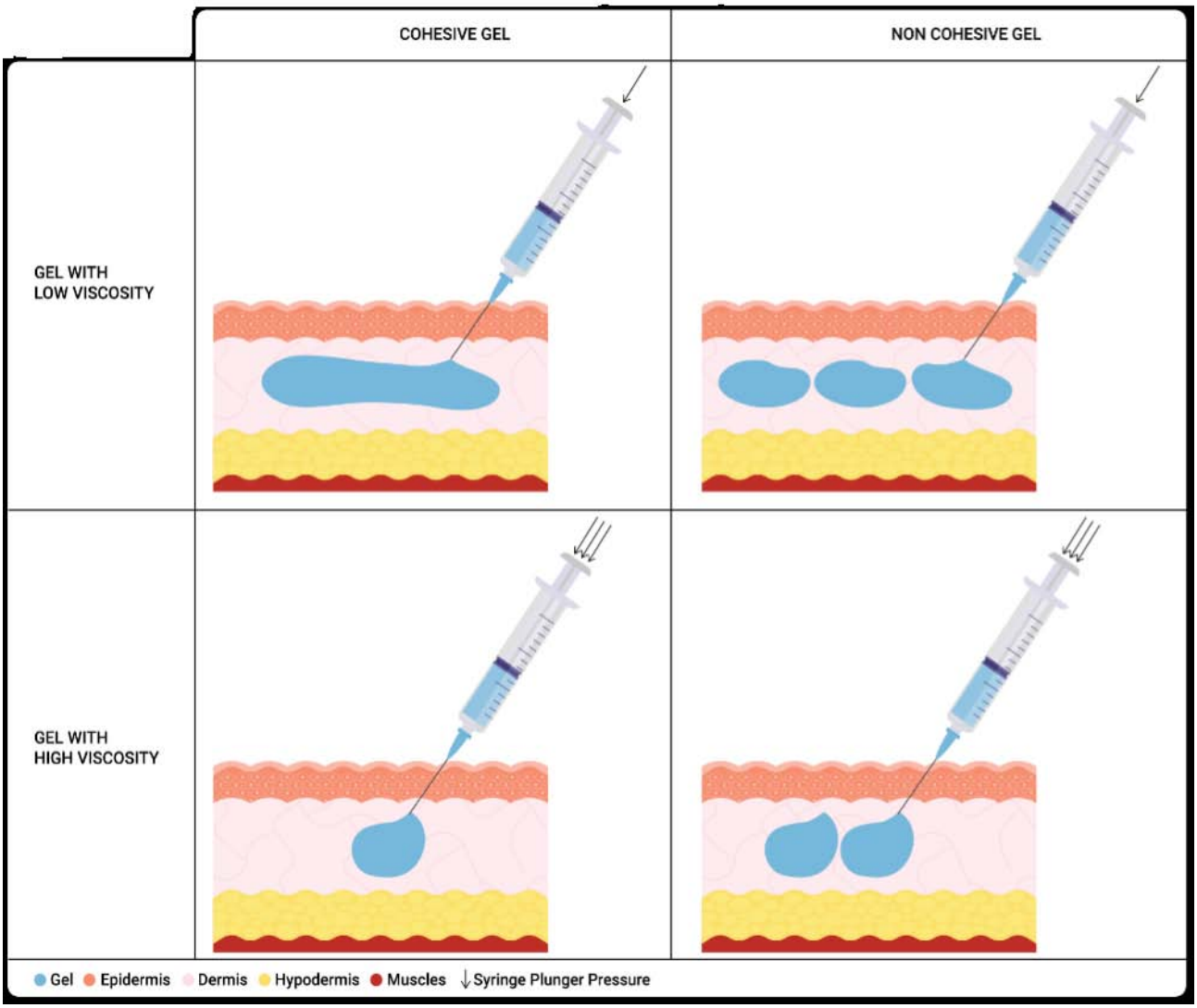


Figure 6: Schematic representation of the cohesion and viscosity of an HA gel reveals a pivotal correlation. The gel's fluidity is greatly enhanced by its low viscosity and low cohesiveness, which results in a lack of unity. On the other hand, a gel that has low viscosity but high cohesiveness maintains its structural integrity while still remaining fluid. This balance also influences the level of force necessary to extrude the gel through a syringe and needle. When examining a filler with high viscosity and strong cohesiveness, it manifests as a denser and more cohesive gel, demanding greater force for extrusion. Conversely, in the absence of cohesiveness, the gel fails to maintain its unity after being injected into the dermis. In summary, the delicate balance between viscosity and cohesiveness significantly influences both the physical properties of the gel and its performance during injection, shaping the final outcome in dermal applications.

Cohesiveness is described as the force between particles in the same substance that acts to bind them together [1,5]. In the case of fillers, cohesiveness is an expression of the internal adhesion forces that hold the individual crosslinked HA units together [25] (Figure 5. This schematic representation illustrates the relationship between cohesiveness and viscosity in an HA gel, emphasizing their effects on the gel's behavior and shape when injected into the dermis and Figure 6. Schematic representation of the cohesion and viscosity of an HA gel reveals a pivotal correlation). A high cohesiveness simultaneously with a low viscosity accompanies homogeneous tissue integration [5]. This property contributes to the natural and harmonious appearance of the treated area, such as lip enhancement, cheek contouring, and jawline definition. Less cohesive fillers may spread more easily, potentially causing uneven distribution or migration. In contrast, highly cohesive HA formulations are less prone to migration, reducing the likelihood of irregularities or asymmetry, which can be essential for achieving harmonious facial proportions.

Viscoelasticity is the capacity to undergo deformation up to a certain point when subjected to

shear stress and then return to its original shape once the force causing the deformation is removed (see Figure 7. Material Properties: Elasticity, Viscosity, and Viscoelasticity) [1,5]. Subsequently, the types of HA gels can be categorized based on their viscoelasticity and cohesiveness, factors that determine their resistance to mechanical stresses (their ability to flow slowly) and their capability to revert to their original form. Viscoelasticity primarily relates to resistance against deformation in the horizontal plane, such as lateral shear or torsion, whereas cohesiveness pertains to resistance in the vertical plane, encompassing compression and stretching [13, 14]. In essence, it is the amalgamation of these properties that enables AH to be molded during application and, simultaneously, to preserve its shape and volume over time. However, when considering the elastic modulus, it clinically signifies the gel's rigidity and its capacity to maintain its shape post-injection. High viscoelasticity fillers are suitable for cheek augmentation, providing long-lasting volume and contouring[14].

Enhancing the polymer's molecular weight and degree of crosslinking has been a well-established approach to improve mechanical strength and prolonging degradation rates. Depending on its concentration and the extent of crosslinking, the product's shelf life can range between 6 to 18 months. Estimating the post-injection product duration is challenging, given its dependency on numerous factors including skin type, age, patient's lifestyle, the treated area, injection technique, and even aspects of the manufacturing process such as crosslinking [13].

The high degree of crosslinking too reduces the HA's hydrophilicity while increasing its hardness [4]. The gel hardness relates to its resistance to be deformed. It varies with HA concentration, degree of crosslinking, and particle size. Usually, softer gels are suitable for filling surface layers and are generally not intended for lifting or greater volume, for which stiff gels are proposed [14].

Highly crosslinked HA gels with a high G' (elasticity) are recommended in situations where minimizing swelling is crucial. This is particularly important in regions where excessive water absorption might result in unfavorable outcomes or the formation of pockets, they are effective for volumizing the midface, as they provide sustained support and contouring. Than fillers should be used cautiously as they are stiff and not suitable for areas with significant motor skills[14].

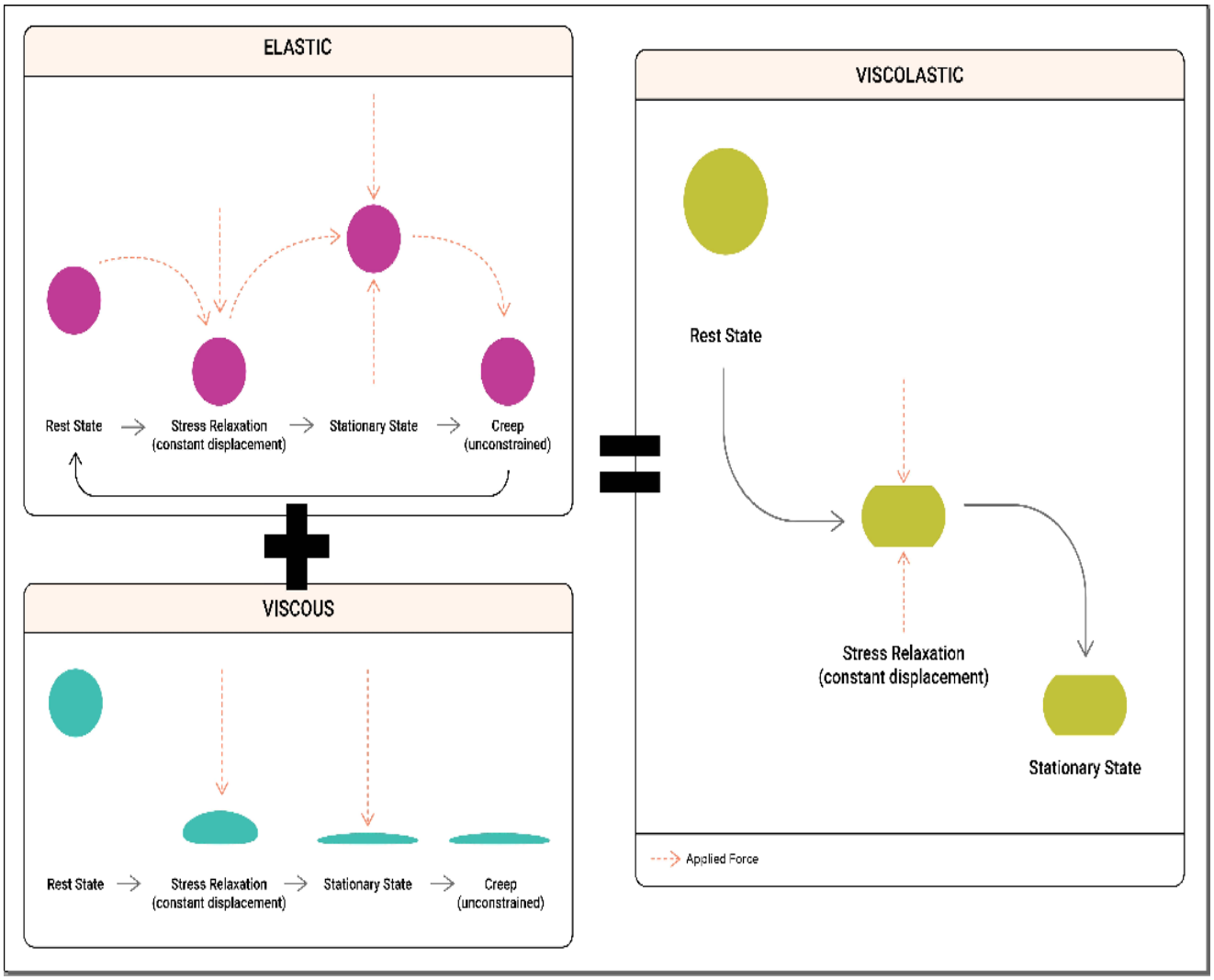


Figure 7: Material Properties: Elasticity, Viscosity, and Viscoelasticity: An elastic material, depicted in the diagram in purple color, exhibits a property known as elasticity. After deformation, when a force is removed, the material promptly returns to its original shape and size. A viscous material, shown in the schematic in cyan color, lacks the elastic property of immediate shape recovery. Instead, it undergoes deformation when a force is applied, and when the force is removed, the material does not return to its original shape. Viscous materials, such as honey, flow continuously under the influence of an applied force. A viscoelastic material, depicted in the diagram in green color, exhibits a combination of both elastic and viscous properties. After deformation, it partially returns to its original shape over time when the force is removed. Understanding the properties helps predict how filler respond to deformation and stress.

The study of a new formulation requires multiple steps to demonstrate safety, efficacy, and stability to ensure consumer protection and satisfaction. During formulation of fillers, use and storage time, exposure to possible external factors such as physical damage, microbiological and chemical influences can lead to instability to varying degrees [12]. For example, a thermal stress can change the product viscosity and the loss of storage modulus (Figure 3. Dynamic forces of the HA in different planes of the dermis). The rheological features influence the integration between the HA and the surrounding soft tissues and they determine the filler's ability to modify the anatomical layer volume, based on this statement, clinical planning can show different HA for different anatomical areas and even the same areas with different goals.

Dermal quality and the degree of correction necessary are references to choice what the product may be selected by G*, however, it is important to emphasize that G* is just one of the rheological characteristics of hyaluronic acid gel. These variables differ between patients, and their nature will determine what degrees of strength and firmness are appropriate for the filler. It is also important to consider how it will be injected for the best result, whether distributed or punctual. In consensus, products with lower G' is

usually more indicated, because they are softer and easier to distribute in the tissue, in thinner skin, where there is palpability/visibility [19].

Higher G' products are recommended for deeper injection plans, where they offer greater support and corrective capacity, especially in areas such as the malar cheek, chin, and jaw, where the product needs to be placed against bone for projection. On the other hand, lower G' products, which are softer, are typically used for shallower injection planes with less severe corrections. In areas where dynamic facial expressions play a significant role, such as around the mouth, lower G' products may be preferred. These softer fillers can accommodate the natural movement of the muscles without creating an overly rigid appearance. They provide a subtle enhancement while allowing for natural facial expressions. In some cases, a combination of lower G' and higher G' products may be used in layered injections to achieve a balanced and customized result. Ultimately, the choice of G' in dermal fillers, even in areas involving facial motricity, should be tailored to the specific needs and aesthetic goals of the patient, taking into consideration both the depth of injection and the dynamic nature of the facial muscles [19].

The delicate balance between flexibility and structural robustness in HA fillers is crucial for achieving natural-looking results and patient satisfaction. This balance plays a pivotal role, as it ensures that the filler integrates seamlessly into the dynamic facial tissues while providing the necessary support for the desired cosmetic enhancement [20].

Several advantages become apparent how natural-looking results, in which the flexibility allows the filler to adapt and move harmoniously with the facial expressions and muscle contractions; patient comfort, on that the flexibility reduce discomfort or sensations of tightness in the treated area; longevity and satisfaction are verify in robust HA, be can provide enduring support to the tissues, extending the duration of the results; the flexibility of HA fillers allows for versatility in addressing various aesthetic concerns, from fine lines to deep wrinkles and volume loss and reduction risk of overcorrection, are supported on right balance that ensures that the filler doesn't overcorrect or create unnatural contours [20].

HA fillers have varied considerably in terms of concentration, injection strength, particle size and rheological properties. These variations can result from the underlying technology used to create each filler, which in turn impacts its molecular structure and clinical performance [13]. Therefore, practitioners rely on manufacturer's recommended indications when choosing fillers. However, rheological properties are measured under different conditions by different manufacturers. Nevertheless, this information is useful for choosing the type of acid according to your clinical need to obtain satisfactory results with minimal amounts of material.

V. Conclusion

A key aspect of using HA in facial treatments is understanding its rheology, which influences product quantity and offers numerous benefits:

- *Treatment Precision:* Knowledge of HA rheology aids in precise filler placement, which is crucial for natural-looking results. For example, lip augmentation benefits from low-viscosity HA fillers to evenly distribute product and avoid overcorrection.
- *Volume Restoration:* High-molecular-weight HA with a hight elastic modulus, often denoted as G', is chosen for areas like the cheeks. This selection is made because it offers exceptional structural support, which helps in achieving long-lasting results. The high G' value indicates increased stiffness and resistance to deformation, ensuring that the filler maintains its shape over time and effectively supports of the facial contours.
- *Fine Line Correction:* Delicate areas, such as crow's feet, benefit from low-viscosity, low-molecular-weight HA fillers to prevent lumps or bumps.
- *Combination Therapies:* Understanding rheological compatibility is vital when combining treatments like botulinum toxin injections with HA fillers for comprehensive rejuvenation.
- *Preventing Vascular Complications:* Knowing the flow characteristics of HA fillers helps avoid vascular issues.
- *Reduced Product Usage:* Selecting the right HA filler minimizes product consumption, lowering treatment costs.
- *Lower Risk of Complications:* Precise filler selection based on rheology reduces complications, saving costs associated with their management.
- *Tailored Treatments:* Rheological knowledge enables customized treatments based on each patient's unique needs.
- *Patient Education:* Educating patients about rheology promotes trust and safety awareness.

In your journey in aesthetic area, remember that knowledge of HA filler rheology ensures safer, more cost-effective, and satisfying treatments for both practitioners and patients.

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Intestinal Neuroendocrine Tumor: A Diagnostic Approach, Clinical Evolution and Review

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Abstract- Introduction and objective: The intestinal neuroendocrine tumor is a rare cancer, with incidence of 1-2/100.000 inhabitants. Most cases are asymptomatic and late diagnosed. The aim of this work is to present a rare neuroendocrine intestinal tumor case (in the distal ileum), well-differentiated, with nonspecific and characteristic disease symptoms.

Case presentation: 56-year-old male smoker diagnosed with well-differentiated neuroendocrine neoplasia, histological grade 1 (G1), located in the terminal ileum, after exploratory laparotomy.

Discussion: It is a rare neoplasm that mainly affects the gastrointestinal tract. Practically always slow-growing. The clinic is nonspecific in most cases, and the principal indication is abdominal pain. There is great potential for metastasis, depending on the tumor size, location and histological grade. Imaging and laboratory tests can assist in diagnosis. The therapy selection depends on the stage, and can range from total tumor resection to antitumor chemotherapy.

Keywords: neuroendocrine carcinoma. neurosecretory systems. carcinoid tumor. neoplasms. intestinal neoplasms.

GJMR-F Classification: LCC: RC280.N4

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Intestinal Neuroendocrine Tumor: A Diagnostic Approach, Clinical Evolution and Review

Tumor Neuroendócrino Intestinal: Uma Abordagem Diagnóstica, Evolução Clínica E Revisão

Gabriela Inocente Kikuchi [α] & Jéssica Laís Caregnato de Meira [σ]

Resumo- Introdução e objetivo: o tumor neuroendócrino intestinal é um câncer raro, com incidência de 1-2/100.000 habitantes. A maioria dos casos é assintomático e de diagnóstico tardio. O objetivo deste trabalho é apresentar um caso raro de tumor neuroendócrino intestinal (no íleo distal), bem diferenciado, com sintomas inespecíficos e característicos da doença.

Apresentação do caso: Homem, 56 anos, tabagista, diagnosticado com neoplasia neuroendócrina bem diferenciada, grau 1 histológico (G1), localizado em íleo terminal, após laparotomia exploradora.

Discussão: É uma neoplasia rara que acometendo principalmente o trato gastrointestinal. Quase sempre de crescimento lento. A clínica é inespecífica na maioria dos casos, e o principal sintoma é a dor abdominal. Há grande potencial de metástase, dependendo do tamanho do tumor, localização e grau histológico. Exames de imagem e laboratoriais podem auxiliar no diagnóstico. A escolha da terapia depende do estadiamento, e pode ser desde a ressecção total do tumor à quimioterapia antitumoral.

Conclusão: Apesar de raros, a incidência dos TNEs intestinais vem aumentando com os anos, fazendo-se necessário seu conhecimento clínico e reconhecimento, possibilitando diagnóstico e tratamento precoces, melhorando o prognóstico destes pacientes.

Palavras-chave: carcinoma neuroendócrino. sistemas neurossecretores. tumor carcinóide. neoplasias. neoplasias intestinais.

Abstract- Introduction and objective: The intestinal neuroendocrine tumor is a rare cancer, with incidence of 1-2/100.000 inhabitants. Most cases are asymptomatic and late diagnosed. The aim of this work is to present a rare neuroendocrine intestinal tumor case (in the distal ileum), well-differentiated, with nonspecific and characteristic disease symptoms.

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Discussion: It is a rare neoplasm that mainly affects the gastrointestinal tract. Practically always slow-growing. The clinic is nonspecific in most cases, and the principal indication is abdominal pain. There is great potential for metastasis, depending on the tumor size, location and histological grade. Imaging and laboratory tests can assist in diagnosis. The therapy selection depends on the stage, and can range from total tumor resection to antitumor chemotherapy.

Conclusion: Although rare, intestinal TNEs incidence has been increasing over the years, requiring clinical knowledge and recognition, and enabling early diagnosis and treatment, to improve these patients' prognosis.

Keywords: neuroendocrine carcinoma. neurosecretory systems. carcinoid tumor. neoplasms. intestinal neoplasms.

I. Introdução

O tumor neuroendócrino é derivado das células enterocromafins-like nas criptas de Lieberkuhn. Considerado raro, com incidência de 1-2/100.000 habitantes, mas esta vem aumentando com o advento de melhores técnicas diagnósticas.[1] O local mais comumente acometido é o trato gastrointestinal (TGI), afetando principalmente intestino delgado, apêndice cecal e reto.[2]

A maioria dos casos é assintomático, sendo o diagnóstico ainda tardio. Esse, tem por base dosagem de aminas, comumente secretados pelos tumores, além da tomografia computadorizada, exame de escolha para determinar metástases. O tratamento curativo é a ressecção cirúrgica do tumor.[1, 3] O objetivo deste trabalho é relatar um caso[4] de tumor neuroendócrino localizado no íleo distal e ressaltar a importância do diagnóstico e ressecção precoce.

II. Relato de Caso

J. B. S., 56 anos, encaminhado ao Hospital Municipal de Maringá – PR queixando-se de dor abdominal difusa, tipo cólica, de forte intensidade há 20 horas, associada à vômitos. Sem história de perda de peso prévia, febre ou hiporexia e astenia. Portador de hipertensão arterial sistêmica (HAS), *Diabetes Mellitus* tipo 2 e hipercolesterolemia. Em uso de Metformina, Losartana, Sinvastatina, Gliclazida e Omeprazol. Tabagista (30 maços/ano) e etilista social. Sem história familiar para neoplasias. No exame físico, bom estado geral, descorado 1+/4+, hidratado, afebril, eupneico. Pressão arterial 140/80 mmHg, frequência cardíaca 80 bpm, frequência respiratória 18 rpm e temperatura

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36,8ºC. Abdome: globoso, flácido, pouco distendido e timpânico, doloroso à palpação difusamente, mais intenso em fossa ilíaca direita, ruídos hidroaéreos presentes. Sem dor a descompressão.

Apresentou: Hb 16,3 g/dl; VG de 49,3%; 12.650 leucócitos/mm^3; 4% de bastões e 256.000 plaquetas e Proteína C reativa (PCR) de 19,8 mg/l (Referência: até 5mg/l). Tomografia Computadorizada (TC): "*Discreto aumento do conteúdo liquido/gasoso no intestino delgado com alguns níveis hidroaéreos; pequena quantidade de líquido livre na cavidade pélvica; divertículos no sigmoide sem processo inflamatório*". Paciente foi submetido à laparotomia exploradora por abdome agudo obstrutivo. No intra-operatório, identificado pequena quantidade de líquido livre, grande distensão de todo o delgado, a partir do ângulo de Treitz até seu terço médio, com ponto abrupto de afilamento no qual a palpação identificou-se nódulo endurecido e aderida à luz intestinal, causando a obstrução. Realizada enterectomia segmentar com enteroenteroanastomose mecânica. Paciente iniciou dieta no segundo pós-operatório e recebeu alta no quinto pós-operatório, sem intercorrências. No anátomo-patológico da peça: "*Neoplasia neuroendócrina bem diferenciada, grau 1 histológico (G1), medindo 0,5 cm no maior eixo, localizado em intestino delgado. A profundidade da invasão foi até a subserosa, com índice mitótico de 1 mitose / 10 CGA e estadiamento patológico (TNM, 8a ed, 2017) pT3 pN0. Não foram detectados invasão angiolinfática, necrose tumoral, infiltração perineural, depósitos tumorais em mesentério. A margem cirúrgica proximal e distal estavam livres e a margem cirúrgica radial estava livre e distando 1,5 cm da lesão. O tecido adiposo mesentérico estava livre de neoplasia*".

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III. Discussão

Os tumores neuroendócrinos (TNE) são tumores bem diferenciados, derivados da hiperplasia e crescimento descontrolado do sistema celular neuroendócrino difuso, que são localizadas em vários órgãos, acometendo o TGI (55%), sistema respiratório (30%) ou locais mais raramente, rins e ovários. Originam-se nas células enterocromafins nas cristas de Lieberkuhn e surgem de células intra-epiteliais.[3, 5] O local mais comum de acometimento é o intestino delgado (29%), seguido pelo reto (14%), estômago e apêndice (5%).[6]

São neoplasias raras, com incidência de 1-2/100.000 habitantes[1], consideradas um mal silencioso, por ficarem tantos anos assintomáticos (5-7 anos). [7, 8] Geralmente o diagnóstico é tardio, embora a incidência dos TNEs vem aumentando devido ao advento de melhores técnicas endoscópicas e de imagem.[2] A incidência superou os adenocarcinomas.[2] Os fatores de risco mais descritos na literatura são os considerados não comportamentais, com predominância feminina em pacientes com até 60 anos, e maiores riscos em afro-americanos, hispânicos e asiáticos, além da forte associação entre história familiar positiva de câncer.[9] Outros estudos relatam maior prevalência em homens.[1, 10]

Aparentam ser esporádicos, mas também há um componente genético relacionado, a deleção no gene supressor tumoral PLC beta3 que leva ao crescimento celular descontrolado. E já foi descrito também em síndromes familiares, neoplasias neuroendócrinas múltiplas (NEM-1 e NEM-2) que acometem indivíduos mais jovens.[11]

De acordo com seu sítio de origem, apresentam diferentes perfis de produção hormonal: tumores com origem embrionária no intestino anterior (Foregut), acometem o trato respiratório e o timo, na fase adulta, e são responsáveis pela liberação, principalmente de 5-hidroxitriptofano e ACTH, causando rubor facial. Já no intestino médio (Midgut), se manifestam em jejuno, íleo e cólon direito, sendo os de maior frequência e com maior liberação de serotonina.[5, 12, 13, 14] Quando originários do intestino posterior (Hindgut), acometem o cólon esquerdo e o reto, possuindo baixa produção de serotonina, sendo assim, rara a apresentação como síndrome carcinóide.[12] Na maioria dos casos, possuem crescimento lento, o grau de diferenciação e a taxa de proliferação (taxa mitótica e KI-67) predizem o comportamento clínico.[3, 15, 16]

O sintoma mais comum (40%) é a dor abdominal, devido efeito mecânico compressor do tumor, isquemia mesentérica, resposta desmoplásica secundária ao tumor, por comprometimento vascular/metástases e enterorragia.[3, 13] Com o avançar da doença, pode surgir a síndrome carcinóide: Rubor facial, diarreia secretória, broncoespasmo, cianose e flutuação da pressão arterial. [11, 17] Essa síndrome acomete uma minoria dos pacientes e quando ocorre, indica fases mais avançadas da doença e prováveis metástases. [11]

TNEs possuem grande potencial de metástase sendo estas chances dependentes do tamanho do tumor, localização e grau histológico.[18, 19] No caso dos intestinais, quando menores de 1 cm as chances de metástases são cerca de 2% e quando maiores que 1-2cm tem chances de 50-90%. [13, 20]

Devido aos fatores citados acima, as classificações dos tumores neuroendócrinos são complexas e confusas. [6] A maioria das classificações, leva em conta principalmente a taxa de proliferação (índice de mitose e Ki-67) e a extensão da disseminação tumoral. Índice ki-67 <3% classifica o como de baixo grau, de 3-20% grau intermediário e

>20% de alto grau. Pela classificação da OMS, as neoplasias neuroendócrinas são separadas em dois grupos quanto ao grau de diferenciação: Tumores bem diferenciados (grau 1 e 2), sólidos ou glandulares, com núcleos uniformes, cromatina grosseira e pontilhada e prognóstico melhor. E carcinomas neuroendócrinos (CNEs), que seriam carcinomas de alto grau, parecidos com os de pequenas células, pouco diferenciados (grau 3) e rapidamente progressivos e agressivos.[21]

Quanto a secreção de hormônios, os tumores podem ser classificados em funcionais ou não funcionais. São considerados, ainda, como fatores de gravidade o grau de invasão angiolinfática, necrose tumoral, infiltração perineural e a invasão a tecidos vizinhos ou resíduos tumorais nas proximidades.[19, 21] A classificação TNM leva em conta a profundidade/invasão, acometimento de linfonodos e metástases.[22]

De acordo com o atual (oitava edição, 2017) sistema de estadiamento TNM do *American Joint Committee on Cancer* (AJCC)/*Union for International Cancer Control* (UICC), esses tumores são divididos em dois grupos: tumores jejunoileais (tabela 1) e duodenal/ampola (tabela 2).[23]

Quando há a suspeita do tumor, os exames indicados são: pesquisa na urinária do ácido 5-hidroxiindolacético (5-HIAA), útil em pacientes com TNEs do intestino médio, pela alta produção de serotonina; dosagem da cromogranina pois aumentam proporcionalmente com o aumento da carga tumoral.[15, 24, 25] Quanto aos exames de imagem, podem auxiliar a tomografia computadorizada (TC), ultrassonografia endoscópica e endorretal (USER), ressonância nuclear magnética (RNM) e videocápsula endoscópica podem ser úteis para diagnóstico, localização e estadiamento da doença.[24]

O tratamento depende do grau do tumor; pacientes com tumores grau 1 e sem metástase, se beneficiam com ressecção local do tumor e tratamento clínico para os sintomas (antagonistas de serotonina); já em casos de metástases irressecáveis ou tumores de graus elevados, o tratamento é a quimioterapia, podendo ser beneficiados com terapia antitumoral.[2, 3, 23, 26]

Com relação ao caso descrito, um TNE bem diferenciado (grau 1), localizado e sem metástases, o tratamento definitivo foi a excisão cirúrgica além da investigação de outros TNEs no intestino durante a cirurgia, já que em 25% dos casos é encontrado TNEs múltiplos no local.[27, 28]

De acordo com um estudo epidemiológico de 2017, foram confirmados como fatores prognósticos, a idade, sexo, local de acometimento, índice de proliferação, grau de diferenciação e estágio do tumor, sendo que as taxas de sobrevida melhoraram muito com as melhorias na terapia e no reconhecimento mais precoce.[21] A sobrevida nos próximos 10 anos em casos de TNE intestinal depende principalmente do estágio do tumor, sendo que no estágio 1 há 95% de chance; no estágio 2A ha 95%, no estágio 2B há 77%, no estágio 3A ha 68% , no estágio 3B há 77% e no estágio 4 há 42%.[23, 29, 30]

a) Elementos De Apoio Para Análise Dos Resultados E Discussão

i. *Tabelas, quadros, figuras e quadros:*

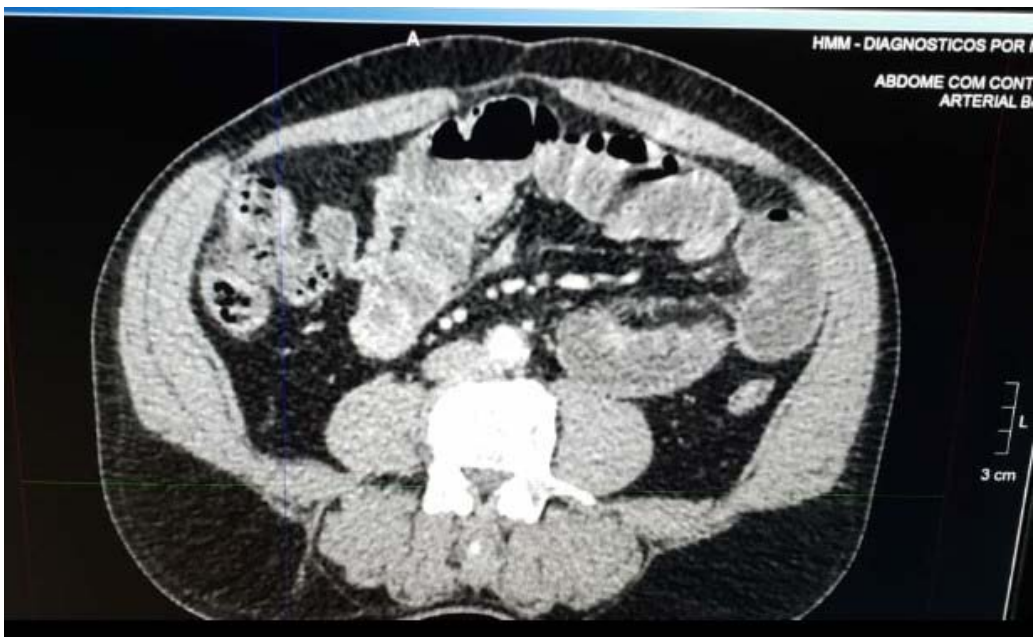

Imagem 1: Tomografia Computadorizada (TC) do caso relatado

Tabela 1: Estadiamento TNM dos tumores neuroendócrinos do jejuno e íleo – AJCC/UICC 8ª edição.

Neuroendocrine tumors of the jejunum and ileum TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Invades lamina propria or submucosa and less than or equal to 1cm in size
T2	Invades muscularis propria or greater than 1cm in size
T3	Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
T4	Invades visceral peritoneum (serosal) or other organs or adjacent structures

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis has ocurred
N1	Regional lymph node metastasis less than 12 nodes
N2	Large mesenteric masses (>2 cm) and/or extensive nodal deposits (12 or greater), especially those that encase the superior mesenteric vessels

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Fonte: STROSBERG, Jonathan. Staging, treatment, and post treatment surveillance of nonmetastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors. UpToDate, 2020.

Tabela 2: Estadiamento TNM dos tumores neuroendócrinos do duodeno e ampola de Vater – AJCC/UICC 8ª edição.

Neuroendocrine tumors of the duodenum and ampulla of Vater TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T1	Tumor invades the mucosa or submucosa only and is ≤1 cm (duodenal tumors). Tumor ≤1 cm and confined within the sphincter of Oddi (ampullary tumors).
T2	Tumor invades the muscularis propria or is >1 cm (duodenal). Tumor invades through sphincter into duodenal submucosa or muscularis propria, or is >1 cm (ampullary).
T3	Tumor invades the pancreas or peripancreatic adipose tissue
T4	Tumor invades the visceral peritoneum (serosa) or other organs

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastases
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Fonte: STROSBERG, Jonathan. Staging, treatment, and post treatment surveillance of nonmetastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors. UpToDate, 2020.

IV. Conclusão

TNE intestinal é uma neoplasia rara, com quadro clínico inespecífico ou assintomático, sendo por muitas vezes diagnosticado acidentalmente em cirurgias de emergência. Sua incidência vem aumentando devido a melhores técnicas diagnósticas disponíveis. O diagnóstico precoce tem grande valia pois reflete em um melhor prognóstico do paciente. O tratamento curativo é a excisão cirúrgica total. E, portanto, o diagnóstico e ressecção tem grande impacto na sobrevida dos pacientes.

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Glaucoma as a Neurodegenerative Disease

By V.E. Korelina & I.R. Gazizova

Abstract- Primary open-angle glaucoma (POAG) remains one of the most controversial eye diseases. Ophthalmologists do not have a consensus on the etiology and pathogenesis of POAG. It is obvious that glaucoma is no longer considered as an exclusively ocular disease associated with impaired hydrodynamics. The search for the causes of the inexorable progression of optic neuropathy has taken researchers far from the eyeball. According to modern concepts, glaucoma is considered as a neurodegenerative disease, located on the border of the professional interests of neurologists and ophthalmologists. Experimental and clinical studies reveal degenerative processes in glaucoma not only in the retina and optic nerve, but throughout the entire visual pathway. Structural changes in the brain in POAG are similar to those in a number of neurodegenerative diseases, for example, Alzheimer's and Parkinson's diseases. These changes correlate with clinical characteristics and severity of glaucoma. More recent studies have shown that neurodegeneration in glaucoma is also associated with neuroinflammatory processes affecting both the retina and brain. Characteristic signs of central nervous system (CNS) degeneration may precede the death of optic nerve fibers. Can neurodegeneration in glaucoma be considered a top-down process, or do events begin to unfold in the retina and gradually move into the brain?

Keywords: *glaucoma, retinal ganglion cells, neurodegenerative disease, neuroinflammation, neuroimaging.*

GJMR-F Classification: *LCC: RE871, RE661*

Glaucoma as a Neurodegenerative Disease

V.E. Korelina [α] & I.R. Gazizova [σ]

Abstract- Primary open-angle glaucoma (POAG) remains one of the most controversial eye diseases. Ophthalmologists do not have a consensus on the etiology and pathogenesis of POAG. It is obvious that glaucoma is no longer considered as an exclusively ocular disease associated with impaired hydrodynamics. The search for the causes of the inexorable progression of optic neuropathy has taken researchers far from the eyeball. According to modern concepts, glaucoma is considered as a neurodegenerative disease, located on the border of the professional interests of neurologists and ophthalmologists. Experimental and clinical studies reveal degenerative processes in glaucoma not only in the retina and optic nerve, but throughout the entire visual pathway. Structural changes in the brain in POAG are similar to those in a number of neurodegenerative diseases, for example, Alzheimer's and Parkinson's diseases. These changes correlate with clinical characteristics and severity of glaucoma. More recent studies have shown that neurodegeneration in glaucoma is also associated with neuroinflammatory processes affecting both the retina and brain. Characteristic signs of central nervous system (CNS) degeneration may precede the death of optic nerve fibers. Can neurodegeneration in glaucoma be considered a top-down process, or do events begin to unfold in the retina and gradually move into the brain?

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I. Введение

Первичная открытоугольная глаукома (ПОУГ) остается одним из самых противоречивых заболеваний глаз. У офтальмологов нет единого мнения об этиологии и патогенезе ПОУГ. Очевидно, что глаукома перестала рассматриваться, как исключительно глазное заболевание, связанное с нарушением гидродинамики. Поиск причин неумолимого прогрессирования оптической нейропатии увел исследователей далеко от глазного яблока. По современным представлениям глаукома рассматривается, как нейродегенеративное заболевание, находящееся на границе профессиональных интересов неврологов и офтальмологов [31, 41, 54].

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Экспериментальные и клинические исследования обнаруживают дегенеративные процессы при глаукоме не только в сетчатке и зрительном нерве, но и на всем протяжении зрительного пути. [65, 88, 91, 93].

Структурные изменения головного мозга при ПОУГ аналогичны таковым при ряде нейродегенеративных заболеваний, например, болезни Альцгеймера и Паркинсона [81, 92]. Эти изменения коррелируют с клиническими характеристиками и тяжестью глаукомы. Более поздние исследования показали, что нейродегенерация при глаукоме также связана с нейровоспалительными процессами, затрагивающими как сетчатку, так и головной мозг[78]. Характерные признаки дегенерации центральной нервной системы (ЦНС) могут предшествовать гибели волокон зрительного нерва[55]. Можно ли считать нейродегенерацию при глаукоме процессом нисходящим или события начинают разворачиваться в сетчатке и постепенно продвигаются в головной мозг?Вопрос остается открытым.

II. Нейродегенерация При Поуг

Болезнь Альцгеймера (БА) и болезнь Паркинсона (БП) являются наиболее распространенными нейродегенеративными заболеваниями. Ключевым патогенетическим событием при БП и БА считается накопление нейротоксичных белковых отложений в различных структурах мозга: α-синуклеина (α-син) при БП, тау-белка (p-tau) и β-амилоида (Aβ) при БА[62].

БА характеризуется потерей нейронов и синапсов в коре головного мозга, что приводит к когнитивному дефициту, прогрессирующей потере памяти и деменции. Отличительными признаками этого заболевания являются внеклеточные отложения бета-амилоида (Aβ) и внутринейрональные скопления гиперфосфорилированного тау-белка (pTau). Эти отложения также обнаруживаются в сетчатке и зрительном нерве [67].

БП представляет собой нейродегенеративное двигательное расстройство с прогрессирующей потерей дофаминергических нейронов. Это сопровождается включением телец Леви, состоящим из агрегатов α-синуклеина. При БП также обнаруживают дегенерацию дофаминергических клеток сетчатки [58].

Глаукома, нейродегенеративное заболевание зрительного нерва, характеризуется гибелью ганглиозных клеток сетчатки (ГКС) с потерей зрительных функций [85, 95].

Что объединяет эти, столь разные на первый взгляд, заболевания? Во-первых, транссинаптический тип нейродегенерации, когда происходит непосредственный переход дегенеративного процесса с больных, измененных клеток на интактные. Во-вторых, гибель определенного типа нейронов с общим механизмом клеточной смерти в результате апоптоза. Все эти заболевания имеют хроническое течение с медленным прогрессированием, приводящим к потере функций. Характерно также увеличение заболеваемости с возрастом [16, 74, 81, 92].

У пациентов с болезнью Альцгеймера глаукома встречается в 5 раз чаще, чем у их сверстников из контрольной группы. Обнаруженные при этом дефекты полей зрения были идентичны глаукомным изменениям [14, 39].

Метаанализ 25 исследований, изучавших состояние сетчатки пациентов с болезнью Альцгеймера (887 больных БА, 216 с легкими когнитивными нарушениями и 864 здоровых человека из контрольной группы) показал положительную корреляцию между толщиной слоя нервных волокон сетчатки (СНВС) и выраженностью когнитивных нарушений. Исследователи связывают смерть ГКС с патологией головного мозга при БА [19, 36, 81].

Выраженную диссоциацию структурных и функциональных параметров сетчатки и зрительного нерва у пациентов с болезнью Альцгеймера обнаружила в своем исследовании Панюшкина Л.А. (2015). По мнению автора увеличение индекса глобальных потерь ГКС является наиболее чувствительным маркером нейродегенеративных изменений на уровне сетчатки у пациентов с болезнью Альцгеймера. При болезни Альцгеймера и глаукоме в нейродегенеративный процессвовлечены как периферические, так и центральные отделы зрительногоанализатора, причем при глаукоме он протекает более агрессивно.

По данным Angela C. Gauthier and Ji Liu (2016) прослеживается положительная связь между глаукомными изменениями и смешанной деменцией. Из 1168 пожилых пациентов, находившихся в исследовании, больные ПОУГ были склонны к развитию БА в 3 раза чаще. Пациенты с БП чаще страдали глаукомой, чем обследуемые из контрольной группы.

Уровень доказательств диагностической роли сетчатки для раннего выявления БА растет, тем самым продвигая глаз как биомаркер нейродегенеративных заболеваний БА [15, 77, 81]. Аналогичные рассуждения можно сделать и в отношении других нейродегенеративных заболеваний, в первую очередь БП, хотя ранее это заболевание рассматривалось как двигательное расстройство[6]. Интересно, что морфофункциональные изменения глаз и головного мозга могут возникать за много лет до начала двигательных нарушений. По мнению многих исследователей это убедительно свидетельствует о том, что глаз, можно рассматривать, также, как биомаркер начала болезни Паркинсона [34, 56].

В тоже время визуализация подкорковых зрительных путей может быть новым способом ранней диагностики глаукомы[72].

Хотя общие изменения ЦНС в значительной степени коррелируют со стадией глаукомы и тяжестью заболевания [18], во многих исследованиях показано, как обширные изменения серого и белого вещества могут быть обнаружены уже на ранних стадиях глаукомной болезни [38]. Это подтверждает гипотезу о том, что поражение ЦНС является не только вторичным явлением, связанным с поражением зрительного нерва, но может представлять собой результат активного каскада патологических механизмов, развивающихся независимо от дегенерации зрительного нерва. Принимая во внимание все вышеописанные изменения зрительных и незрительных связей мозга, можно предположить, что пациенты с глаукомой могут страдать дисфункциями мозговой обработки, локализованными на разных уровнях, включая зрительные и зрительно-моторные задачи, память и эмоции, внимание и другие мультимодальные функции мозга [5].

Методы оценки и мониторинга поражений ЦНС при глаукоме приобретают все большее значение. Магнитно-резонансная томография (МРТ) широко используется в качестве неинвазивного инструмента визуализации для оценки внутричерепных структур. Традиционная МРТ — это высокочувствительный метод диагностической визуализации, однако, глаукомные изменения он не фиксирует [3]. Для выявления глаукомы используют новые методы нейровизуализации, основанные на традиционной МРТ: количественная МРТ-морфометрия; функциональная МРТ, зависящая от уровня оксигенации крови; диффузионно-взвешенная визуализация; магнитно-резонансная спектроскопия (МРС); диффузионно-тензорная визуализация; визуализация диффузного эксцесса; и визуализация с переносом намагниченности [10, 32, 86].

Количественные морфологические исследования позволяют оценить изменения объема и толщины различных специфических структур головного мозга больных глаукомой. Объем всех структур зрительного пути у пациентов с глаукомой был значительно уменьшен. Особое внимание уделяют затылочной доле и расположенным там зрительным центрам. В недавних отчетах с использованием метода объемной МРТ наблюдалось уменьшение площади и/или объема зрительной коры в обоих полушариях пациентов с глаукомой [64, 70].

У глаукомных пациентов с высоким уровнем ВГДбыло обнаружено уменьшение толщины коры в билатеральной верхней височной извилине, билатеральной верхней теменной извилине, билатеральной латеральной затылочной извилине,

левой веретенообразной извилине, левой медиальной орбитофронтальной извилине, правой предцентральной извилине и правой верхней лобной извилине, а также уменьшение объема серого вещества правого гиппокампа, двусторонняя скорлупа и двусторонний таламус [8].

Функциональная МРТ (фМРТ) позволяет оценить функцию корыin vivoна основе церебральных метаболических изменений, вызванных ее активностью.Это наиболее часто используемый метод получения информации о работе мозга. Неинвазивный метод визуализации, в котором дезоксигемоглобин используется в качестве естественного контрастного вещества для мониторинга уровня кислорода в крови мозга в режиме реального времени. Изменения содержания кислорода в крови косвенно отражают активность локальных нейронов. При глаукоме фМРТ показывает выраженное снижение активности во всех областях, связанных со зрением. Эти изменения коррелировали с данными ОКТ о толщине слоя нервных волокон и ГКС [21]. У больных ПОУГ также были обнаружены нарушения связи между зрительной корой и другими зрительными областями; изменение амплитуды низкочастотных колебаний; аномальная спонтанная активность в нескольких областях мозга; снижение корковой активности в зрительной коре, включая центральную область. Все эти изменения могут быть использованы как эффективные клинические индикаторы глаукомы.

Диффузионно-взвешенная визуализация (ДВВ) используется для расчета соотношения кровотока между внутричерепной полостью и субарахноидальным пространством зрительного нерва. Было обнаружено, что этот показатель у пациентов с нормотензивной глаукомой значительно ниже, чем у здоровых участников контрольной группы. Это открытие предполагает, что нарушение динамики спинномозговой жидкости может играть роль в патофизиологии глаукомы низкого давления [22].

Диффузионно-тензорная визуализация (ДТИ) представляет собой метод МРТ, основанный на обнаружении диффузии молекул воды в нервных волокнах и аксонах. Позволяет количественно измерять целостность микроструктур и тканейin vivo.Широко используется для изучения различий пучков белого вещества зрительного пути у пациентов с глаукомой. Микроструктурные различия обнаружены в зрительном нерве, зрительном тракте, перекресте зрительных нервов, зрительной лучистости и затылочной доле у больных глаукомой [21].

Использование новых методов визуализации позволяет выполнять более раннюю, по сравнению с общепринятыми офтальмологическими исследованиями, диагностику ПОУГ.

III. Митохондриальная Дисфункция при ПОУГ

Роль митохондриальной дисфункции в развитии и прогрессировании глаукомной оптической нейропатии активно обсуждается последнее десятилетие [26, 27]. Именно митохондриальный путь апоптоза клеток ганглиозного слоя сетчатки и зрительного нерва при глаукоме считают основным [37, 84]. Изменения митохондрий при ПОУГ были показаны в экспериментальных и клинических исследованиях [23, 52]. Количество митохондрий очень велико в диске зрительного нерва, что обусловлено повышенной потребностью в АТФ клеток с высокой метаболической активностью [76]. Именно эта часть зрительного нерва наиболее уязвима к воздействию повышенного уровня ВГД. Высказываются предположения, что митохондриальная дисфункция у некоторых людей является предрасполагающим фактором в развитии ПОУГ [12, 20, 35, 60, 71]. Вероятно, мутации митохондриальной ДНК (мтДНК) и ядерной ДНК, которые кодируют белки биогенеза митохондрий, могут приводить к аберрации структуры и функции митохондрий, тем самым способствуя развитию и прогрессированию ПОУГ [48].

Митохондриям принадлежит ключевая роль в развитии нейродегенерации и апоптоза клеток сетчатки и зрительного нерва при глаукоме.

Митохондриальная дисфункция возникает в результате совокупности многих факторов. С возрастом происходит накопление мутантной мтДНК. При биологическом старений происходит накопление свободно-радикальных супероксид-анионов, возникает «окислительный стресс». Так же возможно генетически детерминированное нарушение клеточного энергообмена и снижение функции митохондрий. Открываются митохондриальные поры, кальций устремляется в матрикс. Нарушение гомеостаза кальция является пусковым механизмом в развитии нейродегенерации, происходящей по механизму «метаболической» эксайтотоксичности. При набухании митохондрий происходит высвобождение активаторов каспазы (таких, как цитохром С) и необратимая гибель нервной клетки в результате апоптоза. Клетка с поврежденными митохондриями неспособна производить достаточное количество энергии для поддержания своей жизнедеятельности, не может сохранять необходимый уровень кальция и вырабатывает повышенное количество повреждающих ее молекул-окислителей.

К другим факторам относят развитие окислительного стресса из-за повышенного уровня таких свободных радикалов и цитотоксических агентов, как синглентный кислород, гидроперекись, продукты перекисного окисления липидов, супероксид-анион радикал. На этом фоне значительно возрастает концентрация межклеточного нейротрансмиттера глутамата. Увеличение его концентрации приводит к

глутаматной эксайтотоксичности и апоптозу ганглиозных клеток сетчатки.

Митохондрии потребляют более 90 % доступных молекул свободного кислорода, 15 % из которых превращаются в активные формы кислорода (АФК) даже в нормальных физиологических условиях. Средняя респираторная активность митохондрий снижается с возрастом, что приводит к более высокой продукции АФК и образованию свободных радикалов [17]. Производство митохондриальной АТФ снижается, а количество АФК увеличивается с возрастом [50, 66]. Механизм гибели ганглиозных клеток сетчатки (ГКС) при глаукомной оптической нейропатии вследствие апоптоза аналогичен другим оптическим невропатиям, связанным с дисфункциями митохондрий [9, 97]. Как известно, ключевую роль в процессе необратимой запрограммированной гибели клетки играют митохондрии с измененными функциями [59]. Исследования при индуцированном повышении уровня ВГД на экспериментальной модели глаукомы крыс показали, что митохондриальная дисфункция и AIF (апоптозиндуцирующий фактор) играют решающую роль как при гибели ГКС, так и в дегенерации аксонов зрительного нерва [52]. Как известно, митохондрии — внутриклеточные органеллы, вырабатывающие энергию в виде аденозинтрифосфата (АТФ) в результате окислительного фосфорилирования различных субстратов. Нарушение функции митохондрий по высвобождению энергии органических веществ и аккумуляции ее в виде макроэргических фосфатных соединений играет важную роль в патогенезе ПОУГ. Снижение дыхательной функции митохондрий, избыточная продукция активных форм кислорода (АФК), увеличение окислительного повреждения мтДНК приводят к нарушению тканевого дыхания и внутриклеточной сигнализации, развитию митохондриального оксидативного стресса и апоптоза. Повышение концентрации активных форм кислорода внутри митохондрий мтДНК приводит к ее мутации значительно быстрее (до 20 раз), нежели в ядерной ДНК.

Очевидно, что мутации, возникающие в структуре мтДНК, могут негативно влиять на функционирование комплексов окислительного фосфорилирования. Однако работ, связывающих мутантные варианты мтДНК и клинические проявления заболевания, не так много. Так, секвенирование мтДНК пациентов с ПОУГ позволило выявить 27 новых несинонимичных (приводящих к замене аминокислоты в структуре белка) мутаций, 22из которых были отнесены к потенциально патогенным. Интересно также, что количество копий мтДНК в группе пациентов варьировало в более широком диапазоне, нежели в контрольной группе [1]. В другом исследовании были проанализированы 101 мтДНК пациентов и 71мтДНК контрольной группы после того, как не удалось обнаружить мутации в ядерной ДНК, ассоциированные с ПОУГ. Сравнение нуклеотидных последовательностей мтДНК показало, что в гене ND5 пациентов с ПОУГ несинонимичные замены располагаются достоверно чаще, чем в контрольной группе. Обратная тенденция наблюдается для генома ND1 и ND2. Также авторы исследования наблюдали увеличение нуклеотидного разнообразия в гене 12SrRNA пациентов по сравнению с контрольной группой. Сравнение пациентов и контрольной группы по принадлежностям их мтДНК к определенным гаплогруппам не позволило выявить каких-либо зависимостей [49]. Еще одно исследование касалось изучения последовательности мтДНК афроамериканцев, страдающих ПОУГ. Авторы обнаружили несколько полиморфизмов, ранее не представленных в базе данных MITOMAP (https://www.mitomap.org/MITOMAP) в ассоциации с ПОУГ. Однако найденные мутации не выдержали критериев отнесения к патогенным [46]. Анализ мтДНК у 20 пациентов с глаукомой нормального давления позволил обнаружить 148 различных новых полиморфных сайтов, из которых три (m.4883C>T, m.9540T>C, m.14766C>T) статистически чаще встречались в группе пациентов с ПОУГ. Применив поправку Бонферрони, авторы выделили лишь синонимичную мутацию m.4883C>T [83]. В другом исследовании была проанализирована мтДНК 16 пациентов с ПОУГ из Индии и 16 пациентов из Ирландии. Авторы обнаружили 7 новых и 8 ранее известных полиморфных вариантов мтДНК [51]. В японском исследовании приняли участие 123 пациента, из которых 89 с глаукомой нормального давления и 34 с первичной открытоугольной глаукомой. Используя количественную ПЦР, авторы исследования сравнили количество копий мтДНК в образцах крови пациентов с ПОУГ и контрольной группы. Была показана связь между количеством копий мтДНК и измеренной с помощью лазерной спеклфлуографии средней скоростью «размывания ткани» (снижение кровотока) в головке зрительного нерва [7]. Ассоциация принадлежности мтДНК к определенной гаплогруппе с развитием ПОУГ была изучена на 90 пациентах и 95 представителях контрольной группы. Показано, что принадлежность мтДНК к гаплогруппе U, а также некоторые редкие полиморфизмы в гене ND2 могут оказывать протективный эффект на развитие заболевания [47]. Другое большое когортное исследование было выполнено на 4081 афроамериканцев, из которых 1919 являются пациентами с ПОУГ. Было обнаружено, что мужчины, не принадлежащие гаплогруппе L, имеют повышенный риск развития ПОУГ. Данная работа еще раз подтверждает необходимость персонализированного подхода, как к диагностическому скринингу, так и к лечению ПОУГ [75]. В целом представленные к настоящему времени данные не позволяют делать однозначные выводы об ассоциации конкретных мутаций и количестве копий мтДНК с патогенезом

глаукомы. Кроме того, ни для одной из представленных мутаций не была создана клеточная линия для оценки ее функциональных последствий. Таким образом, можно заключить, что роль мтДНК в патогенезе глаукомы все еще не доказана. Однако, исследования мутаций мтДНК значительно улучшат наше понимание генетической основы глаукомы[98].

IV. Нейровоспаление При ПОУГ

Развитие нейродегенеративных процессов в настоящее время связывают с нейровоспалением. Многочисленные исследования подтверждают ключевую роль воспаления в прогрессировании большинства дегенеративных процессов нервной ткани. В ответ на любые патогенные факторы (метаболические, токсические, инфекционные, травматические, в том числе и хронический стресс) воспаление приходит на помощь, как защитный механизм. Вызываемый иммунный ответ приводит к активации провоспалительных цитокинов, запускающих неконтролируемый процесс гибели нейронов и глии. Таким образом, нейровоспаление – многоуровневый клеточный механизм, обеспечивающий компенсаторную реакцию нервной ткани, но приводящий в последующем к нейродегенерации [11, 33, 82]. В сетчатке за иммунные реакции отвечает нейроглия.

По мнению многих авторов, в развитии нейровоспаления ключевую роль играют клетки микроглии [42, 44, 79]. Нейроны секретируют специальные сигнальные пептиды. В нормальных здоровых глазах человека, когда нейронам не угрожает опасность, активность макрофагов подавляется [68]. При нарушении гомеостаза микроглия активируется и обнаруживает готовность защищать ГКС от любых повреждений. Макрофаги приобретают амебовидную форму, становятся подвижными и способными к фагоцитозу. Так микроглия помогает предотвратить дальнейшие нарушения в сетчатке, очищая ткань от поврежденных или мертвых нервных клеток [43]. Выделяемый при гибели нейронов глутамат, также удаляется микроглией [45]. Известно, что глутамат, хранящийся внутри клеток, не вреден, но во внеклеточном пространстве он может вызывать эксайтотоксичность. Защищая нейроны от глутамата, микроглия проявляет свою антиапоптотическую активность. Кроме того, клетки микроглии продуцируют нейротрофические факторы [96] и оказывают антиокислительное действие, вырабатывая антиоксидантные ферменты [40, 80].

Активировавшись, макрофаги выбрасывают в межклеточное пространство белки системы комплимента, цитокины и хемокины, для привлечения большего количества иммунных клеток крови в сетчатку [100]. Под влиянием цитокинов, микроглия синтезирует матриксные металлопротеиназы. Вследствие такого синтеза происходит усиленный распад коллагеновых волокон решетчатой пластинки и формирование глаукомной оптиконейропатии. Высокое содержание металлопротеиназ при ПОУГ отмечалось многими исследователями [4, 99].

Сохраняя высокий уровень активности, микроглия продолжает выделять воспалительные цитокины, такие как фактор некроза опухоли (TNF-α), интерлейкин 1β (IL-1β), IL-6, лиганды Fas и активные формы кислорода (АФК). Нервная ткань особенно чувствительна к повреждающему действию АФК, что может быть связано с высоким поглощением O_2, необходимым для производства АТФ. Большие количества АТФ необходимы для поддержания внутриклеточного ионного гомеостаза нейронов посредством открытия и закрытия ионных каналов, которые участвуют в действии распространения потенциала и нейросекреции [90]. Как уже известно, процесс старения неразрывно связан со снижением способности клеток реагировать на окислительное повреждение. Следовательно, активные формы кислорода и азота, имеют тенденцию накапливаться в стареющих нейронах. Собственная антиоксидантная система, в свою очередь, не может эффективно им противодействовать. Нейротоксический эффект накапливается, нарушается взаимоотношение нервной ткани и сосудистой, что способствует развитию митохондриальной дисфункции, нарушению транспорта ионов. Окислительный стресс, изменение митохондриальной ДНК, увеличение концентрации Ca^{2+} являются мощными факторами ускорения апоптоза ГКС и развитию нейродегенеративного процесса [13].

Таким образом, микроглия при глаукоме оказывает сначала нейропротекторное, а затем нейротоксическое действие. Активируясь на ранних стадиях, быстро мигрирует к месту повреждения. Макрофаги стабилизируют микроокружение сетчатки за счет фагоцитоза и секреции противовоспалительных цитокинов, тем самым защищая зрительный нерв и ГКС. Однако на поздней стадии глаукомы сверхактивированная микроглия продуцирует провоспалительные цитокины, комплемент и другие токсические факторы, которые вызывают ускорение апоптоза ГКС и нейродегенерацию.

В иммунорегуляции сетчатки участвуют не только клетки микроглии, но и макроглии (астроциты и клетки Мюллера) [2]. В нормальной сетчатке эти клетки обеспечивают питание и структурную поддержку, участвуют в метаболизме и регулируют гомеостаз. Они координируют друг с другом, следя за состоянием нейронов, с помощью фагоцитоза, секреции воспалительных цитокинов и нейротрофических факторов [28]. Таким образом, микроглия и макроглия функционируют содружественно, и между ними всегда существует тонкий баланс.

Астроциты, занимающие стратегическое положение между эндотелиальными клетками сосудов и нейронами, реагируют на сигналы опасности, исходящие от нейронов и на вещества выделяемые активированной микроглией. При необходимости они увеличиваются в размере и начинают выделять нейрорегуляторные пептиды, например, BDNF (brain derived neurotrophic factor) нейротрофический фактор мозга, который способствует выживанию повреждённых нейронов.

В тоже время, они секретируют фибриллярные белки, восстанавливающие внеклеточный матрикс и формируя глиальный рубец, что блокирует аксональный транспорт, ограничивает возможность восстановления поврежденного аксона. Процесс формирования глиального рубца при экспериментальной глаукоме Аничков Н.М. и соавт. (2012) описывает, как дегенеративные изменения нервной ткани с заменой нейронов на незрелые астроциты, которые не могут полноценно выполнять свою опорную, трофическую и защитную функции [93]. В глиальном рубце астроциты вырабатывают ингибиторы роста аксонов (хондроитин-сульфат протеогликаны) – это способствует прогрессированию атрофии волокон зрительного нерва. Клетки Мюллера играют решающую роль в поддержании гомеостаза сетчатки. Они способны выделять глутаминсинтетазу, обеспечивающую защиту ГКС от токсического действия глутамата. Иммуногистохимические исследования сетчатки выявили усиленное выделение мюллеровскими клетками глутаминсинтетазы и NO-синтетазы у животных с адреналин-индуцируемой глаукомой [102]. Также клетки Мюллера способны высвобождать фактор роста нервов [30]. Однако, выделяемый глиальным рубцом виментин, не способствует возобновлению роста аксонов, а фактически активирует деградацию ткани [61]. Таким образом, преувеличенный реактивный ответ макроглии приводит к деградации внеклеточного матрикса, что способствует прогибу решетчатой пластинки и формированию экскавации.

По данным ReichenbachA., BringmannA. (2020) на ранней стадии глаукомы астроциты и клетки Мюллера ограничивают распространение воспаления и прогрессирование глаукомы. Но в поздних стадиях заболевания сверхактивные глиальные клетки образуют глиальные рубцы, которые усугубляют прогрессирование глаукомы [61].

Многие исследователи сходятся во мнении, что активация микро- и макроглии при глаукоме предшествует потере ГКС и является одним из первых событий повреждения нервной ткани [69].

При нейродегенеративных заболеваниях ЦНС (например, БА, БП) также описана активация микро- и макроглии и показано участие нейровоспаления, как пускового фактора в развитии заболевания [82].

Известно огромное число триггерных факторов, запускающих активацию микроглии и воспалительный ответ (ишемия, хронический стресс, высокий уровень внутриглазного давления), а также генетическая предрасположенность конкретного индивидуума к данному воспалительному ответу [57].

Повышенный уровень внутриглазного давления (ВГД) из основного патогенетического механизма развития ПОУГ постепенно занял место одного из факторов риска, наряду с возрастными изменениями, наследственностью и сопутствующей соматической патологией.

Считается, что хроническое повышение ВГД приводит к накоплению Aβ и p-тау в ГКС, что, в свою очередь, способствует потере нейронов [29].

При глаукоме отложения Aβ присутствуют во всех слоях сетчатки, включая слой ганглиозных клеток, слой нервных волокон, слой фоторецепторов и внутренний плексиформный слой, где они способствуют фосфорилированию и накоплению тау белка в виде аморфных отложений в ГКС [73]. В эксперименте выявлена прямая корреляция между p-tau, отложениями Aβ и гибелью ГКС [105]. Интересно, что повышенное ВГД увеличивает накопление тау и гибель ГКС, а подавление тау спасает ГКС. Более того, отложения Aβ инициируют каскад событий, которые активируют астроциты сетчатки и микроглию с секрецией воспалительных цитокинов, включая интерлейкин-1β (IL-1β), IL-6 и фактор некроза опухоли α (TNFα). Вместе с Aβ-генерируемыми АФК они создают токсическое микроокружение, приводящее к гибели ГКС и истончению СНВС [89]. Вследствие накопления бета-амилоида и гибели аксонов зрительного нерва происходит нарушение межсинаптических связей и развитие дегенеративных изменений в проводящих путях всего зрительного анализатора.

V. Заключение

Таким образом, многие факторы, в том числе активация глиальных клеток, митохондриальная дисфункция, окислительный стресс и дефекты в иммунном ответе, запускают процесс апоптоза ГКС и повреждение зрительного нерва. Активация нейроглии на первых порах играет защитную роль, но в последующем приводит к так называемому цитокиновому шторму, нарушающему гомеостаз сетчатки и имеющему трагические последствия для зрения.

Знания нейрохимических механизмов развития нейродегенерации при глаукоме позволяют получать информацию о начале патологического процесса на доклиническом этапе. Умение оценивать уровень активности глиальных клеток сетчатки поможет выявлять специфические биомаркеры начинающегося глаукомного процесса. Ранняя диагностика глаукомы создает больше шансов попасть в терапевтическое окно и противостоять необратимым последствиям.

Нейровоспаление является одним из ключевых факторов возникновения и прогрессирования

глаукомы. Понимание взаимодействия между клетками макро- и микроглии необходимо для разработки новых лекарственных препаратов для лечения глаукомы. Особое внимание уделяется попыткам создать контролируемое нейровоспаление. Обсуждается возможность регулировать активность глии, стимулировать выброс нейротрофических факторов и подавлять ее гиперактивность.

Углубленное изучение механизмов, лежащих в основе иммунного ответа, могло бы оказать положительное влияние на терапию глаукомы[99].

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Thrombotic Complications in Children in the Postcovidae Period: Clinical Cases

By G.M. Saatova, B.A. Musurkulova, A.J. Bolotbekova, R. Almazbekova, A.B. Furtikova & M.K. Koshukeeva

Resume- The high incidence of arterial thrombosis and venous thromboembolic complications in patients with SARS-CoV-2 coronavirus infection indicates the need for an in-depth study of the pathogenetic moments of procoagulant status and a more rational approach to preventive measures.

The aim of the work was to study clinical cases of thrombotic complications in children with coronavirus infection to substantiate the principles of practical approach to treatment and prevention.

This article presents clinical cases of thrombotic complications after COVID-19 in four children 12 months, 12, 16 and 3 years of age.

Keywords: children, COVID-19, thrombosis, hypercoagulability, blood vessels, post-Covidae syndrom, congenital heart disease, stroke, thrombotic complications, prevention.

GJMR-F Classification: LCC: RC660-RC669

Thrombotic Complications in Children in the Postcovidae Period: Clinical Cases

ТРОМБОТИЧЕСКИЕ ОСЛОЖНЕНИЯ У ДЕТЕЙ В ПОСТКОВИДНОМ ПЕРИОДЕ: КЛИНИЧЕСКИЕ СЛУЧАИ

G.M. Saatova [α], B.A. Musurkulova [σ], A.J. Bolotbekova [ρ], R. Almazbekova [ω], A.B. Furtikova [¥] & M.K. Koshukeeva [§]

Резюме- **Высокая частота артериальных тромбозов и венозных тромбоэмболических осложнений у пациентов с коронавирусной инфекцией SARS-CoV-2 свидетельствует о необходимости углубленного изучения патогенетических моментов прокоагулянтного статуса и более рационального подхода к профилактическим мероприятиям.**

Целью работы была изучение клинических случаев тромботических осложнений у детей, перенесших коронавирусную инфекцию для обоснования принципов практического подхода к лечению и профилактике.

В статье представляются клинические случаи тромботических осложнений после перенесенной COVID-19 у четырех детей 12 месяцев, 12, 16 и 3 лет.

В первом и втором случаях у детей с врожденным пороком сердца после перенесенной коронавирусной пневмонии выявлены тромботические осложнения в виде тромба в правом предсердии и тромба в печеночном сегменте нижней полой вены. В третьем случае выявлен окклюзионный тромбоз общей и наружной подвздошных вен слева и наружной подвздошной вены справа. При этом у ребёнка выявлен вторичный антифосфолипидный синдром. В клиническом случае у ребенка 3 лет после перенесенной коронавирусной инфекции COVID-19 развилось острое нарушение мозгового кровообращения с ишемическим инсультом в бассейне средней мозговой артерии.

Ключевые слова: Дети, COVID-19, тромбоз, гиперкоагуляция, сосуды, постковидный синдром, врожденные пороки сердца, инсульт, тромботические осложнения, профилактика.

Resume- The high incidence of arterial thrombosis and venous thromboembolic complications in patients with SARS-CoV-2 coronavirus infection indicates the need for an in-depth study of the pathogenetic moments of procoagulant status and a more rational approach to preventive measures.

The aim of the work was to study clinical cases of thrombotic complications in children with coronavirus infection to substantiate the principles of practical approach to treatment and prevention.

This article presents clinical cases of thrombotic complications after COVID-19 in four children 12 months, 12, 16 and 3 years of age.

In the first and second cases of children with congenital heart disease after coronavirus pneumonia, thrombotic complications in the form of a thrombus in the right atrium and a thrombus in the hepatic segment of the inferior vena cava were detected. In the third case, occlusive thrombosis of the common and external iliac veins on the left and the external iliac vein on the right was detected. In this case, the child was diagnosed with secondary antiphospholipid syndrome. In a clinical case, a 3-year-old child developed acute cerebral circulation disorder with ischemic stroke in the middle cerebral artery basin after a COVID-19 coronavirus infection.

Keywords: children, COVID-19, thrombosis, hypercoagulability, blood vessels, post-Covidae syndrom, congenital heart disease, stroke, thrombotic complications, prevention.

I. Введение

Публикации по исследованиям системы гемостаза при COVID-19 у детей не так многочисленны, как у взрослых.

Расстройства гемостаза в виде тромбозов в различных сосудистых бассейнах являются одной из основных причин смерти при COVID-19, причем их угроза сохраняется и после выздоровления в рамках постковидного синдрома.

Высокая частота артериальных тромбозов и венозных тромбоэмболических осложнений, нередко приводящих к гибели пациентов с новой коронавирусной инфекцией SARS-CoV-2, несмотря на проводимую антитромботическую терапию, свидетельствует о необходимости углубленного изучения патогенетических моментов прокоагулянтного статуса и более рационального подхода к профилактическим мероприятиям (Lim W. 2019). Особый интерес вызывает развитие тромботических осложнений у реконвалесцентовCOVID-19.

В статье представлены клинические случаи детей, у которых после перенесенной коронавирусной инфекции сформировались тромбы в полости сердца, флеботромбоз глубоких вен нижних конечностей, ишемический тромбоз сосудов мозга.

Цель исследования: изучить клинических случаев тромботических осложнений у детей, перенесших коронавирусную инфекцию для обоснования принципов практического подхода к лечению и профилактике.

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II. Клинические Случаи

Дети с врожденными пороками сердца (ВПС) могут относиться к группе высокого риска в случае заболевания COVID-19. Тем не менее, вследствие гетерогенности врожденных пороков сердца (ВПС) и спектра вторичных осложнений, профили рисков у них отличаются.

a) *Клинический случай формирования внутрисердечного тромба у ребенка с ВПС после перенесенной COVID-19*

Мальчик А. Я. 04.01.2021 года рождения (12 месяцев).

Дата поступления в отделение кардиоревматологии Национального центра охраны материнства и детства (НЦОМиД): 09.12.2021

Дата выписки: 18.01.2022 г

Клинический диагноз: ВПС. Дефект межпредсердной перегородки (ДМПП). Острая двусторонняя нижнедолевая пневмония.Состояние после перенесенной коронавирусной инфекции. Тромб в правом предсердии.

У ребенка с рождения диагностирован ВПС: Открытый аортальный проток (ОАП). ДМПП. Легочная гипертензия. Часто болеет простудными заболеваниями, эпизоды госпитализации по поводу пневмонии. С 11.11. 2021 г. по 24.11.21г госпитализация по поводу коронавирусной инфекции с двусторонней полисегментарной пневмонией с обструктивным синдромом, ДН II-III степени. Лечение: ампициллин 400мг 4р/день, цефтриаксон 600мг 1р/день, дексаметазон 4мг+эуфиллин 0,9 в/в капельно, гепарин 0,1мл, ципрокс 35мл, маннит 10 мл в/в капельно, беродуал по 7 кап, верошпирон ½ таб.

06.12.2021 года при плановом обследовании на ЭХОКГ выявлено образование в правом предсердии (тромб). Состояние тяжелое. Выраженный горизонтальный нистагм. Кожные покровыи слизистые бледные, обычной влажности, высыпаний нет. Периодически нарастает одышка до 64 в мин. SpO_2 60-87-96%. При аускультации над легкими дыхание жесткое, рассеянные мелкопузырчатые и сухие проводные хрипы. Границы относительной сердечной тупости расширены в поперечнике. Тоны сердца ритмичные, приглушены, систолический шум в 3-4 межреберье слева от грудины. Частота сердечных сокращений (ЧСС) -170 в мин. Живот мягкий, безболезненный при пальпации. Печень и селезенка в пределах возрастной нормы. Отеков нет. Стул и мочеиспускание регулярные.

Данные обследования:

Таблица 1: Общий анализ крови

Дата	ЭР $x10^{12}$/л	HB г/л	Тр - 10^9/л	Лейк - 10^9/л	Лимф %	Mid%	Gran %	СОЭ - мм/ч
10.12.21	4,87	146	252	11,2	67,6	9.1	23.3	2
14.12.21	4.82	140	258	9.8	49.6	10.2	40.2	5
21.12/21	5.00	142	311	14.3	52.6	9.6	37.8	9
29.12/21	4.98	143	309	18.7	29.4	6.3	12.0	2
14.01.22	4.93	140	319	10.5	49.5	8.3	42.2	11

Таблица 2: Биохимический анализ крови

Дата	Общ.бил мкмоль/л	Тимол. Проба, ед	Общ. Белок, г/л	Креатинин мкмоль/л	Сахар ммоль/л	АСТ/АЛТ мккат/л	Мочевина ммоль/л
10.12.21	5,0	4,53	61,8	38,5	4,57	69,3/43,4 ед/л	2,85
21.12.21	4,20	1,74	63,8	60,80	9,37	0,22/0,24мм оль/л	3,47
03.01.22	5,36	1,74	м/с	66,3	3,84	0,30/0,34мм оль/л	6,1

Таблица 3: Микроэлементы крови

Дата	Кальций мкмоль/л	Калийммоль/л	СРБ	РФ	Железо
10.12.21	2,15	м/с	Отр.	отр	9,9
14.12.21г	2,20	5,0			
13.01.22	1,78		отр		12,9

Таблица 4: Свертывающая система крови

Дата	Протромбиновое время	Протромбиновый индекс	MNO	Фибриноген
13.12.21г	12,2"	109,8%	10,9	1,36 г/л
21.12.21	18,9"	73,1%	1,3	1,30г/л
28.12.21	12,8	110%	0,9	1,42г/л
03.01.22	90,9	14,7%	6,78	1,94г/л
13.01.22	21,1	61,2%	1,63	5,58г/л
17.01.22	53,0	25,2%	3,95	3,38 г/л

Антитела к коронавирусу SARS - CoV-2 от 10.12.21г IgG – положительные (КП=16,5), IgM - отрицательные.

УЗИ внутренних органов от 10.12.21г: печень, желчный пузырь, поджелудочная железа, селезенка, почки – без эхоструктурных изменений.

ЭКГ от 13.12.21г: ритм синусовый, ЧСС 150 уд в мин., электрическая ось сердца отклонена вправо. Синусовая тахикардия, гипертрофия правого жедудочка. ЭХОКГ от 09.12.21г. ВПС: ДМПП (секундный тип). Эхогенное образование в полости правого предсердия 1,7 х 1,6 см. Перикардиальная жидкость (рис. 1).

Figures 1 and 2 go here. File name: Figure 1 Echo Cardiogram from 09.12.2021.gpeg

Figure 2 Echo Cardiogram from 09.12.2021.gpeg

Рис. 1, 2 ЭХОКГ от 9.12.21 года в межпредсердной перегородке дефект диаметром 0,5 см, тип секундум, сброс крови слева направо. По латеральной стенке правого желудочка перикардиальная жидкость - 0,9 см, на верхушке - 0,5 см. В полости правого предсердия эхогенное образование 1,7х1,6 см. Гипертрофия правого желудочка.

Было проведено лечение: антибактериальная терапия (ампициллин 350мг х 4 р/день №6; цефиксим 3,0 мл 1 р/день №11; амикацин 110 мг в/в), антикоагулянтная терапия (гепарин 500 ЕД по 0,1 х 4 р/день п/к с постепенной отменой, варфарин 2,5мг¼ таб →1/2 т →1/3 т в день), мочегонные препараты (верошпирон ½ таб х 1 р/день), противовоспалительная терапия (ибуфен 3,0 мл х 2 р/день).

Состояние на фоне лечения стабилизировалось, одышки нет, сатурацию удерживает на уровне 93-96%, периодически рассеянные проводные хрипы. В динамике эхогенное образование в полости правого предсердия сохраняется с тенденцией к уменьшению до 1,1 х 1,0 см. Осмотрен кардиохирургом - «показаний к экстренному оперативному лечению нет». Продолжен варфарин 2,5мг по 1/4 таб х 1 раз вечером длительно. Выписан с улучшением.

Рекомендовано повторить анализ крови на свертывающую систему через 4 дня (МНО, ПТВ, ПТИ). Контрольный осмотр через 7 дней. ЭхоКГ и осмотр в кардиохирургом через 1 месяц.

b) *Клинический случай тромба печеночного сегмента нижней полой вены у ребенка с ВПС*

Ребенок Ж.Т.: 14.01.2009 года рождения.

Дата поступления: 14.06.2021

Клинический диагноз: ВПС. Аномалия развития митрального клапана (МК) с недостаточностью митрального клапанаIII степени (аномалия папиллярных мышц МК). Относительная недостаточность трикуспидального клапана (ТК)III степени. Высокая легочная гипертензия (ВЛГ). СНФК I-II. Инфекционный эндокардит?

Синдром Бадда-Киари (тромб в нижней полой вене).

Постковидный синдром.

Ребенок жалуется на одышку в покое, слабость, быструю утомляемость, отеки на лице, конечностях, нарушение самочувствия.

ВПС был выявлен поздно - в 2020 году (в 11 - летнем возрасте), когда обратили внимание на симптомы сердечной недостаточности. Бессимптомно перенес COVID-19 (ИФА lgGSARS-Cov-2- титр 16,5).

Состояние тяжелое. Самочувствие страдает. Телосложение астеническое, пониженного питания, отеки на нижних конечностях, на лице. Грудная клетка деформирована, цилиндрической формы. Дыхание жесткое, хрипов нет. Тоны сердца ясные, ритм правильный, выслушивается грубый систолический шум на верхушке. Область сердца изменена, выбухает, заметна пульсация. Набухание и пульсация сосудов шеи. Верхушечный толчок усилен в IV-Vмежреберье. Границы относительной тупости: правая на 1 см кнаружи от края грудины, верхняя на IIмежреберье, левая на 1,5 см кнаружи от левой среднеключичной линии. ЧСС 100-108 ударов в минуту, ЧД 18 в минуту. Живот обычной формы, мягкий безболезненный, печень увеличена. Стул и мочеиспускание регулярное.

Данные обследования

Таблица 5: Общий анализ крови

Показатели крови	**15.06.21**	**22.06.21**
Эритроциты * 10^{12}/л	4,26	4,25
Hb, г/л	123	125
ЦП	0.8	0,9
Тромбоциты *10^9/л	378	386
Лейкоциты *10^9/л	7,4	7,6
Эозинофилы,%	1	1
п/я,%	4	2
с/я,%	52	53
Лимфоциты,%	40	41
Моноциты,%	3	3
СОЭ	4	4

Таблица 6: Свертывающая система крови:

ПТВ	16,7”
ПТИ	77,8%
МНО	1,21
Фибриноген	2,4

Общий анализ мочи от 15.06.2021: цвет с/ж, прозрачность полная, отн.плотность 1020, реакция кислая, глюкоза-отр., белок 0,675 г/л, Лейкоциты 2-3-4 в поле зрения, Эртроциты 6-7-8 в поле зрения, Оксалаты++; анализ мочи по Нечипоренко: лейкоциты 2,750,эртроциты 6,000

Общий анализ мочи от 22.06.2021г.: Цвет с/ж, прозрачность полная, отн.плотность 1015, реакция кислая, глюкоза-отр., белок следы, эпит.плоскийед., Лейкоциты 1-3-4-4; анализ мочи по Нечипоренко: лейкоциты 2,500.

Таблица 7: Биохимический анализ крови:

Общ. Билирубин, мкмоль/л	18,65	19,4
Тимоловая проба, ЕД	3,51	2,16
Общий белок, г/л	66,0	69,0
Мочевина, ммоль/л	7,24	8,42
Креатинин, мкмоль/л	70,0	59,0
АСТ,ЕД/Л	59,0	36,0
АЛТ, ЕД/Л	95,0	50,0
сахар	5,11	5,18
Са	2,47	2,57
Фосфор	1,48	1,67
СРБ	13,0	

Инструментальные обследования

ЭКГ от 15.06.2021: электрическая ось сердца отклонена вправо. Ритм синусовый с тенденцией к тахикардии. ЭКГ признаки гипертрофии левого предсердия, обоих желудочков.

- УЗИ брюшной полости и почек от 17.06.2021: Кардиальная печень. Эхо-признаки гепатита, холецистохолангита. Токсическая нефропатия.
- ЭХО-кг от 14.06.2021: ВПС. Аномалия развития МК с недостаточностью МК IIIст.(аномалия папиллярных мышц МК). Не исключается инфекционный эндокардит. Дилятация всех отделов сердца. Относительная недостаточность ТК – IIIст.ВЛГ.
- УЗИ от 18.06.2021: данные за тромб печеночного сегмента нижней полой вены, гепатомегалию, асцит (рис.3).

Figure 3 goes here. File name: Figure 3 Ultrasound from 18.06.2021.gpeg

Рис. 3. УЗИ от 18.06.2021: данные за эмбологенный тромб печеночного сегмента нижней полой вены, гепатомегалию, асцит

Проведено лечение: ибупрофен по 1 таб. 2 раза в день №8, фуросемид по 1,5 мл. 2 раза в день в/м, верошпирон по 1 таб. 2 раза в день.

Ампициллин по 1 гр. 4 раза в день в/в струйно, гентамицин по 60 мг. 2 раза в день в/в струйно №8, урсодекс по 1 капсуле 1 раз в день, панангин по 1 таб. 3 раза в день, омепразол по 1 капсуле утром перед едой №1.

Гепарин по 800 Ед (0,2) 4 раза в день №4, затем по 1250 ЕД (0,25) 4 раза в день п/к вокруг пупка.

Рекомендован контроль ЭХОКГ, ЭКГ через неделю, УЗИ органов брюшной полости повторить 24.06.2021, кровь на свертывающую систему каждые 3 дня, кровь на прокальцитонин.Продолжить прием препаратов: фуросемид по 1,5 мл. 2 раза в день в/м, ампициллин по 1 гр. 4 раза в день в/в струйно (06:00,12:00,18:00,00:00), верошпирон по 1 таб. 2 раза в день длительно, урсодекс по 1 капсуле 1 раз в день, панангин по 1 таб. 3 раза в день, гепарин по 1250 ЕД (0,25) 4 раза в день п/к вокруг пупка.

В целом, дети менее подвержены развитию **тяжелых форм коронавирусной инфекции (Karikalan S. 2022). Однако, в случае наличия у них серьезных патологий сердца**, при инфицировании **COVID-19**, следует учитывать их предшествующее состояние и иметь ввиду возможности развития поражений, обусловленных нарушениями свертывающей системы крови.

На клинических примерах продемонстрирована проблема выявления и лечения тромбоза правого предсердия и печеночного сегмента нижней полой вены у детей, перенесших коронавирусную инфекцию.

Коагуляционные изменения, связанные с COVID-19, предполагают наличие гиперкоагуляционного состояния, увеличивающего риск тромбэмболических осложнений. В зоне риска тромбоза находятся все дети в постковидном периоде, в том числе пациентов с ВПС**.**

Исходя из представленных клинических случаев, возможен вывод о необходимости применения фармакологической профилактики тромбозов у всех пациентов группы риска, перенесших COVID-19 и рекомендовать назначение им профилактических доз антикоагулянтов. Пациентам ВПС, перенесшим коронавиирусную инфекцию, необходим регулярный эхографический контроль!

Всегда следует оценивать риски, прежде чем пациент перестанет принимать обычные лекарства.

Ранее существовавшая патология сердца (ВПС) является основным фактором риска неблагоприятного исхода (Bigdelian H. 2021; WHO 2021; KlokF.A. 2020).

Совсем недавно появились отдельные публикации о повышенном риске осложнений от коронавируса у пациентов, принимающих такие лекарства, как каптоприл, эналаприл, лозартани др. Однако пока нет достоверных доказательств данного предположения. По этой причине, рекомендации кардиологических обществ на данный момент не содержат указаний на то, что лечение этими препаратами следует приостановить.

c) Клинический случай тромбоза сосудов нижних конечностей у относительно здорового ребенка после перенесенной коронавирусной инфекции COVID-19

Ребенок К.С.20.09.2005 года рождения, 16 лет

Дата поступления в отделение кардиоревматологии: 25.03.2022

Клинический диагноз: Постковидный синдром, вторичный антифосфолипидный синдром: окклюзионный тромбоз общей и наружной подвздошных вен слева и наружной подвздошной вены справа, поверхностной бедренной вены слева, острое течение (ассоциированная SARS-COV-2 инфекцией). Состояние после имплантации кава-фильтра от 26.01.2022г. Синдром Мэя -Тернера**.**

Летом 2021 года ребенок перенес COVID-19 (ПЦР +). В январе 2022 года находился в контакте с больнымCOVID-19, отмечалась лихорадка. В конце января внезапно появились сильные боли в левой нижней конечности и подвздошной области, в амбулаторных условиях проведено УЗДГ сосудов нижних конечностей, где был выявлен акустически свежий окклюзионный тромбоз общей подвздошной вены (ОПВ), нисходящий тромбоз нижней подвздошной вены (НПВ), общей бедренной вены (ОБВ) слева.

26.01.2022 госпитализирован в частную клинику “Бикард” с диагнозом: Синдром Мея-Тернера. Тромбоз общей и наружной подвздошных вен слева и наружной подвздошной вены справа. АФС ассоциированный с СКВ.

По тяжести состоянии, в экстренном порядке проведена ангиография, в связи с острым тромбозом был имплантирован кава-фильтр и проведена инфузияактилизой, антикоагулянтная терапия. На этой терапии: полная посттромботическая реканализация. Через день отмечался рецидив тромбоза, стаз крови в венах голени.

Лабораторно маркеры АФС и СКВ: повышение антител к кардиолипинуIgM, IgG, IgAизотипов в высоких титрах; В2 гликопротеину IgM, IgG, IgAизотипов в высоких титрах, Д-Димер 10000нг/мл, СРБ-180мг/л, ускоренное СОЭ до 43мм/ч. Госпитализируется в отделение кардиоревматологии НЦОМиД для уточнения диагноза и подбора терапии.

Общее состояние при госпитализации тяжелое. Отек и уплотнение на всем протяжении левой нижней конечности.Гиперемия кожи по внутренней поверхности левой голени, местная гипертермия. В легких дыхание без хрипов.ЧД 18 в мин SpO2-99%. Сердечные тоны приглушены, ритмичные, ЧСС 88-98 в минуту, АД - 110/70. Живот мягкий, боли вокруг пупка, печень не увеличена.

Лабораторно

Figure 4goes here. File name: Figure 4General blood test.gpeg

Рисунок 4. Показатели анализа крови

ОАМ (от 28.03.21): цвет сол/желтый, прозрачная, отн.плотность-1020, реакция кислая, белок нет, глюкоза-отр., эпит пл. 3-4-4, лейкоциты 2-3-4-4, соли оксл. +, анализ мочи по Ничепоренко лейкоциты 2750

ОАМ (от 12.04.21): цвет сол/желтый, прозрачная, отн.плотность-1013, реакция кислая, белок нет, глюкоза-отр., эпит пл. един., лейкоциты 1-1-3, соли оксл. +

Биохим ан. крови(от 28.03.22): СРБ – 20,0 мг/л, общ билирубин-8,45 мкмоль/л, тимоловая проба- 2,43 ед, общий белок – 77,1 г/р, мочевина – 4,51 ммоль/л, креатинин- 68,3 мкмоль/л, сахар крови-5,52; АСТ-63,2, АЛТ-99,5, АСЛО +, РФ – отр., Са -2,13, Fe – 8,4 ммоль/л, Р-1,29

(31.03.22): Вр. свертывание по Ли –Уайту – 9'38", ПТВ-14,3"; ПТИ-85,7%, МНО-1,17, АЧТВ – 25,3", фибриноген – 3,9%

(04.04.22): ПТВ-12,7"; ПТИ-98,4%, МНО-1,03, АЧТВ – 24,1", фибриноген – 4,2

Биохим ан. крови(от 08.04.22): общ билирубин-7,73 мкмоль/л, тимоловая проба- 3,51 ед, общий белок – 70 г/р, мочевина – 5,37 ммоль/л, креатинин- 77,4 мкмоль/л, сахар крови-4,47; АСТ-15, АЛТ-43,0, Са -2,29, Р – 1,43

Таблица 8: Свертывающая система крови

Дата обследования	ПТВ	ПТИ	МНО	АЧТВ	Фибриноген
08.04.2022	13,1"	95,2%	1,06	24,0"	4,2%
12.04.2022	15,5"	76,1%	1,28	38,0"	4,3%
14.04.2022	15,6"	75,3%	1,28	32,0"	3,9%

Аутоиммунная диагностика (от 06.02.2022): Антифосфолипидный синдром АТ к кардиолипину 890,0 МЕ/мл (норма 0-10); антитела к бета-2 гликорпротеину -580,0 МЕ/мл (норма 0-10); волчаночный антикоагулянт -1,23+

Аутоиммунная диагностика (от 31.03.2022): Антитела к кардиолипинуIgG -90,46, IgM-35,75, антиядерные антитела на субстрате клеток HELP-2 –свечение отсутствует

*Генетическое исследование (от 08.02.22)***:** тромбофилия расширенная. Выявлен полиморфизм в гетерозиготной форме, предрасполагающий к нарушению обмена фолатов, гипергомоцистинемии.

Ультразвуковая диагностика патологии вен нижних конечностей (от 22.03.22): состояние после имплантации кава-фильтра в области фильтра тромб 23х18 мм. *Левая нижняя конечность:* данные за окклюзионный тромбоз ОПВ, тромбоз НарПВ, тромбоз ОБВ, ПБВ и вен голени с признаками начальной реканализации на ОБВ. Артерии – кровоток магистральный не измененный, прослеживается на всем протяжении до стоп. *Правая нижняя конечность:* глубокие и п/к вены н/к проходимые, сжимаемы, компрессионные пробы положительные, клапаны состоятельные. Прокрашивание в режимах ЦДК и ЭД полное. Артерии – кровоток магистральный, не низменный, прослеживается на всем протяжении доступа (рис.5).

Figure 5 goes here. File name: Figure 5State after implantation.gpeg

Рис. 5. 06.04.22: Состояние после имплантации кава-фильтра, НПВ и зона фильтра проходимые, без признаков тромбоза. Левая нижняя конечность данные за окклюзионный тромбоз ОПВ, тромбоз НПВ, тромбоз ОБВ, ПБВ и вен голени с признаками начальной реканализации на ОБВ. Артерии – кровоток магистральный не измененный, прослеживается на всем протяжении до стоп.

ЭКГ: вариант нормы.

В отделение проведена терапия: фраксипарин 0,6 х3 п/к №2 → 0,6х 2 п/к №1 →0,6 х3 п/к №1 → 0,6 х2 п/к №1→ 0,3 х2 п/к №1→ 0,3 х1 п/к №1; авето 500 мг х 1 раз в день №6; декса 8мг →16мг →8мг на физ.р-ре 100,0 с переходом на медрол в таблетках; цефтри 2,0 в/в кап. №5; плаквенил 1 таб.в обед №19; местно аппликации с мазью Вишневского; Биовен моно (внутривенный иммуноглобулин) 0,4 гр/кг(курсовая доза в течение 5 дней); варфарин½1таб. №5→ 2 таб утром №9; медрол 16мг утр.1 таб.,1 таб обед →утр.1 таб.,1 таб обед,1/2 вечером; аспирин кардио 0,1 вечером; эналаприл ½ таб х 2 раза в день №4 → ½ утром №2

В результате лечения состояние мальчика значительно улучшилось, болевой синдром не беспокоит, визуальных изменений со стороны левой конечности нет, хотя при проведении УЗДГ сосудов признаки тромбоза сохраняются, появилась частичная реканализация сосудов.

В данном клиническом случае COVID-19 спровоцировал развитие аутоиммунного состояния, подобного АФЛ синдрому, называемого «COVID-19-индуцированный АФЛ - подобный синдром». Антифосфолипидный синдром – аутоиммунное заболевание, которое манифестирует как венозный или артериальный тромбоз.

Подтверждением данного заболевания явилось повышение титра антител к бета-2-гликопротеину-1 или кардиолипину, повышенная концентрация волчаночного антикоагулянта. У многих пациентов с COVID-19 отмечается удлинение АЧТВ, что может быть маркером повышения уровня волчаночного антикоагулянта (Radke, Frenzelt 2020).

Повышение уровня волчаночного антикоагулянта у пациентов с COVID-19 ассоциируется

со значительным увеличением риска тромботических осложнений, данный маркер может быть использован для отбора пациентов, которым целесообразно вводить полную (лечебную) дозу гепарина (Karikalan S. 2022).

АФЛ синдром может быть преходящим у генетически предрасположенных пациентов. Катастрофический антифосфолипидный синдром при тяжелом течении COVID-19 не исключает вероятности развития в качестве одного из проявлений тромбофилии, имеющей место у таких пациентов.

d) *Клинический случай острого нарушения мозгового кровообращения (ОНМК), ишемический инсульт в бассейне средней мозговой артерии у ребенка после перенесенной коронавирусной инфекции COVID-19*

Девочка С.А. 2017 года рождения (3 года).

Основной диагноз: ОНМК. Ишемический инсульт в бассейне средней мозговой артерии справа, с диффузным поражением правого полушария, вследствие перенесенной коронавирусной инфекции. Левосторонняя гемиплегия.

Сопутствующий: Нефропатия. Антибиотико-ассоциированная диарея. Железодефицитная анемия умеренной степени. Острый фарингит. Двусторонний конъюнктивит. Минимальная недостаточность митрального клапана.

Ребенок от 6 беременности 5 родов. Беременность протекала на фоне токсикоза до 3-4 месяцев, перенесла ОРВИ в 1 триместре. Состоит на учете с 3 недели. Анализы на ВУИ - отрицательные. Во время беременности на 2-3 триместре повышалось АД. Роды в сроке 39 недель, экстренные, путем КС по причине повышения АД до САД 210 мм рт ст. ВПР 3400 гр. Закричала сразу, к груди приложена на 2 день, сосала активно. Полученные прививки – по календарю.

Наследственность не отягощена. Родственные браки отрицает. Во время беременности принимала йодомарин, элевит, фолиевую кислоту.

Ребенок перенес COVID-19 (от 04.07.2020. ПЦР SARSCoV-2 положительный)

28.07.20 утром ребенок стал вялым, отсутствовал аппетит, отмечалось резкое ограничение движений в левых конечностях. В этот же день обратились в поликлинику по месту жительства, где был однократный приступ судорог на фоне лихорадки. Введен диазепам в/м, ребенок был госпитализирован в реанимацию по тяжести состояния в угнетенном сознании, с наличием судорог тонико-клонического характера с потерей сознания, аффектами, на фоне повышения температуры тела до 39 градусов. Присутствовало ограничение движений в левых конечностях, наличие геморрагических высыпаний на нижних конечностях. По тяжести состояние была госпитализирована в реанимацию.

Выявлены МРТ признаки энцефалита справа, ОНМК по ишемическому типа справа, и выставлен диагноз “Менингоэнцефалит неуточненной этиологии. ОНМК по ишемическому типу. Двусторонняя пневмония”.

Получено лечение: антибактериальная, гормональная, инфузионная и симптоматическая терапии. Динамики не наблюдалось, состояние ребенка оставалось тяжелым, температура тела была в пределах 37,7-38,5С.

Неврологический статус: Сознание - кома (3 б по ШКГ). На осмотр не реагирует. На звуковые раздражители не реагирует. Череп округлой формы. БР закрыт. Зрачки диаметром средней величины, D=S, реакция зрачков на свет отсутствует, D=S. Движения глазных яблок нет. Косоглазия нет, нистагма не отмечено. Лицо симметричное. Мышечный тонус понижен по гипотоническому типу во всех конечностях, D<S. Левосторонняя гемиплегия. Сухожильные рефлексы справа снижены, слева отсутствуют. Ригидность затылочных мышц.

NIHSS на момент поступления в НЦОМиД (7 день инсульта)- 26 б.

NIHSS на 10 день инсульта- 26 б.

NIHSS на 17 день инсульта- 21 б.

Соматический статус. Состояние тяжелое за счет неврологической симптоматики и признаков интоксикации.

Кожа и видимые слизистые бледной окраски, отмечалась геморрагическая сыпь на нижних конечностях до 11 дня болезни. Шелушение кожи подушечек пальцев рук и ног и миастения появились на 25 день болезни. Затылочные и околоушные лимфатические узлы были увеличены, безболезненные. Зев гиперемирован. Носовое дыхание свободное. Над легкими дыхание жесткое. Сердечные тоны приглушены, ритмичные, шумов нет. Живот при пальпации мягкий, печень и селезёнка не увеличены. Стул жидкий, без патологических примесей, до 6-7 раз в день. Мочеиспускание через мочевой катетер. Питание через назогастральный зонд до 22 дня болезни. После восстановления глотания, у ребенка отмечалась булимия.

Данные лабораторного обследования:

Исследование мазка на ПЦР COVID 19 – положительный (от 04.08.20г);

Исследование крови на SARS CoV – 2, IgG COVID 19 – КП 7,8; антитела к коронавирусу SARS CoV – 2, IgM COVID 19 – КП 1,07 (от 21.08.20г).

Ферритин – 82,1; нг/млД – димер 5,10 мг/мл; Фибриноген «А» - 9,4 г/л вр. рекальцификации 115, ПТВ 20, ПТИ 80,0; МНО 1,2; АЧТВ 40.

общий белок - 40,0 г/л;

прокальцитонин 0,6 нг/мл;

СРБ отрицательный.

Данные инструментального обследования:

МРТ от 31.07.20г. - признаки, наиболее вероятно, как проявление энцефалита справа. Не исключено ОНМК по ишемическому типу.

Figure 6 goes here. File name: Figure 6MRI from 31.07.2020.gpeg	Figure 7 goes here. File name: Figure 7MRI from 31.07.2020.gpeg
Рис. 6, 7. МРТ от 31.07.2020 г. - признаки, наиболее вероятно, как проявление энцефалита справа. Не исключено ОНМК по ишемическому типу.	

Figure 8,9 goes here. File name: Figure 6 MRI Angiography from 07.08.2020.gpeg

Рис. 8, 9. МРТ ангиография от 07.08.2020г – картина обеднения конечных ветвей средних и задних мозговых артерий с обеих сторон. Гипоплазия поперечного синуса слева

УЗИ головного мозга – тромбоз в БСМА справа

ЭХО КГ– минимальная недостаточность митрального клапана, тахикардия.

ЭКГ– ритм синусовый. ЧСС 160 уд. в мин. ЭОС отклонена вправо. Неполная блокада правой ножки пучка Гиса.

Рентгенограмма органов грудной клетки: двусторонняя прикорневая пневмония.

Лечение патогенетическое (антиагрегантная и гормонотерапия), симптоматическое (НПВС, инфузионная и антибиотикотерапии).

После проведенной терапии отмечалась положительная динамика: Ферритин - 30,84 нг/мл; D-димер - 0,53; Фибриноген А - 4,6.

На рентгенограмме органов грудной клетки в динамике определяется инфильтрация с обеих сторон в стадии рассасывания. NIHSS (36 день инсульта)- 13 б.

Данный клинический случай является подтверждением возможного нарушения мозгового кровообращения вследствие перенесенной коронавирусной инфекции.

Поражение ЦНС в данном случае может быть следствием мультивоспалительного синдрома, при котором поражаются сразу несколько систем детского организма. Разумеется, возможны другие причины ишемического инсульта у детей, например, анатомические особенности сосудов.

Хотя дети переносят COVID-19 легче взрослых, в редких случаях у них развиваются опасные неврологические синдромы. Как показал международный экспертный обзор, опубликованный в TheLancet, у пациентов младшего возраста, переболевших COVID-19, возможны поражения головного мозга (вплоть до инсульта), нервной ткани и позвоночника (ReyesGil M. 2019; ESO 2023; Bowles L. 2020; HarzallahI. 2020)

Антикоагулянтная терапия желательно должна быть представлена пероральным приемом антикоагулянтных препаратов и мониторироваться показателями МНО и АЧТВ ежедневно в остром периоде инсульта.

III. Обсуждение

Высокая частота артериальных тромбозов и венозных тромбоэмболических осложнений у пациентов с новой коронавирусной инфекцией SARS-CoV-2, свидетельствует о необходимости углубленного изучения патогенетических моментов прокоагулянтного статуса и более рационального подхода к профилактическим мероприятиям у данной категории лиц.

Кроме того, значимость нарушений свертываемости крови у детей, перенесших COVID-19, становится все более очевидной, поскольку у значительной части пациентов развиваются, иногда нераспознанные, венозные и артериальные тромбоэмболические осложнения.

Тромбообразование (артериальные и венозные тромбозы, микро- и макро-) у пациентов, перенесших COVID-19, может быть вызвано эндотелиальной дисфункцией и эндотелиитом, «цитокиновым штормом», гипоксическим повреждением, гиперкоагуляцией и/или повышенной активностью тромбоцитов. На сегодняшний день роль хронического воспаления (в первую очередь, эндотелиита – васкулита с микротромбозами и микроциркуляторными нарушениями) и других иммунных реакций считается главной теорией патогенеза постковидного синдрома.

С повышенным тромбообразованием связана высокая частота тромботических осложнений ковидной инфекции, обусловленных повышением факторов прокоагуляции, таких как фибриноген, D-димер, протромбиновое время.

Все это определяет сложность подбора медикаментозной патогенетической терапии данной вирусной инфекции, в частности применения антикоагулянтов, вследствие риска геморрагических осложнений, как в остром периоде заболевания, так и после – в форме отсроченных тромбэмболических осложнений.

Исходя из результатов исследования, можно сделать заключение о необходимости строго применять фармакологическую профилактику тромбозов у всех пациентов, перенесших COVID-19, группы риска, и настоятельно рекомендовать профилактические дозы антикоагулянтов.

На сегодняшний день особо актуальным остается вопрос: является ли постковидный синдром осложнением COVID-19 или продолжающимся патологическим процессом, что является принципиальным условием для обоснования тактики ведения пациентов.

IV. Заключение

Представляя ряд клинических случаев тромботических осложнений у детей после перенесенной COVID-19, авторы стремились подтвердить теоретические предположения о вероятности таких осложнений и их разнообразии. В данном сообщении отражены варианты тромботических осложнений после коронавирусной инфекции у детей с ВПС, а также случаи тромбозов вен конечностей и

сосудов мозга у детей с неблагополучным преморбидным фоном.

С нашей точки зрения, представленные данные должны аргументировать клиницистов на возможное более раннее применение превентивных мер по отношению к тромботическим осложнениям у всех пациентов, перенесших инфекцию COVID-19, а также на раннее выявление начальных признаков таких осложнений.

В связи с этим необходима разработка и апробация алгоритмов профилактики тромботических осложнений у детей с перенесенной новой коронавирусной инфекцией независимо от ее тяжести.

На данном этапе еще предстоит дальнейшее обобщение клинического материала по ближайшим и отдаленным исходам тромбозов сосудов различных систем организма, что будет основой и доказательной базой необходимости совершенствования лечения и реабилитации постковидных осложнений, обусловленных формированием дефектов гемостаза.

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ИНФОРМИРОВАННЕ СОГЛАСИЕ

«От пациента (родителя, законного представителя) получено письменное добровольное информированное согласие на публикацию результатов его обследования и лечения (дата подписания ДД.ММ.ГГГГ)»).

ИСТОЧНИК ФИНАНСИРОВАНИЯ

Клиническое наблюдение выполнено в рамках Научно-исследовательской работы Национального Центра охраны материнства и детства при финансовой поддержке Министерства образования и науки Кыргызской Республики,

Конфликт интересов отсутствует.

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Are Known Lung Dose Limits Valid for All Patients?

By Dalenogare, M. O., Andrade, C. F., Zardo, L., Leal, M. H. & Matiello, J.

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Introduction- Radiotherapy is one of the pillars of the treatment of lung cancer and it can be used as an ablative therapy alone in the early stages of the disease or combined with chemotherapy in more advanced stages (1). Despite its curative role in many settings, radiotherapy is not without side effects. One of the most unwanted side effects is radiation pneumonitis (RP). RP is an inflammatory response resulting from damage to the irradiated lung parenchyma (2) that typically occurs within six months of treatment completion (3).

Several factors appear to be associated with the risk of developing RP and its severity, including patient-related, tumor-related, and treatment-related dosimetric factors, as well as tumor size and location (4). Patients receiving chemoradiotherapy or with prior lung resection are also in the group of patients at high risk of developing RP (5-6). However, the analysis of all these variables in the calculating toxicity potentials is uncommonly performed due to the lack of suitable algorithms.

GJMR-F Classification: NLMC Code: WN 250

Strictly as per the compliance and regulations of:

Are Known Lung Dose Limits Valid for All Patients?

Dalenogare, M. O. [α], Andrade, C. F. [σ], Zardo, L. [ρ], Leal, M. H. [ω] & Matiello, J. [¥]

I. Introduction

Radiotherapy is one of the pillars of the treatment of lung cancer and it can be used as an ablative therapy alone in the early stages of the disease or combined with chemotherapy in more advanced stages (1). Despite its curative role in many settings, radiotherapy is not without side effects. One of the most unwanted side effects is radiation pneumonitis (RP). RP is an inflammatory response resulting from damage to the irradiated lung parenchyma (2) that typically occurs within six months of treatment completion (3).

Several factors appear to be associated with the risk of developing RP and its severity, including patient-related, tumor-related, and treatment-related dosimetric factors, as well as tumor size and location (4). Patients receiving chemoradiotherapy or with prior lung resection are also in the group of patients at high risk of developing RP (5-6). However, the analysis of all these variables in the calculating toxicity potentials is uncommonly performed due to the lack of suitable algorithms.

There is essential heterogeneity among patients receiving radiotherapy. Currently, the rate of lung cancer in non-smokers has been increasing synchronously with the increase in the diagnosis of adenocarcinoma and inversely with the diagnosis of squamous cell carcinoma and small cell lung cancer (7). In any case, the number of smokers and patients with previous lung diseases who develop lung cancer is high (8). Such diseases include chronic obstructive bronchopulmonary disease (COBPD) and interstitial lung disease (ILD) and are significant risk factors for cancer. A study published in 2015 demonstrated that patients with COBPD had a higher incidence of pneumonitis associated with consolidation in the irradiated volume (52%) than those without COBPD (16%) (9). The benefits of radiotherapy are well known, but it is essential to pay attention to the particularities of patients to adjust their treatment to minimize pulmonary complications and improve clinical outcomes (10).

Lung densitometry is a method that can differentiate healthy tissue from emphysematous or fibrotic tissue (11, 12). This diagnostic method measures lung density and classifies the tissue according to its ability to attenuate X-rays in computed tomography (CT) studies. CT lung density measurements are expressed in Hounsfield units (HU) (13), and the different densities obtained characterize the tissue, reflecting the degree of lung damage. For example, decreased X-ray attenuation occurs in emphysema and cystic lung disease, whereas increased X-ray attenuation occurs in pulmonary fibrosis.

In patients with lung cancer who are candidates for radiotherapy treatment, densitometry provides additional information about the patient's clinical condition (14,15), in addition to the possibility of visually mapping the whole lung tissue and its different densities (figure 1).

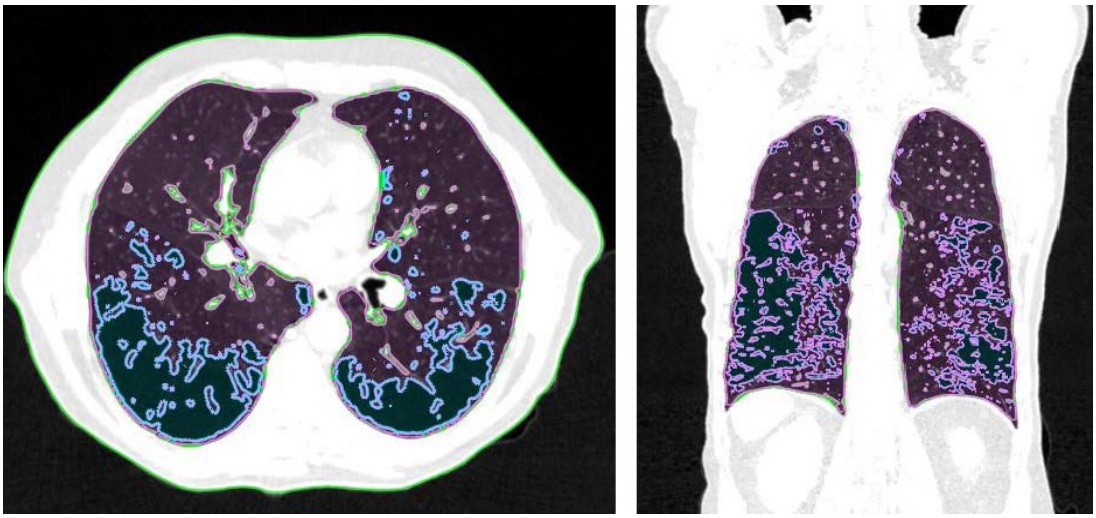

Figure 1: Visual representation of emphysema (blue), normal tissue (pink), and fibrosis (green)

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II. Materials and Methods

Patients receiving lung stereotactic body radiotherapy (SBRT) for early-stage primary lung tumors (stages I and II) between 2017 and 2022 at Santa Casa de Porto Alegre, Brazil, were selected. Patients with CT scans with a millimetric slice thickness obtained at 120 kV and 80 mAS during forced inspiration were included.

All CT scans were examined for their lung density characteristics. Lung density measurements were made on radiotherapy planning CT scans, obtained with a 64-slice CT scanner (Ingenuity Core 64; Philips Healthcare, Cleveland, OH, USA). The structures of interest were outlined using the Eclipse radiotherapy planning system v15.6 (Varian Medical Systems, Palo Alto, CA, USA). The structures of interest were defined as "Right Lung," "Left Lung," and "Lungs" (both lungs drawn as a single structure) and automatically segmented, as were the structures corresponding to the different density ranges to be analyzed.

CT lung density measurements are expressed in HU, a quantitative scale for describing radiodensity divided into 2048 density values, where water is arbitrarily defined to be 0 HU, air is defined as −1000 HU, and bone density as 1000 HU (16). Quantitative indices of emphysema show low attenuation values, corresponding to the proportion of lung volume with attenuation between −1000 and −950 HU (17). Functional lung volume can be measured with attenuation between −950 and −700 HU, and for fibrosis, attenuation values range from −700 to −200 HU (18).

The structures corresponding to the attenuation ranges were obtained using the "Image Thresholding" tool (figure 2), which allows manual selection of HU values. They were defined as "Emphysema" for attenuation ranging from −1000 to −950 HU, "Normal Tissue" (functional lung volume) for attenuation ranging from −949 to −700 HU, and "Fibrosis" for attenuation ranging from −699 to −200 HU. The attenuation values of −949 HU and −699 HU were used to avoid data duplication. The volumes were then measured and recorded in a table.

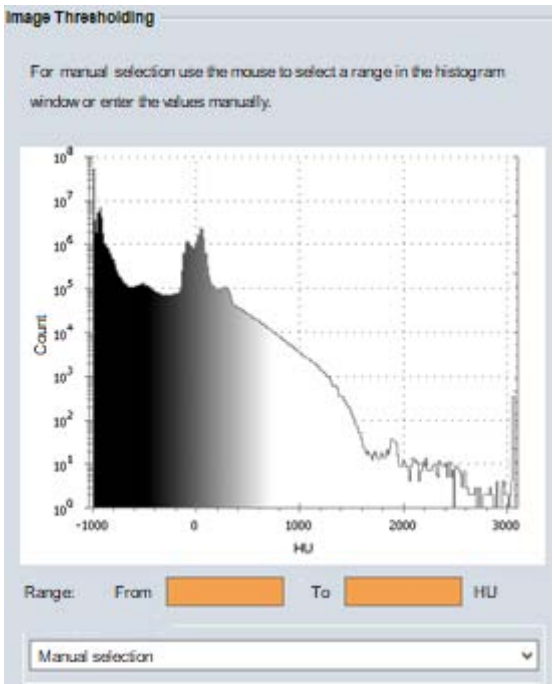

Figure 2: Image Thresholding Tool

Given its importance in the clinical and oncological treatment of patients with lung cancer, emphysema was divided into three groups. Emphysema was considered insignificant when it involved less than 5% of the total lung volume, and severe emphysema was defined as involvement more significant than 15% (19). Fibrosis was considered a single group.

Continuous variables are expressed as mean (SD) if normally distributed. Categorical variables are expressed as counts and percentages. Continuous variables were compared using t-tests or the Wilcoxon rank sum test. Data were analyzed in SPSS, version 29.0 (SPSS Inc., Chicago, IL, USA).

III. Results

CT data from 39 patients were analyzed. The mean patient age was 71.5 years, and most were female, accounting for 61.5% of the sample. The most common histological type in biopsied patients was adenocarcinoma (62.5%), and the tumor site showed no predilection for any particular lobe.

Table 1: Baseline characteristics of the sample

Variable	n=39
Age (years) – mean ± SD [min – max]	71.7 ± 7.9 [55 – 87]
Sex – n(%)	
Male	15 (38.5)
Female	24 (61.5)
Staging – n(%)	
Primary tumor with pathological diagnosis	31 (79.5)
No pathological diagnosis, or inconclusive	8 (20.5)
Histological type – n(%)	
Adenocarcinoma	20 (51.3)
Squamous cell carcinoma	12 (30.8)
No biopsy	7 (17.9)
BED (Gy) – mean ± SD [min – max]	152.2 ± 37.2 [85 – 180]
Tumor site – n(%)	
RLL	9 (23.1)
LLL	9 (23.1)
RML	1 (2.6)
RUL	10 (25.6)
LUL	10 (25.6)

BED, biologically effective dose; RLL, right lower lobe; LLL, left lower lobe; RML, right middle lobe; RUL, right upper lobe; LUL, left upper lobe.

Of the total sample, 26 patients (66.7%) had no or insignificant emphysema (less than 5% of the total lung volume), 7 (17.9%) had 5% to 15% of whole lung tissue with emphysema, being defined as mild-to-moderate emphysema, and 6 (15.4%) had severe emphysema, with greater than 15% of the total lung volume being emphysematous. Tissue with attenuation areas corresponding to fibrosis was found in 7.5% (SE, 1.21).

Table 2: Percentages of emphysema, normal tissue, and fibrosis on CT scans obtained at sustained maximal inspiration

Percentages	Inspiration Mean ± SE
Emphysema	5.51 ± 1.30
<5%	26 (66.7%)
5% to 15%	7 (17.9%)
>15%	6 (15.4%)
Normal	82.1 ± 1.56
Fibrosis	7.5 ± 1.21

IV. Discussion

There is consensus on the indication of radiotherapy in non-operated patients, both in the early and advanced stages of disease. A 5-year tumor control rate of 90% can be achieved with ablative radiotherapy (20-22) or hypofractionated radiotherapy for early-stage tumors (23), generally with low toxicity, but not without toxicity, with reports of grade 5 toxicity (24), especially in more centrally located tumors. In the treatment of more advanced tumors, the 5-year local control rate is less than 30% (25), with high rates of severe pneumonitis (grades 3 to 4) affecting one-third of patients when radiotherapy is combined with chemotherapy (26, 27), the standard of care for locally advanced tumors (28).

When evaluating radiotherapy planning, dose limits for irradiation of normal lung tissue are tabulated generically. Studies on lung toxicity in three-dimensional treatment suggest that the mean dose to both lungs, excluding tumor volume, should remain below 20 Gy. In comparison, it is prudent to limit the lung volume receiving 20 Gy to 30%, perhaps reaching 35% (V_{20Gy}≤30-35%) (29), regardless of tumor stage. In ablative radiotherapy, the allowed doses have a different absolute number, but they also treat all patients with dose escalations, regardless of patients' pre-existing lung function and tumor stage. Such doses are V_{20Gy}<10%, not exceeding the limit of 15%. In addition, the doses must not exceed 12.5 Gy for the critical

volume of 1500 cc and 13.5 Gy for 1000 cc (30-31). The use of V_X-based dose analysis ("V" volume of normal lung receiving a dose of "X" Gy) is attractive because this metric can be readily obtained via the dose-volume histogram (DVH). However, as pointed out in the QUANTEC report on pulmonary toxicity, V_X cutoffs may not be universal. The percent volume receiving a dose of "X" may depend on the treatment technique and does not allow the inclusion of other toxicity factors associated with the actual final toxicity (32).

In general, in the dose limits suggested in the literature, patients with severe lung disease have their normal tissue considered within the same dose limits as those for patients without any functional changes. The tissue volume considered normal is the tissue without tumor (32, 33), that is, excluding the target volume. Therefore, emphysematous or fibrotic areas, known to be entirely non-functional, are regarded as "normal" tissue in the volume.

For lung density analysis, we only included patients with a well-documented inspiration breath-hold technique. For this reason, we chose to analyze patients who would receive SBRT, as this group has a more detailed CT analysis than patients who receive conventional fractionation. It is known, however, that most patients receiving SBRT have clinical conditions unfavorable to surgery, which is still the standard treatment for early-stage tumors (34, 35), whether due to chronic lung disease or other comorbidities. Therefore, our sample has more patients with advanced lung disease than the group of all patients with lung cancer.

Despite the small sample size, the data corresponding to mild-to-moderate emphysema (17.9%) in patients with lung tumors are consistent with data from the literature (36). In the current study, severe emphysema was present in 15.4% of patients, which implies that these patients have limitations, that is, symptoms of their underlying lung disease. When receiving ablative or conventionally fractionated radiotherapy, these patients are more likely to develop clinical and radiological pneumonitis.

V. Conclusion

Several studies have demonstrated that accurate quantification of lung density can be helpful in various clinical applications, such as the diagnosis and monitoring of lung diseases, medical procedure planning, and assessment of treatment response. In this study, it was possible to expand the use of tools currently available in the SBRT protocol, such as CT scan at inspiration and resources available in the planning system. The results based on lung densitometry provide essential information about the clinical characteristics of patients who are candidates for radiotherapy treatment, which can be helpful for future research and understanding specific lung conditions, allowing a personalized DVH assessment.

In conclusion, radiation dose-volume effects on the lung play an essential role in the developing pulmonary complications after radiotherapy. A personalized approach, considering risk factors and using advanced techniques, can help minimize these effects and, consequently, improve the quality of life of patients undergoing treatment.

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1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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