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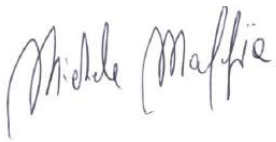

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The mechanobiology of the nucleus

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Abstract

In addition to biochemical and molecular signals coming from the microenvironment, cells are able to sense and integrate mechanical stresses, additional fundamental regulators of cell behaviour. Emerging demonstrations indicate that mechanical cues go far beyond the plasma membrane and the cytoskeleton, since, exerting tension on the outside local microenvironment via adhesions, cells develop an equal cytoskeletal stress on the nucleus inside, leading to 3D nuclear modifications. In this context, dynamic changes in nuclear lamina and the surrounding cytoskeleton modify mechanical properties of the nucleus affecting its structural arrangement, chromatin anchoring, 3D chromosome conformation and gene expression. Here we discuss findings supporting the role of the nucleus in cellular mechanosensing, ranging from how mechanical cues are transduced to the nucleus to how genome organization is influenced by cell mechanics.

Keywords: nucleus, mechanosensing, mechanotransduction, nuclear lamina, nucleoskeleton

1. *Introduction*

It is well established that cells are able to sense and integrate information from the microenvironment, consequently influencing cell morphology and biological processes, such as development (Mammoto and Ingber 2010), cell migration (Mierke 2020) and tissue homeostasis (Barnes, Przybyla, and Weaver 2017). Beside the biochemical and the molecular composition of the cellular microenvironment, extensively studied as regulators of cell behaviour and cell fate, mechanical forces play an important role in this context (Humphrey, Dufresne, and Schwartz 2014; Iskratsch, Wolfenson, and Sheetz 2014; Cho, Irianto, and Discher 2017; Janmey, Fletcher, and Reinhart-King 2020). Physical forces, to which we are referring, originate from neighbouring cells (cell-cell interactions), from the extracellular matrix (cell-ECM interaction) and from the biofluids that surround cells. Since the discovery of the mutual relationship existing between cells and ECM (Bissell and Aggeler 1987), the molecular mechanisms by which cells sense and respond to ECM mechanical cues have become the subject of intense explorations and several molecular key players have been identified, able to react to mechanical stimulation and to transform these signals in biological response.

Mechanical forces exerted on tissues are sensed by resident cells as stimuli to be processed and transmitted through ECM constituents (collagen and elastin), trans-membrane structures (stretch-activated ion channels, adhesion complexes, cell-cell junctions) and intracellular structures (cytoskeleton). In general, cells are able to sense extracellular mechanical inputs by multiple manner. For instance, the mechanoelectrical transduction of signals, through mechanosensitive channels, leads to the conversion of forces in electrical signals and plays an important role in several physiological dynamics such as hearing, equilibrium, touch and the regulation of blood pressure (Douguet and Honoré 2019). Moreover, integrins trans-

membrane receptors (in focal adhesions) connect ECM with actomyosin-cytoskeleton mainly through integrin linker proteins, such as talin and vinculin; likewise, cadherins (in adherent junctions) mechanically connect neighbouring cells. Several demonstrations showed that mechanosensing and mechanotransduction are not only restricted to cell surface, but can take also place in the nucleus, due to determinants linked to the correct interplay between the cytoskeleton and the nucleoskeleton, the integrity of the nuclear lamina and the degree of chromatin compaction.

The first proof describing the mechanical connection between plasma membrane and the nucleus goes back to the discoveries of Maniotis and colleagues, in 1997: mechanical forces exerted on integrins, caused cytoskeletal rearrangements, nucleoli repositioning along the stressed area and nuclei distortion (Maniotis, Chen, and Ingber 1997). Since then, several theories have been developed about the role of the nucleus as cellular mechanosensor and mechanotransducer, recognizing the nuclear envelop as a dynamic force-sensitive connection between cytoplasm and chromatin (Fedorchak, Kaminski, and Lammerding 2014; N. Wang, Tytell, and Ingber 2009; Cho, Irianto, and Discher 2017). Among these, Guilluy and colleagues showed that isolated nuclei, much like plasma membrane, were able to resist to applied tensions by adapting their stiffness, due to a properly-functioning nuclear lamina and the phosphorylation of emerin, a mechanosensitive protein placed in the inner nuclear membrane (Guilluy et al. 2014). The modulation of the 3D nuclear organization leads, as consequence, to the reorganization of chromosomes inside and regulation of gene expression (Lanctôt et al. 2007; Dekker and Mirny 2016).
In this review, we will provide a brief overview about the key players of the nuclear mechanosensing and their modifications, shedding light on how mechanical forces affects chromatin structure and gene transcription.

2. *Nucleus, nuclear lamina and lamin A/C*

A basic overview of the molecular architecture of the nucleus, and its envelope, may be useful in order to understand how mechanical stresses are transmitted to, and perceived by, the largest organelle of a cell, linking the structure to the function.
The nucleus is enclosed in the inner (INM) and the outer lipid nuclear membrane (ONM), and nuclear pores connect the cytoplasmic space with the nuclear compartment, allowing the passage of large molecules such as RNA and transcriptional factors (TFs). The nuclear lamina is located immediately below the INM. It consists of a dense fibrillar network (~25-50 nm), mainly built by filamentous lamin proteins, providing mechanical support to the nucleus (Crisp et al. 2006; Versaevel et al. 2014). Importantly, lamin building blocks interact with other nuclear transmembrane proteins, such as LAP-2, emerin and MAN1 (LEM-domain containing members) (Barton, Soshnev, and Geyer 2015), as well as with chromatin domains, regulating its organization and gene expression (Zullo et al. 2012), and with diverse transcriptional factors (Rodríguez et al. 2010; Lloyd, Trembath, and Shackleton 2002; Wilson and Foisner 2010). Lamins connect the nucleus with cytoskeleton through the "linker of nucleoskeleton and cytoskeleton" (LINC) complex, responsible for the transmission of forces from the cell surface to the nucleus (Maniotis, Chen, and Ingber 1997). It consists of nesprin proteins, which are located in the outer nuclear membrane and communicate with all major cytoskeletal components on the cytoplasmic side. The C-terminal KASH domain of nesprin proteins allow them to interact with SUN domain-containing proteins, in the inner nuclear membrane, which interface with nuclear lamina, nuclear pores and chromatin (Chang, Worman, and Gundersen 2015). Figure 1.

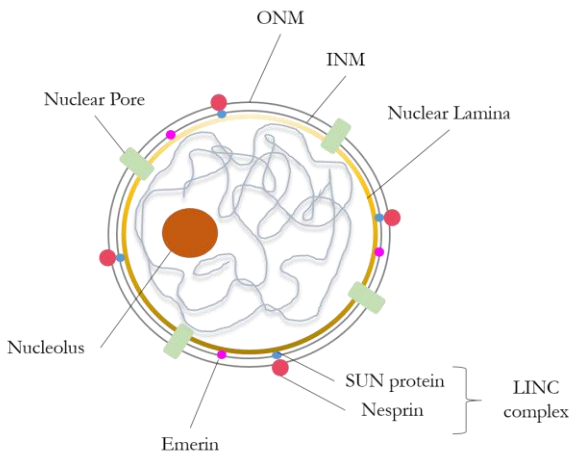

Figure 1. schematic representation of the nucleus and nuclear envelope.

Based on this description, it is easy to deduce how strategic the spatial location, and the interactions, of the nuclear lamin proteins can be. Probably taking inspiration from this, several studies have been published underlying the contribution of its components, as relevant mechanosensitive and mechanotransducer elements. Lamins, members of intermediate filament family, are classified into A- and B- type (Prokocimer et al. 2009). Lamin A and C are the major A-type lamin isoforms represented in mammalian somatic cells, derived by alternative splicing of LMNA gene. Instead, lamin B1 and B2, encoded by LMNB1 and LMNB2 genes respectively, are the major B-type isoforms. As evidenced by diverse works, the lamin A/C seems to have great impact in mechanosensing events, without affecting lamin B1/B2. Mechanical forces, exerted by matrix stiffness on cells and nuclei, or by cells themselves, induce conformational modifications and subsequent changes in phosphorylation state and protein level in lamin A/C dimers (Buxboim et al. 2014). In particular, Swift and colleagues demonstrated that mesenchymal stem cells cultured on soft matrix gels resulted round with wrinkle nuclei, due to the higher phosphorylation of serine and threonine specific residues on lamin A/C, resulting in destabilization and protein turn-over. On the contrary, cells cultured on stiffer matrixes appeared stretched with flattened nuclei, due to lamin A/C conformational changes responsible for sterically hidden serine and threonine phosphorites and subsequent higher stabilization of the dimers. Overall, mechanical tension exerted on nuclei suppresses lamin A/C degradation, while an unstressed condition induced dimers turnover, correlating protein and nucleoskeleton stability with matrix elasticity.

It has been shown that the proper ability to respond to mechanical forces is damaged by nuclear fault. In this context, the role and the functions of lamin A/C on nuclear mechanotransduction have been derived also from the study of LMNA gene mutations-inducing laminopathies. In general, laminopathies are associated with a wide range of disease phenotypes, including metabolic disorders and premature aging syndromes (Maggi, Carboni, and Bernasconi 2016), but the most frequent are linked to skeletal muscle and cardiac muscle, causing diseases like Emery-Dreifuss muscular dystrophy (Vigouroux and Bonne 2002). The dominant association of many LMNA mutations to such mechanically dynamic tissues, further confirms the great implication of these lamin components in the nuclear mechanotransduction machinery, taking part in nuclear stability (Zwerger et al. 2013) and nucleo-cytoskeleton coupling (Folker et al. 2011).

3. Mechanical forces and chromatin organization

The three dimensional nuclear organization has an important role in modulating gene expression, through the control of the relative position of chromosomes inside. Diverse genomic processes, such as transcription (Sutherland H., 2009) and DNA recombination (Misteli T., 2009), are influenced by chromatin topology within the nucleus. Transcriptionally active, and less condensed, euchromatin is mainly distributed in the center of the nucleus and close to the nuclear pores; transcriptionally inactive, and more condensed, heterochromatin typically interacts with nuclear lamina, via lamin-associated domains (LADs), and with nucleoli (Lemaître C., 2015). Based on this, alterations of the dynamic structural conformation of the nuclear lamina affect both nucleus arrangements, as argued before, chromatin anchoring and 3D chromosomes conformation (Bascom G., 2017), getting impact on transcriptional activity without biochemical mediation.

Cells plated on soft matrixes showed high chromatin motility in the nucleus, in addition to a higher nuclear motility, as demonstrated by Makhija and colleagues. Their work highlighted that the reduced interaction between cells and ECM, led to tiny actomyosin structures, reduced lamin A/C expression levels, softer nuclei and increased dynamics of heterochromatin and telomere structures (Makhija E., 2016). The down-regulation of lamin A/C, not only leads to reduced interaction between chromosomes and INM, but also to the establishment of regions of chromosomes intermingling, hosting clusters of genes spatially organized by related TFs and associated with active RNA pol II, optimizeing the mechanical state of the cell (Wang Y., 2017). Moreover, the disruption of actomy-

osin contractility, through Blebbistatin, resulted in cytoplasmic-to-nuclear translocation of HDAC3, finally resulting in increased chromatin condensation in an actomyosin dependent manner (Jain N., 2013). These works represented pivotal descriptions of the mechanical control of chromatin condensation and gene expression, mediated by the differential positioning of chromosomes, transcriptional factors (TFs) and chromatin modifiers.
Stem cells have been interesting models through which to study the interplay between cytoskeletal and nuclear mechanics. Lamin A/C levels in these cells, indeed, increase with differentiation according with tissue stiffness (Swift J., 2013). Isolation of stem cell nuclei, through micromanipulation methods, showed a nuclear plasticity and a deformation responsivity which progressively decreased as cells undergo differentiation (Pajerowski, J. D., 2007). Later, timelapse experiments showed a progressive chromatin topology stabilization, due to a stiffer and more mature nucleus, and the development of mechanosensitive properties (Mazumder A., 2009) (Heo SJ, 2016).
Such genomic modulations are fundamental for establishing cell type specific organization of chromosomes and their accessibility to TFs and chromatin modifiers.

4. Mechanosensitive TFs

The best-characterized mechanosensitive TFs, downstream transducers of Hippo cascade, are YAP and TAZ (Dupont et al. 2011), whose cellular distribution depends on F-actin cytoskeleton conformation and tension. Aspects related to cell shape, mechanical stress, ECM stiffness and topography are closely correlated to this point (Aragona et al. 2013; Calvo et al. 2013; Halder, Dupont, and Piccolo 2012; Schroeder and Halder 2012). Although it has been shown that YAP and TAZ mechanotransduction require actin cytoskeleton integrity (Piccolo, Dupont, and Cordenonsi 2014), the specific mechanisms by which actin cytoskeleton impact this signaling in the context of mechanotransduction is not clear (Zou et al. 2020). In general, as discussed above, cells plated on large and stiffer substrates appear to spread and with flattened nuclei, due to cytoskeletal tensions generated by high ROCK- and non-muscle myosin II, ultimately resulting in YAP/TAZ nuclear translocation. Conversely, cells appear to have reduced adhesive area on softer substrates, resulting in YAP/TAZ cytoplasm retention (Aragona et al. 2013; Dupont et al. 2011). Phosphorylation by LATS represents the main sequestration-tag of YAP/TAZ in the cytoplasm (Basu et al. 2003), even if this theory is not completely coherent with all the experimental findings (Wada et al. 2011). Nuclear entry of YAP and TAZ can induce a wide range of downstream responses specific for each type of cells and mechanical stress. Cell proliferation is probably one of the best-investigated biological response to YAP/TAZ activity (Mizuno et al. 2012; Zanconato et al. 2015), regulating expression of genes directly (cyclins and mitotic kinases) or indirectly involved in cell cycle (other TFs, such as Myc) (Croci et al. 2017). Furthermore, YAP/TAZ activity was found to be regulated by metabolic pathways (aerobic glycolysis and mevalonate synthesis) which, in turn, determine cellular metabolic reprogramming through the transcriptional regulation of genes involved in nucleotide biosynthesis (Cox et al. 2016), glutamine metabolism (Edwards et al. 2017) and glycolysis enzymes (W. Wang et al. 2015; Zheng et al. 2017). It has been shown that fibroblasts plated on polarized geometries expressed more genes related to cytoskeleton and matrix components and, instead, the same type of cells plated on isotropic geometries expressed more cell cycle and cell-junctions genes, in comparison. This was due to the resulting nuclear import of TFs implicated in serum response pathway and NF-κB pathway, respectively. MRTF (also known as MKL/myocardin-like protein) is a TF bound to G-actin monomers in the cytoplasm. Increased cell polarization results in G-actin polymerization in F-actin stress fibers and consequent increased release of MRTF in the nucleus, where it interacts with serum responsive factor (SRF). A reduced cell polarization, results in actin depolymerization (and resulting reduction in actomyosin contractility), increased concentration of G-actin monomers and MRTF retransfer from the nucleus to the cytoplasm; meanwhile, p65, TF related to NF-κB pathway, translocate from the cytoplasm to the nucleus. In addition, as described previously, actin depolymerization is, accompa-

nied by HDAC3 shuttling to the nucleus making the chromatin more condensed.

5. Conclusions

Since the first evidence proving the mechanical connection between plasma membrane and the nucleus in 1997, significant efforts have been made in understanding the molecular complexity of cellular mechanosensing and mechanotransduction. Many recent studies demonstrate that nuclear lamina, as well as chromatin itself, can sense and integrate mechanical forces exerted on, or by, the cytoskeleton, consequently determining the activation of cell-/tissue-specific molecular dynamics. Alterations of, or lack in, these structures may lead to a variety of recognized diseases. Although many steps forward have been taken, deeper insight are required in order to boost our understanding in these processes as well as new therapeutic approaches for the large number of disease linked to changes in components of nuclear envelope.

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The impact of COVID- 19 in women with intimate partner violence (IPV): a psychological and psychophysiological study.

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Abstract

Domestic violence is characterized by coercive actions of various kinds (psychological, physical, sexual and economic) that persist over time; the chronicity of these same actions implies the development of short, medium and long term consequences that compromise the daily functioning of the woman. The aim of this study was to investigate, through a web Survey based on psychophysiological assessments, the relationship between the stress perceived with intimate partner violence and the dysfunctional coping strategies used during the pandemic phase 1 of the health emergency in Italy. The results highlighted a greater sensitivity to perceived stress, resulting in the use of dysfunctional strategies in the management of emergency situations. The levels of perceived anxiety are decreased. High levels of perceived stress produced effects in the management of the health emergency situation, consequences of behavioral, emotional, perceptual and psychophysiological nature (i.e, pain perception, sensory perception, sleep habits).

Keywords: traumatic event, intimate partner violence (IPV), covid-19, psychological consequences, smell, sleep disorder, coping strategies, perceived stress.

1. *Introduction*

The current view means that we are talking about gender violence with direct reference to violence against women, taking into account the cultural imbalance between the sexes and the desire for control and possession by the male gender over the female gender. The violence exercised by men against women can be of different types: physical, verbal, sexual, economic, psychological, domestic and stalking.
Domestic violence or also defined as Intimate Partner Violence is a gender-based violence that affects one in three women (WHO, 2013; Heise and Garcia 2002) and consists of a pattern of continuous abusive and coercive behavior over time by the partner or ex-partner in order to obtain total control over the woman's life.
The abusive relationship becomes the yardstick of one's personal value, the only meaning of one's life, leading the victim to maintain a relationship with frustrating partners, who undermine the self-esteem of the other by attributing to the victim the responsibility for the behavior of others, favoring in the latter feelings of guilt to the point of feeling forced into sacrificial acts, remedial trying to always be available towards the other by putting the needs of the other before their own, accepting increasingly unpleasant situations in the face of an inability to refuse inappropriate requests .
A dependent, pathological relationship then develops which leaves to putting aside individuality and which produces closure, alienation, insecurity and in the worst cases death of victims.
Data in the literature suggests that violence, including IPV, increases during humanitarian crises and emergencies (Roesch et al. 2020; Stark and Ager 2011; Schumacher et al. 2010; Bell and Folkerth 2016); this data is confirmed by the trend of new reports received during the health emergency caused by COVID, highlight-

ing an initial block of requests for help from women victims of violence which were only subsequently reinstated.
This picture resulting in serious health problems for victims (Buttell and Ferreira 2020; Chandan et al. 2020; Moreira and Pinto da Costa 2020).

2. *The short, medium and long-term consequences of IPV*

The major consequences found cover different areas and are characterized by the chronicity with which they occur. From a behavioral point of view, a tendency towards avoidance, impulsiveness and procrastination has been highlighted (Matlow and DePrince, 2013). Emotionally difficulties such as anxiety, shame, guilt, difficulty regulating and / or managing emotions are particularly present (Street and Arias, 2001; Barlow et al. 2004;). Psychosomatic reactions (alexithymia resulting from the exceptionally high level of anxiety that from functional becomes chronic and abnormal), intrusive reexperience, hyperreactivity, dulling of sensitivity (they use their energies to avoid the internal sensations that cause stress or to control them by manifesting withdrawal emotional in the form of depression, anhedonia, lack of motivation, dissociative states) and intense emotional reactions (loss of ability to regulate affects with immediate and intense response) (Liotti and Farina, 2011). Attempting to manage a past traumatic emotional experience that tends to be experienced daily as still current (Ehlers and Clark, 2000) can lead to the use of maladaptive strategies aimed at avoiding the intense unpleasant symptomatology experienced.
Regarding the cognitive and neuropsychological aspects (Wong et al. 2014) there are often learning difficulties related to concentration difficulties and physiological hyperactivity (high levels of arousal) which over time with chronicization the difficulty turns into physiological hypoactivity as well as impaired memory and functioning of executive skills; a significant difficulty emerges in the recognition of emotional stimuli such as to determine and maintain difficulties in interpersonal relationships (Hayward, Honegger, and Hammock 2018; Barnawi 2017). Physiologically and cognitively, recent studies have found a particularly high sensitivity threshold regarding emotional and nociceptive stimuli such as to support the normalization of particular acted out and a difficulty in functional reading of the same stimuli (Invitto, et al., 2017; Almli et al. 2014). Recent discoveries in the field of cognitive neuroscience have highlighted the main brain regions involved in addiction and what role they operate in a pathological condition. Today we can attribute a key role to the following areas: prefrontal cortex, responsible for cognition and planning; ventral tegmental area (VTA) of the midbrain and nucleus accumbens (NAc), both part of the so-called "Circuit of gratification"; amygdala and hippocampus, part of the limbic system, modulator of impulses, emotions and memory (Young, 2007; Winsolw et al. 2003).
Emotional dysregulation appears to be a particularly relevant factor in understanding the development and maintenance of abusive relationships (Riggs, Caulfield, and Street 2000). Many models have been hypothesized to explain emotional dysregulation Gross 1998; Lazarus and Folkman 1984). In general, it highlights how the reactivity of the sympathetic nervous system, the serotonergic activity (resistance to stress, sleep regulation, impulse control, conditioned avoidance, aggression and mood) and the limbic nuclei (responsible for the regulation of emotions and fear) following a traumatic event are altered, highlighting an excessive reactivity which often persists over time. Using neuroimaging techniques, recent studies suggest that emotional dysregulation is associated with reduced cortical inhibition of limbic circuits and imbalances in γ-aminobutyric acid (GABA) aminergic and glutaminergic transmission. Therefore, considering the consequences developed following domestic violence, it is reasonable to hypothesize that the mere interruption of the abusive relationship is not sufficient to protect the health of the woman, but that in a condition of health emergency it can be considered a risk factor for the development of management. and adaptation difficulties in the current health emergency. The aim of the following work was therefore to investigate the perceived stress and its relationship with emotional, cognitive, behavioral and sensory functioning during the period of lockdown due to

Covid 19 in Puglia in a group of women victims of domestic violence who had already interrupted the abusive relationship.

3. Participants

A sample of 15 women with intimate partner violence, was recruited in a Center Against Violence, the 'Centro Antiviolenza Renata Fonte' in Lecce, (Italy) . All the participants interrupted the cohabitation and the relationship with the perpetrator before the quarantine. The IPV women were healthy adults (mean age = 41.3; sd ± 9.7). The sample was recruited in the period from 30 April to 30 May 2020; all subjects participated to the study via a link sent to them directly by the operators of the Center Against Violence. All the participants spontaneously joined the research and did not receive any financial compensation following their participation. All data were anonymous, unidentifiable and numerically coded for statistical purposes.
All participants read and signed the informed consent before starting the questionnaire, as required by the Helsinki declaration. They have also signed (law no. 675, 676 of 31 December 1996, Official Gazette of 08/01/1997, art. 7 of Legislative Decree 30 June 2003, no. 196 and EU Privacy Regulation 2016/679, General Data Protection Regulation - GDPR) on the processing of personal data and respect for privacy, all data (including sensitive data) have been treated strictly anonymously. The research was approved by the Ethics Commission for Research in Psychology of the University of Salento on 29-04-2020.

4. Materials and Methods

The IPV women compiled, during the Italian lockdown, an online survey. The survey was divided into two section: the first one included questions of personal, socio-economic and exploratory nature regarding the coping methods adopted by women for the management of the emergency period; the second section included a series of behavioral questionnaires aimed at investigating the neuropsychological, cognitive, emotional and perceptive functioning of women.
In particular, the tests administered were: the Perceived Stress Scale (PSS) (Mondo, Sechi and Cabras, 2019) a self-administered tool for measuring the perception of stress and to measure the level at which people find their lives unpredictable, uncontrollable or overloaded;PSS item concern feelings and thoughts relating to the last month. For each item, people are asked to indicate how often they felt a certain way (likert scale), the Cognitive Estimates Test (Mondini et al. 2011) five questions to evaluate the subject's critical response capacity of requests that do not necessarily require an unambiguous and precise answer but that must be estimated and evaluated with respect to the general knowledge of the world., The Beck Anxiety Inventory (Sica et al. 2006), a self-assessment scale which allows to assess the severity of anxiety symptoms in adults.
The Body Perception Questionnaire BPQ (Porges, 1993), a self-assessment scale of one's perceptual and sensorial sensitivity (sight, hearing, taste, smell, touch), and an item on any perceived variation in eating habits.

5. Data Analysis

Descriptive statistics were performed to describe the demographic and socio-demographic characteristics of women. By analyzing the distributions of the data, correlations were carried out in order to evaluate any associations between the variables. In the case of significative correlation, regression analysis was also performed in order to determine the link between the variables. All statistical analyzes were performed using R Studio.

6. Descriptive analysis

The younger IPV women reported higher educational qualifications, while educational. The greater percentual of the sample (i.e, 66.6%) showed different types of violence. Psychological violence was more evident in the lower age groups (age<40), while multiple violence was more evident in older women (age>40) .
In relation to the family structure, younger age women spent the quarantine with their family of origin, while older women spent the quarantine alone or with their children. The PSS showed higher values in conditions of sharing the quarantine with the family of origin. IPV women showed sleep disorders, linked to an in-

creased perceived stress in women who developed difficulty in falling asleep. 54% of the sample highlighted obsessive search for information relating to Covid-19 as the strategy used during the quarantine, 27% employed avoidance and the remaining 27% used functional modalities (adaptation of their routines to the new daily life) (Figure 1).

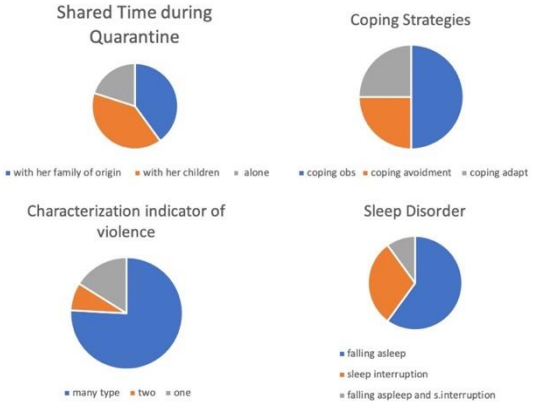

Figure 1: Descriptive data of IPV sample

7. *Behavioral Data*

Behavioral data analysis showed the PSS values increased, with the use of dysfunctional coping strategies, linked to the development of sleep disorders and a variation in sensory perception (i.e, olfactory perception). Furthermore, the PSS correlated with the use of dysfunctional coping strategies, with the development of sleep disorders and with a decrease of olfactory perception. Therefore, the relationships between the variables investigated were analyzed in order to analyze a possible dependency relationship.

The PSS values were higher in a positive correlation (r=0.874) of the quality and quantity of violence the IPV group suffered; a positive correlation (r = 0.628) was linked to body sensitivity and the types of violence; the type of violence was positive correlated to an increase of dysfunctional coping strategies (r=0.687) and sleep disorders (difficulty falling asleep) (r=0.887) ; the perceived olfactory capacity decreases according to how many types of violence are be perpetrated on the woman. Furthermore, the frequency with which dysfunctional coping strategies increased with PSS and with the onset of sleep disorders.

Multiple regression analysis found that there is a significant interaction between perceived stress and suffered violence ($\beta_1 = 2.09$); specifically, stress appears to be higher in conditions in which women have experienced multiple types of violence. Therefore, the hypothesis that the amount of violence suffered would moderate the sensitivity to perceived stress in emergency situations is supported.

Furthermore, the multiple regression analysis found that there is a significant interaction between perceived stress and the use of dysfunctional coping strategies ($\beta_1 = 0.252$); specifically, the use of dysfunctional coping strategies is more frequent in conditions in which perceived stress is higher. It was also possible to highlight a significant interaction between perceived stress and sleep disturbances ($\beta_1 = 0.373$); this interaction reveals that the onset of sleep disturbances is higher in conditions in which perceived stress is higher. A significant interaction was also found between perceived stress and olfactory perception ($\beta 1 = 0.388$). The hypothesis that perceived stress moderates the use of dysfunctional coping strategies, the onset of sleep disturbances and the reduction in olfactory perception is supported.

8. *Discussion, Conclusions and future perspectives*

This work has made it possible to highlight the close relationship between having experienced domestic violence and the perceived stress during the lockdown caused by the health emergency. Having interrupted the abusive relationship, even though it may be a protective factor, is not sufficient to protect the health of the woman victim of violence. Regardless of the nature of the violence suffered, having suffered different types of violence puts women in a condition of greater sensitivity to stress, resulting in the use of dysfunctional strategies in the management of emergency situations.

In fact, having suffered numerous types of domestic violence causes greater perceived stress during the lockdown as well as greater body sensitivity. The levels of perceived anxiety, on the other hand, are found to be below average. However, high levels of perceived stress in turn

have significant consequences in the management of the health emergency situation, consequences of a behavioral, emotional, perceptual and neuropsychological nature. Specifically, from an initial exploratory analysis it emerged that perceived stress was higher in younger women. A greater perceived stress is also found in unmarried women, with higher educational qualifications, with regular employment, but carried out due to the lockdown in smart working mode and in women who have spent the lockdown with numerous families. On the other hand, with the advancing of age there is a lesser awareness of one's own body reactivity, greater perceived anxiety and greater neuropsychological difficulties. The perceived stress level is therefore configured as a factor correlated with the violence suffered and in a relationship of dependence with a greater frequency in the use of dysfunctional coping strategies (obsessive search for information relating to Covid-19).

In fact, the results obtained show that as perceived stress increases, there is a greater frequency in the use of dysfunctional coping strategies, as women with greater perceived stress have more frequently emitted obsessive behaviors in search of information relating to Covid-19 as well as higher frequency in the incidence of difficulty falling asleep. The consequences experienced by this population in this specific situation of health emergency make daily functioning difficult and reinforce some basic cognitive processes that are recognized in the literature as risk factors in experimenting with domestic violence, making the risk of re-victimization higher. However, the small number of the sample, the methods of data collection (self-administration in a single country), the absence of a control group, as well as the absence of an evaluation of the same women before the health emergency, are configured as limits of this work. However, the health emergency conditions resulted in the absence of reference parameters and limited the possibility of data collection to the online mode, thus affecting the characteristics of the survey conducted. However, the work carried out made it possible to explore the functioning of the population in question during that specific period, highlighting the long-term effects of the abuse suffered. Emotional regulation difficulties emerge from perceived stress levels, leading to dysfunctional behavioral consequences. The results achieved also make it possible to highlight the importance of supporting women who are victims of violence even in this period, which cannot end with the interruption of the abusive relationship as this condition is found to be insufficient to protect her health. The achievement of an interoceptive awareness is configured as a protective factor for women, in order to develop a new self-awareness and new meanings to the lived experiences such as to allow the functional management of emergency situations as well as the implementation of functional behavioral actions.

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Automatic detection of Voice Disorders: recent literature advancements

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Abstract

A short review of some recent findings in the field of automatic voice disorders detection and classification is provided in this article. The matter is getting more and more interest due to appealing non-invasiveness of the methods as well as the good achievable performances. An increasing role is played by Artificial Neural Networks (ANN), especially Deep ones, despite the need for large amounts of data for such networks, that are not always available for the task in question. The research in this field is directed in other directions too, including the investigation of new features and the capability to process running speech other than sustained sounds.

Keywords: voice disorders, machine learning, detection, classification

1. Introduction

The analysis of abnormal voice patterns or voice disorders plays an important role in diagnosing/treating several diseases and reducing the impact on the individual's communication skills. Voice disturbances include alterations in the quality, pitch, or amplitude, among other characteristics, that diverge from voices of similar age, gender, and social groups. Voice pathology detection and classification can be accomplished by means of automatic and a non-invasive method, by capturing patient's voice samples by a microphone, a smartphone, or any voice recorder, then submitting such samples to digital systems running specific software. Even though the terms detection and classification are used interchangeably very often, they actually refer to different tasks. Voice disorder detection refers to determining whether the given voice sample was produced by a person having a voice disorder or not; voice disorder classification task involves the ability to infer the type of disorder.

In this paper, some of the most recent studies in the field of automatic detection and classification of voice disorders are outlined. The found researches cover the use of sustained vowel as well as running speech, the investigation of novel features as well as novel classification methods to improve the accuracy of the outcome. Artificial Neural Networks (ANN) are more and more employed but traditional Machine Learning classifiers such as Support Vector Machines (SVM) still have their own advantages.

The remaining sections of the paper are organized as follows. The Section 2 reviews the most popular databases used to "learn" pathological and normal speech characteristics. Sections 3 and 4 respectively present some representative recent research papers on automatic voice disorders detection (including mobile apps solutions) and classification. Section 5 focuses on speech impairments by central nervous system disorders, while Section 6 present some articles about Specific language impairment (SLI), also known as development dysphasia. Section 7 present our conclusions.

2. Databases

2.1. Massachusetts Eye and Ear Infirmary (MEEI) database

The SVD database is publicly available via the Internet, (Barry and Putzer 2020) contains not only voice samples but also electroglottographic

(EGG) signals. The signals contain the information of the glottis movement during voice phonation. The materials include vowels /a/, /i/, /u / pronounced at different pitch (low, normal and high) for 1-3 s., the sentence "Guten Morgen, wie geht es Ihnen?" (Hello, how are you?), and EGG. The files have averages of around 1 and 3 s for sustained vowels and voice samples were sampled at 50 kHz with 16 bits of resolution.

2.3. Arabic voice pathology database (AVPD)

The AVPD (Mesallam et al. 2017) was recently developed at King Saud University, Riyadh. The database contains samples of sustained vowels, words, and paragraphs. All the speakers were native to Arabic language. Dysphonic patients suffering from five different types of organic voice disorders (cysts, nodules, polyps, paralysis and sulcus) were included in the database. The database contains repeated vowels, a running speech, Arabic digits and some common words. All subjects, including patients and normal persons, were recorded after clinical evaluation.

2.4. VOice ICar fEDerico II (VOICED)

The freely available VOICED database (Cesari et al. 2018) has been realized by the "Institute of High-Performance Computing and Networking of the National Research Council of Italy (IC-AR-CNR)" and the Hospital University of Naples "Federico II". It consists of 208 healthy and pathological voices collected during a clinical study performed following the guidelines of the medical SIFEL (Società Italiana di Foniatria e Logopedia) protocol and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement. For each subject, the database contains a recording of the vowel /a/ of five seconds in length, lifestyle information, the medical diagnosis, and the results of two specific medical questionnaires.

2.5. The Cantonese perceptual evaluation of voice (CanPEV) database

The CanPEV database (Law et al. 2010) was developed by the Division of Speech Therapy, the Chinese University of Hong Kong (CUHK). It consists of speech recordings from 232 native Cantonese speakers with either normal or pathological voices. The speech was recorded with a close-talking microphone in a quiet room at 44,100 Hz sampling rate. Each subject was required to produce repetitions of sustained vowels /a/, /i/ and /u/ (each one about 3 to 5 seconds long), 30–90 seconds of read speech, spontaneous speech from few seconds to few minutes.

2.6. The HUPA Database

This database was recorded at the Príncipe de Asturias hospital in Alcalá de Henares, Madrid, Spain (Moro-Velázquez et al. 2015; Arias-Londoño et al. 2011). The dataset contains sustained phonations of the vowel /a/ by 439 adult Spanish speakers (239 healthy and 200 pathological). Originally, the data was recorded with a sampling frequency of 50 kHz and later downsampled to 25 kHz. Pathological voices contain a wide variety of organic pathologies such as nodules, polyps, oedemas and carcinomas. More details of the database can be found also in Godino-Llorente et al. (2008).

2.7. The Advanced Voice Function Assessment Database (AVFAD)

The AVFAD database (Jesus et al. 2017) contains 363 healthy voices (253 females and 110 males) and 346 abnormal voices (247 females and 99 males). All clinical conditions were registered according to the Classification Manual of Voice Disorders-I (Verdolini, Rosen, and Branski 2006). Participants were audio-recorded, producing the following vocal tasks: sustaining vowels /a, i, u/; reading of six CAPE-V sentences; reading a phonetically balanced text; spontaneous speech (Behlau 2003).

2.8. The Voice disordered and Healthy Adults Speech Database

The recordings for this database (Tulics et al. 2019) were collected at the Outpatients' Department of the Head and Neck Surgery Department of the National Institute of Oncology, Budapest, Hungary, during consultations. The most common recordings are from patients with functional dysphonia and recurrent pare-

sis. Samples from healthy people were recorded as well, these are used as comparison. All the participants had to read out loud the same eight sentence long text, titled 'The North Wind and the Sun'. This folk tale is frequently used in phoniatrics as a demonstration of continuous speech. The text was read in its Hungarian translation. The database contains a total of 450 recordings, 257 from patients with voice disorders (156 females and 101 males) and 193 people with a healthy voice (108 females and 85 males).

2.9. The LANNA children speech corpus

This database by the Laboratory of Artificial Neural Network Applications (Grill and Tučková 2016) contains speech samples of children suffering from SLI and healthy controls, i.e. normally developing children with no language or speech disorders diagnosed. The patients' group consists of 54 Czech children diagnosed with SLI in the 4 to 13 age group. Their speech was recorded in private speech and language therapist's office and doctor's office in Motol University Hospital. No information on the severity of the disorder is provided. The other (controls) group consists of 44 healthy Czech children in the 4 to 10 age group. The utterances from them were collected in school-rooms. The healthy controls subset comprises 1658 samples, while the SLI children subset comprises 2103 samples. All the recordings contain background noise as they were registered in situations simulating environment natural to the children to ensure their natural behaviour. The corpus consists of seven types of utterances: vowels, consonants, one-, two-, three-, and four-syllable words, and difficult words.

2.10. Parkinson's UI Machine Learning database

Acoustic data in this database (Little et al. 2009) consists of 195 sustained vocal phonations of 31 male and female subjects, of which 23 were diagnosed with Parkinson's disease. The age of the patients varies between 46 and 85 years (average of 65.8, standard deviation of 9.8). For each patient, averages of six phonations were recorded, with a length ranging from 1 to 36 s.

3. Some representative recent research papers on automatic voice disorders detection

AL-Dhief et al. (2020) presented a voice pathology detection system using Online Sequential Extreme Learning Machine (OSELM) to classify the voice signal into healthy or pathological, based on Mel-Frequency Cepstral Coefficients (MFCCs) as input feature. OSELM combines the advantage of good generalization performance at extremely fast learning speed of ELM (feedforward neural networks, "invented" in 2006 by G. Huang, 2006) with the capability to handle data samples obtained within packets over time (Abbas, Albadr, and Tiun 2017), instead of all at once. The voice samples for the vowel /a/ were collected equally from Saarbrücken voice database (SVD). The obtained results show that the maximum accuracy, sensitivity and specificity are 85%, 87% and 87%, respectively, showing that the proposed approach can differentiate healthy and pathological voices effectively.

While most approaches rely on feature extraction of the analysed signal with features subsequently fed into a classifier, Georgopoulos, 2020, investigated the direct use a time-frequency distribution (namely, the Wigner-Ville Distribution) of the voice signal and a deep learning classification method to automatically classify voice signals as normal or pathological. The time-frequency distribution is used as an image representation of the signal. The classification method is based on transfer learning of GoogleNet (Wu et al. 2018)) a well-trained Convolutional Neural Network (CNN) on large-scale natural images (unrelated to this problem) available in ImageNet. Voice data came from KAY Elemetrics (now Pentax Medical) database, developed by the MEEI Voice and Speech Lab. The samples used for analysis here is sustained phonation of vowel /a/. Achieved accuracy ranged from 69% to 74%.

Kadiri and Alku (2020), presented a systematic analysis of glottal source features in normal and pathological voice and investigated their effectiveness in voice pathology detection. Voice pathology detection experiments were carried out using the HUPA and the SVD databases. The glottal source features were derived from three signals: from the glottal flows estimated with

the quasi-closed phase (QCP) glottal inverse filtering method (Airaksinen et al., 2014), from the approximate source signals computed with the zero frequency filtering (ZFF) method (Sri, Murty, and Yegnanarayana 2008) and directly from acoustic voice signals. The QCP method is based on the principles of closed phase (CP) analysis which estimates the vocal tract model from few speech samples located in the CP of the glottal cycle using linear prediction (LP) analysis. In contrast to the CP method, QCP takes advantage of all the speech samples of the analysis frame in computing the vocal tract model. ZFF is based on the fact that the effect of an impulse-like excitation (that occurs at the instant of glottal closure) is present throughout the spectrum including the zero frequency, while the vocal tract characteristics are mostly reflected in resonances at much higher frequencies. In this method, the acoustic speech signal is passed through a cascade of two zero frequency resonators and the resulting signal is equivalent to integration of the signal four times. Hence, the output grows or decays as a polynomial function of time. The trend is removed by subtracting the local mean computed over the average pitch period at each sample and the resulting output signal is referred as the zero-frequency filtered (ZFF) signal.

Analysis of features revealed that glottal source features help in discriminating normal voice from pathological voice. A Support Vector Machine (SVM) with a radial basis function (RBF) kernel has been used as classifier. The studied glottal source features provide better discrimination compared to spectral features such as MFCCs and perceptual linear prediction (PLPs) features. Further, the combination of the existing spectral features with the glottal source features resulted in improved detection performance, indicating the complementary nature of features. The best achieved accuracy was about 78%.

Oliveira et al. (2020), investigated the feasibility of combining sustained vowels for computer-based pathological voice characterization. The Authors conducted experiments on samples of sustained vowels /a/, /i/ and /u/ from SVD and AVFAD datasets, exploring the wavelet decomposition levels in the range of 4 to 18, revealing that wavelet coefficients extracted from the combination of vowels improved signal description and, hence, identification of subtle features of pathological voices, using Random Forest classifier (Breiman 2001). They also showed that the Haar wavelet-based features (Shia and Jayasree 2017) extracted from combined vowels achieved accurate voice classification with fewer decomposition levels. This approach enabled accuracy improvements of at least 15.61 and 2.61% for SVD and AVFAD datasets, respectively, regardless of the biological gender, achieving a final accuracy ranging from 78% to 83%.

Tulics et al. (2019) investigated two types of input vectors (acoustic features and Automatic Speech Recognition -ASR- posterior probabilities) with a SVM- and DNN-based classifiers, using read text materials from Hungarian-speaking patients suffering from multiple types of diseases from the Voice disordered and Healthy Adults Speech Database. They found that using acoustic parameters instead of the use phone-specific posteriors as input features increases the accuracy for the detection and classification of disordered voices. The most important parameters, as suggested by the employed Forward Feature Selection (FFS) algorithm, were the mean of MFCCs, the range of SPI on voiced plosives and affricates, the standard deviation of HNR, the range of IMF on nasals, the mean and standard deviation of jitter, the standard deviation of MFCCs, the mean of SPI on voiced plosives and affricates, the range of SPI on the vowel [E] and the standard deviation of SPI on voiced plosives and affricates. Also, the DNN approach outperformed the SVM classifier. Later, the same Authors (Tulics et al. 2020) examined the combination of the two input vectors can contribute to improve classification accuracy. They concluded that it is not worthwhile to calculate ASR phone posteriors, as it has no significant impact on classification outcome, but it can greatly complicate and slow down a diagnosis support system that models the cognitive decision-making process of an expert. ASR phone posterior derived features are less effective in the automatic classification of healthy and dysphonic voices, than using the acoustic feature set directly. Adding ASR phone posterior derived features to the acoustic features does not significantly improve the automatic classification accuracy of healthy and dysphonic voices.

They explained this finding by the fact that ASR acoustic models are trained with the objective of being robust to variation, which is likely to shade the differences between dysphonic and non-dysphonic voices. If the training corpora used to train the ASR models were controlled and labelled w.r.t. dysphonia, phone posteriors could become useful for detecting dysphonia, however, as ASR training relies on very large datasets (ideally several hundred, rather thousands of hours of speech), this requirement is quasi hard to fulfil in practice.

3.1. Mobile apps for automatic detection of voice disorders.

Ilapakurti et al. (2019), aiming at developing mobile diagnostic voice disorder app, investigated Mel-Scale Spectrogram and MFCCs as input features for several NN architectures: a 5-layer plain network, 5-layer CNN and a Recurrent Neural Network (RNN). Voice samples were obtained from a voice clinic in a tertiary teaching hospital (Far Eastern Memorial Hospital, FEMH), which included 50 normal voice samples and 150 samples of com-mon voice disorders, including vocal nodules, polyps, and cysts (collectively referred to Phono trauma); glottis neoplasm; unilateral vocal paralysis. Voice samples of a 3-second sustained vowel sound /a:/ were recorded at a comfortable level of loudness. The best model was a 5-layer CNN trained with MFCC and Mel-Spectrogram. It had a Sensitivity: 96% & Specificity: 18% on the test data.
Verde et al. (2019) propose a machine learning (ML)-based mobile voice disorder detection system. A trained model was directly embedded in a mobile application, allowing the user to evaluate the health of his/her own voice anywhere and at any time, without the necessity of trans-mitting user data to or storing user data on any server. This constitutes, at the time of writing, a significant innovation on account of the fact that most of the existing studies in literature limit the use of the mobile device to the tasks of acquiring the useful signal, transmitting it to an external server to be analysed and visualizing and communicating the results obtained to the users (Alhussein and Muhammad 2018; Muhammad et al. 2018). Unfortunately, the transmission of these patient data can be subject to a security attacks on security or privacy violations. The proposed mobile system, instead, has no need to transmit any data, so limiting the probability of any security attack.

4. Automatic classification of voice disorders

Liu et al. (2019) investigated phone posterior probabilities from a large-vocabulary ASR system trained with normal speech (Cantonese) to classify spoken utterances of 80 subjects extracted from the CanPEV database, which were already rated and divided into several categories: normal+mild, moderate, and severe. In addition to the proposed ASR voice features, the effectiveness of a set of conventional voice features that can be extracted from the utterance without using acoustical model has been investigated. The Authors adopted a minimalistic acoustic parameter set for voice analysis, known as eGeMAPS, which is implemented with the OpenSMILE toolkit (Eyben et al. 2016). Given the sequence of posterior vectors, the Authors proposed to use it to compute four types of feature parameters (a total of 18-dimension features), which are used to locate and quantify irregular posterior variations at specific speech sounds: PPV (Phone Posterior Variation), GOP (Goodness of Pronunciation), GOPV (GOP Variation) and BFR (Blurred Frame Ratio). By combining the contributions from the ASR voice features and conventional voice features, a subject-level prediction accuracy of over 80% on three severity classes has been achieved. Subjects with mild disorder and those with severe disorder could be perfectly distinguished by the proposed method.
(Miliaresi, Poutos, and Pikrakis 2021) addressed the task to classify functional dysphonia, phonotrauma, laryngeal neoplasm and vocal paralysis and showed that it is possible to treat MFCC derived features and data from medical records as two different input sources to a single neural network architecture consisting of two subnetworks. The first one, a CNN is used to treat the acoustic signal as an image, that captures spectral shape by operating on MFFC derived features and simple filterbank outputs. The second (feed-forward) network analyses an enhanced input vector, consisting of the demographic parameters and mid-term signal fea-

tures. The outputs of the aforementioned sub-networks are concatenated and fed to a dense layers with 1024 nodes, with each node's output being processed by a Rectified Linear Unit (ReLu) activation function. Finally, a softmax output layer of four units is used to produce posterior probability estimations of the four classes of the problem under study.

5. Speech impairments by central nervous system disorders.

Lauraitis et al. (2020) adopted Bidirectional Long Short-Term Memory (BiLSTM) neural network and Wavelet Scattering Transform with Support Vector Machine (WST-SVM) classifier for detecting speech impairments of patients at the early stage of central nervous system disorders (CNSD). The study includes 339 voice samples collected from 15 subjects: 7 patients with early stage CNSD (3 Huntington, 1 Parkinson, 1 cerebral palsy, 1 post stroke, 1 early dementia), other 8 subjects were healthy. Speech data is collected using voice recorder from Neural Impairment Test Suite (NITS) mobile app. Features are extracted from pitch contours, Mel-frequency cepstral coefficients (MFCC), Gammatone cepstral coefficients (GTCC), Gabor (analytic Morlet) wavelet and auditory spectrograms. 94.50% (BiLSTM) and 96.3% (WST-SVM) accuracy is achieved for solving healthy vs. impaired classification problem. The developed method can be applied for automated CNSD patient health state monitoring and clinical decision support systems as well as a part of Internet of Medical Things (IoMT).

5.1. Parkinons' desease (PD)

Kodrasi and Bourlard (2020), proposed to use the spectro-temporal sparsity characterization as a robust feature for dysarthric speech detection, based on the motivation that since dysarthric speech of patients suffering from PD is breathy, semi-whispery, and is characterized by abnormal pauses and imprecise articulation, it can be expected that its spectro-temporal sparsity differs from the spectro-temporal sparsity of healthy speech. The Authors first provided a numerical analysis of the suitability of different non-parametric and parametric measures (i.e., l1-norm, kurtosis, Shannon entropy, Gini index, shape parameter of a Chi distribution, and shape parameter of a Weibull distribution) for sparsity characterization. It is shown that kurtosis, the Gini index, and the parametric sparsity measures are advantageous sparsity measures, whereas the l1-norm and entropy measures fail to robustly characterize the temporal sparsity of signals with a different number of time frames. Second, they proposed to characterize the spectral sparsity of an utterance by initially time-aligning it to the same utterance uttered by a (arbitrarily selected) reference speaker using dynamic time warping. Experimental results on a Spanish database of healthy and dysarthric speech showed that estimating the spectro-temporal sparsity using the Gini index or the parametric sparsity measures and using it as a feature in a support vector machine results in a high classification accuracy of 83.3%.
Asmae et al. (2020), used ANN and K-Nearest Neighbours (KNN) algorithms, in the purpose of distinguishing between PD patient and healthy individual. Voice data in the Parkinson's UI Machine Learning has been used. Standard features derived from fundamental frequency, jitter and shimmer, have been used, as well as non-standard features such as Correlation Dimension (Kantz and Schreiber 2003), Recurrence Period Density Entropy and Detrended Fluctuation Analysis (Dixit 1988): 22 features in total. The ANN has two hidden layers and the Levenberg-Marquardt (LM) has been used as training optimization algorithm (Hagan and Menhaj 1994). Experimental results have showed that the ANN classifier achieved higher average performance than the KNN classifier in term of accuracy. The established system can distinguish healthy people from an acceptable range of people with PD with an accuracy rate of 96.7% by using ANN, and 79.3% by using KNN when the number of neighbours taken was k=1, by using the cosine distance.

6. Specific language impairment (SLI)

Several very recent researches regarded Specific language impairment (SLI), also known as development dysphasia.
Kotarba and Kotarba (2020), proposed an efficient approach to automatic detection of SLI based on log-power spectrograms of speech samples. The utterances from the LANNA

children speech corpus were used to calculate the normalized log-power spectrograms. Deep neural network algorithm based on ResNet architecture (He et al. 2016) was used to perform the classification task. The accuracy rate of proposed SLI detection method exceeds 99% in the speaker independent scenario.
Reddy, Alku, and Rao (2020), proposed a method for SLI detection in children that utilizes time- and frequency-domain glottal parameters, which are extracted from the voice source signal obtained using quasi-closed phase (QCP). In addition, 12 MFCCs and openSMILE based acoustic features are also extracted from speech utterances, including min (or max) value and its relative position, standard deviation, range, median, skewness, kurtosis, 2 linear regression coefficients, and quadratic error of the following features: root mean square (RMS) energy, zero crossing rate, pitch and voicing probability. SVMs with RBF kernel and feed-forward neural network (FFNN), are trained separately for the MFCCs, openSMILE and glottal features. A leave-fourteen-speakers-out cross-validation strategy is used for evaluating the classifiers. The experiments are conducted using the LANNA corpus. Experimental results show that the glottal parameters contain significant discriminative information required for identifying children with SLI. Furthermore, the complementary nature of glottal parameters is investigated by independently combining these features with the MFCCs and openSMILE acoustic features. The overall results indicate that the glottal features when used in combination with MFCCs feature set provides the best performance with the FFNN classifier in the speaker-independent scenario (98.82%).
Sharma and Singh (2020) used sustained phonation of vowel /a/ uttered by children, from the LANNA database, to detect and classify control (healthy) and experimental (SLI) group using linear predictive coding (LPC) feature set. LPC order was set to 8, and a set of 408 features was build using 17 statistical function applied to the 8 coefficients, their delta and delta-delta ("delta" refers to the difference between two consecutive feature frames). A standard non-parametric Mann-Whitney non-parametric U-test was applied to filter the significant features for 95% level of confidence. The top-20 and top-10 features were then selected by computing the Spearman's rank correlation coefficients. Naïve-Bayes (NB) and SVM were employed for machine learning task. The best accuracies were obtained from NB classifiers i.e. 97.9% (for top-20 LPC features) and 97.8% (for top-10 LPC features) with 5-fold cross-validation protocol.

7. Conclusions

From this unexhaustive review of the most recent attempts to improve automatic voice disorders detection and classification, it is clear that the role of ANN is going to increase in the near future. More and more complex networks are investigated such as Online Sequential Extreme Learning Machine (OSELM) and GoogleNet and transfer learning is applied to face the availability of limited amount of data compared to the amount that would be required to train from scratch the most complex networks.
Accuracy achievable with ANN can be higher than 90%, with peaks close to 99% in some specific tasks.
One of the most promising approach is to embed the capability to detect voice disorders in mobile devices as software app, allowing a portable and usable solution to monitor the quality of voice in real time.
An intense research activity is also devoted to find and select new features to augment or replace the classical one to improve the recognition accuracy, including a trend to use directly spectrographic or time-frequency representations of voice samples as images to feed ANN good at image-recognition.
Finally, running speech is increasingly considered instead of sustained vowels to take into account more realistic speech scenarios.

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Prevention Strategy of Intrauterine Adhesions: update and future perspective

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Abstract

Intrauterine adhesions (IUAs) caused by endometrial injury have a serious impact on women's fertility and morbility and involves a wide range of patients. Although the first case of IUAs was published in 1984 by Heinrich Fritsch, a full description of Asherman syndrome was done by Joseph Asherman. IUAs lead to a lot of complications in women, as the partial or complete closure of the uterine cavity, which may result in symptoms including abnormal menstruation, pelvic pain, recurrent pregnancy loss, secondary infertility, and pregnancy complications. Hysteroscopy, which has relegated blind curettage, is currently considered the gold standard diagnostic and therapeutic approach also as for outpatients. However, an integrated approach, including preoperative, intraoperative and postoperative procedures is needed to improve the reproductive outcome of the complex syndrome. In the post-operative care, the patient can benefit from some therapeutic and prophylactic methods used alone or in combination with each other. In this review, authors discuss on the efficacy of traditional methods for the prevention of complications of IUAs after surgery, such as hormonal therapy, physical barriers, vasodilators and antibiotics, as well as novel strategies such as stem cell therapy and novel therapeutic agents.

Keywords: Asherman syndrome, intrauterine adhesion, synechiae, infertility, reproduction.

1. Introduction

Intrauterine adhesions (IUAs) are a result of mechanical or infectious injury to the basalis layer of the endometrium, caused by curettage, hysteroscopic surgery, uterine artery embolization, B-Lynch sutures, abdominal myomectomy, hysteroscopic myomectomy, genital tuberculosis and surgical treatment of Mullerian anomalies (Doroftei et al. 2020).
In some women, the normal repair mechanisms of the endometrium are aberrant, including hypoxia, reduced neovascularization and altered expression of adhesion-associated cytokines, resulting in IUAs formation (Buttram et al. 1988).
IUAs can lead to partial (Figure 1) or complete obliteration of the cervix and the uterine cavity, which may result in clinical sequelae including abnormal menstruation, amenorrhea, pelvic pain, infertility (caused by the obstruction of sperm transport into the cervix, impaired embryo migration within the uterine cavity and failure of embryo implantation (Dreisler and Kjer 2019)), recurrent pregnancy loss and pregnancy complications.
The traditionally widely used classification system of the IUAs is the American Fertility Society (Buttram et al. 1988) score (Figure 2), classifying IUAs in three stages: mild (grade I), moderate (grade II), and severe (grade III).
Currently, Hysteroscopy can be considered the gold standard for diagnostic and therapeutic approach also for outpatients. The occurrence of new adhesions after primary hysteroscopic adhesiolysis is so much frequent and the recurrence rate is associated with the grade of adherences (Figure) as found by Hanstede et al, that re-

ported 21%–25% recurrence with grade 1–2 adherences, 29.1% with grade 3, 38.5% with grade 4, and 41.9% with grade five (Bosteels et al. 2015).

Although numerous observational studies suggest potential benefit with the use of anti-adhesion therapies (intrauterine device or balloon, hormonal treatment, antibiotics, barrier gels or human amniotic membrane grafting) for decreasing IUAs, currently, there are no strong recommendation in favor of the use of anti-adhesion therapies after operative hysteroscopy.

At present the effectiveness of the anti-adhesion treatment following operative hysteroscopy for decreasing IUAs remains uncertain as suggested the Cochrane Review of 2017, because of the low quality of the evidence (Hanstede et al. 2015).

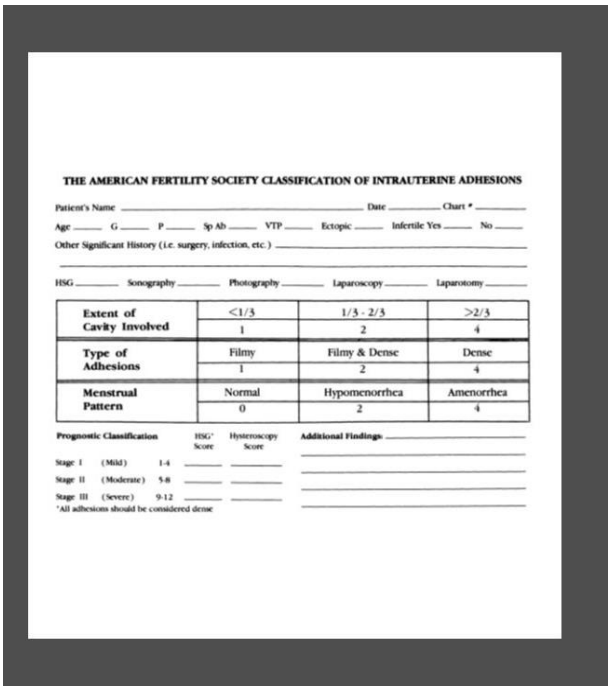
Figure 1. Uterine cavity partially occluded by adhesions.

FERTILITY AND STERILITY

The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions

The American Fertility Society*†

Birmingham, Alabama



THE AMERICAN FERTILITY SOCIETY CLASSIFICATION OF INTRAUTERINE ADHESIONS

Patient's Name _____ Date _____ Chart # _____

Age ____ G ____ P ____ Sp Ab ____ VTP ____ Ectopic ____ Infertile Yes ____ No ____

Other Significant History (i.e. surgery, infection, etc.) _____

HSG _____ Sonography _____ Photography _____ Laparoscopy _____ Laparotomy _____

Extent of Cavity Involved	<1/3	1/3 - 2/3	>2/3
	1	2	4
Type of Adhesions	Filmy	Filmy & Dense	Dense
	1	2	4
Menstrual Pattern	Normal	Hypomenorrhea	Amenorrhea
	0	2	4

Prognostic Classification — HSG* Score — Hysteroscopy Score — **Additional Findings:** _____

Stage I (Mild) 1-4 _____ _____

Stage II (Moderate) 5-8 _____ _____

Stage III (Severe) 9-12 _____ _____

*All adhesions should be considered dense

Figure 2. Classification system of the Intra Uterine Adhesions of the American Fertility Society (AFS).

1.2. Prevention of adhesion recurrence

Adhesions recurrence after surgery is one of the most important factors which can delay reproductive outcome after IUA treatment. Adhesions recurrence rate is significantly higher in those cases where a severe AS is diagnosed (Figures 3 and Figure 4).

Several methods to prevent IUA reformations after surgery have been proposed. Nonetheless few comparative studies have been developed (Xu et al. 2018). This could be probably due to the multitude treatment approach adopted and particularly to the lack of a unified standardized classification system for IUA diagnostic characterization.

Figure 3. The image shows a hysteroscopy with resectoscope for ablation of intrauterine adhesions in a patient with Asherman syndrome.

Figure 4. Uterine cavity cleaned after ablation of intrauterine adhesions.

1.3. Intrauterine device

The intrauterine device (IUD) may provide a physical barrier between the uterine walls, separating the endometrial layers to prevent their fusion during the initial healing phase (Buttram et al. 1988).
The characteristics of IUD to prevent intrauterine adhesion formation should be the tolerability of the device, the suppression of IUA formation and the restoring of healing of the endometrium. There are several observational studies that recommended the insertion of a device after lysis of IUAs such as IUD and Foley catheter balloon after lysis of IUAs or septoplasty.
There are different kinds of IUD (copper-containing IUD, T-shaped IUD, loop IUD) with particular characteristics and mechanism of actions, also, there are no sizes of IUD available for too large or too small uterine cavities (Kodaman and Arici 2007).

1.4. Intrauterine balloons

An intrauterine balloon stent is another mechanical method frequently used to prevent the reformation of adhesions. The Cook Medical balloon (Indianapolis, IN, USA) has designed a heart-shaped intrauterine balloon for prevention of secondary intrauterine adhesions thanks to its triangular shape, which conforms to the configuration of a normal uterus and maintain separation at the margins of uterine cavity (March 2011).

1.5. Foley catheters

A standard pediatric Foley catheter is another commonly used method to prevent recurrence of IUAs.
In a randomized controlled trial, Lin et al compared the efficacy of intrauterine balloon (removed after 7 days) and IUD demonstrating similar efficacy (Lin et al. 2015).
Orhue et al compared an IUD with a pediatric Foley catheter and found that the catheter was a safer and more effective adjunctive method of treatment of IUA compared with the IUD. The persistent post-treatment amenorrhea and hypomenorrhea occurred less frequently in the Foley catheter group (18.6%) than in the IUD group (37.3%) ($P<0.03$), and the conception rate in the catheter group was 33.9% compared with 22.5% in the IUD group. The need for repeated treatment was also significantly less in the Foley catheter group (Orhue, Aziken, and Igbefoh 2003).
Recently, Shi et al compared the efficacy of intermittent intrauterine balloon dilatation versus standard care in the prevention of adhesion reformation in two hundred patients with moderate to severe IUAs who underwent hysteroscopic adhesiolysis. In this randomized controlled trial, the balloon group received intrauterine balloon dilatation therapy at 2 weeks and 6 weeks after surgery, whereas the control group did not. A total of 191 patients successfully completed the study protocol (94 cases for the balloon group and 97 cases for the control group). According to hysteroscopic evaluation at the 8th week, the overall adhesion reformation rate was significantly lower in patients in the balloon group than patients in the control group (20.2% versus 40.2%, respectively; $P < 0.05$).
This study shows that postoperative intermittent intrauterine balloon dilatation therapy can significantly reduce postoperative adhesion reformation and significantly increase menstruation flow (Shi et al. 2019).
Recently Huang at al have patented intrauterine stent of various sizes, flexible and thin, but at the moment their studies have been performed on a small number of patients with moderate or severe IUAs and so we have no encouraging data (Huang et al. 2020).

1.6. Anti-adhesion barrier

Hyaluronic acid-derived products showing a possible role in gynecologic surgery to prevent

intra-abdominal IUAs, reducing the risk of adhesion recurrence after surgical treatment of IUAs (Guida et al. 2004; Tsapanos et al. 2002; Acunzo et al. 2003), but may not be suitable alone for endometrial surfaces due to a short half-life and weak attachment to the endometrium (Acunzo et al. 2003). The material usually needs to be used in combination with other devices.

Use of biodegradable gel surgical barriers is based on the principle of keeping adjacent wound surfaces mechanically separate (Renier et al. 2005). The exact mechanisms by which ACP (auto-cross-linked polysaccharide) and HA-CMC (sodium hyaluronate and carboxymethylcellulose gel) can reduce adhesion reformation are not well known but may be related to 'hydro flotation' or 'siliconizing' effects. Hyaluronic acid gel or polyethylene oxide-sodium carboxymethylcellulose gel for the prevention of intrauterine adherences have been investigated demonstrating conflicting results. Acunzo et al found a significant effect of hyaluronic acid compared to no treatment (14% versus 32%) (Acunzo et al. 2003). Instead, Lin et al demonstrated that the balloon and IUCD were more effective than hyaluronic acid (Lin et al. 2015). Ducarne et al compared application of ACP gel (30 women) versus no gel (24 women) at the end of an operative hysteroscopic procedure performed to treat myomas, polyps, uterine septa or IUAs, finding no statistically significant differences between comparison groups in the rate of adhesion formation, or in mean adhesion scores and severity of adhesions (Ducarme et al. 2006). Different results were obtained from the recent meta-analysis conducted by Fei et al. finding a significant reduction of the incidence of moderate and severe IUAs (RR 0.18, 95% CI: 0.07~0.47; p=0.0004) and an improvement in the pregnancy rate after miscarriage (RR 1.94, 95% CI 1.46~2.60; p<0.00001) with the use of hyaluronic acid gel (Zheng et al. 2020).

1.7. Human amniotic membrane grafting

Human amniotic membrane HAM is the innermost layer of the fetal membranes and possess many properties that make them suitable for use in regenerative medicine, such as low immunogenicity, anti-fibrotic, anti-inflammatory, angiogenic and anti-angiogenetic and anti-microbial properties (Gary and Jones, 2017). HAM acts as a biologically active mechanical barrier to suppress adhesion formation while promoting endometrial healing (Amer and Abd-El-Maeboud 2006), through regeneration of epithelium facilitating migration of epithelial cells, reinforcing adhesion of the basal epithelium, promoting epithelial cell differentiation (Meller and Tseng 1999), preventing cellular apoptosis (Hori et al. 2006), producing factors or creating a microenvironment for effective tissue repair and endometrial regeneration, possibly by stimulating endogenous stem cells (Padykula 1989).

According to a randomized controlled trials of Zheng et al including 300 patients, which evaluated the ability of HAM to prevent the recurrence of IUAs after hysteroscopic adhesiolysis, the use of HAM increased menstrual blood volume (mean difference 6.15, 95% CI 4.20–8.11; P<0.001) but failed to improve the rate of intrauterine adhesion recurrence or spontaneous abortion (Zheng et al. 2018).

Yan et al in a network Meta-Analysis of randomized controlled trials has found a significant advantage with the use of freeze-dried amniotic agents plus a balloon to reduce IUAs recurrence and IUAs scores after adhesiolysis (Yan and Xu 2018).

A prospective randomized controlled trial conducted among 88 women with severe IUA who underwent hysteroscopic adhesiolysis analyzed the efficacy of freeze-dried amnion graft covered the balloon portion of the Foley catheter for prevention of IUAs. Also, this study concluded that the use of HAM was effective in improving menstruation, but the rates of IUAs reformation and pregnancy were not significantly different (Gan et al. 2017).

2. Medical therapy to restoration the endometrium

2.1 Vasodilators

In recent years, many studies described use of medications to increase vascular flow to endometrium such as aspirin, nitroglycerine and sildenafil citrate. But evidence was insufficient to show whether vasodilators increase the live birth rate (Gutarra-Vilchez et al. 2018).

Studies have demonstrated that aspirin combined with estrogen may significantly prevent the postoperative disease recurrent rate, improve

endometrial receptivity and improve the conception rate by increasing endometrial blood supply and angiogenesis more effectively. The aspirin inhibits endometrial fibrosis by suppressing the TGF-□1-Smad2/Smad3 pathways (Z. Zhang et al. 2020).
Zinger reported two cases of woman with history of a postpartum uterine curettage, inadequate endometrium thickness after surgical resection of IUAs that are treated with sildenafil citrate and with the results of having achieved pregnancy (Zinger, Liu, and Thomas 2006).
However, the number of women treated using these therapies remains small, and because all such treatment is off label, these medications cannot be endorsed outside of rigorous research protocols.

2.2 Antibiotics

There is no clear recommendation in the literature on whether it is necessary to use prophylactic antibiotics for minor operative procedures such as dilatation and curettage for evacuation of conceptive products, fractional curettage for abnormal uterine bleeding, hysterosalpingography for infertility evaluation and hysteroscopy for intrauterine cavity diagnosis and treatment.
The Cochrane of 2013 regarding the prophylactic antibiotics for transcervical intrauterine procedures versus placebo concluded that there are no randomized controlled trials that asses the effects of prophylactic antibiotics on infection complications and therefore is not possible to draw any conclusions (Thinkhamrop, Laopaiboon, and Lumbiganon 2007). However, when obvious infection is seen, antibiotics are mandatory.
In India genital tuberculosis appears to be an important and common cause of IUA causing primary and secondary infertility with various grades of adhesions (Sharma et al. 2008) and so it is important to investigate the patients who come from those areas.

2.1 Hormonal therapy

Already in 1964 Wood and Pena hypothesized the beneficial effects of estrogen therapy on endometrial regeneration after surgical treatment for IUAs (Wood and Pena 1964). Postoperative treatment with estrogen in order to promote the regeneration of the endometrium has been recommended in several studies, either as estrogen only (Capella-Allouc et al. 1999; Dawood, Al-Talib, and Tulandi 2010), either with IUD (March, Israel, and March 1978; Chen et al. 2017; Yu et al. 2016; Roy et al. 2014; Zikopoulos et al. 2004; Myers and Hurst 2012; Salma et al. 2014; Liu et al. 2019) or Foley catheter (Dawood, Al-Talib, and Tulandi 2010; March, Israel, and March 1978; Salma et al. 2014).
In several studies different regimens consisting of estrogen with or without a progestogen have been used (Kodaman and Arici 2007). There are no comparative studies that examine dosage, administration or combinations of hormones (Buttram et al. 1988). In a recent randomized study, 4 mg and 10 mg estradiol orally was compared. No superior effect of the high dosage was demonstrated (Liu et al. 2019). When comparing 2 mg and 6 mg in a prospective randomized trial, no benefit was demonstrated in the 6 mg arm.
In the randomized controlled trials of Farhi et al, 60 women undergoing dilatation and curettage during the first trimester of pregnancy were allocated to receive estrogen combined with progestogen or no treatment (Farhi et al. 1993). The authors have found that women in the intervention group had a significantly thicker endometrium compared with women in the control group (8.4 with intervention vs 6.7 mm with no treatment; P = 0.02) and so they concluded that postoperative hormonal treatment may be useful for IUAs prevention following curettage. Nevertheless, but this study does not report the data about pregnancy rates and IUAs recurrence (Farhi et al. 1993). The systematic review of Johary et al, concluded that estrogen therapy, may be beneficial for women with IUAs, but as adjunctive therapy combined with other anti-adhesion strategies (Johary et al. 2014). Also, in three prospective randomized studies, the administration of oral estrogen did not reduce the risk of IUAs (Tonguc et al. 2010; Dabirashraft et al. 1996; Roy et al. 2014).

3. Future perspective

Recently, some experimental study has demonstrated that stem cells on rat models is a promising therapeutic approach for the regeneration of the inadequate endometrium. In particular,

Zhao's study aimed to identify exosomes derived from adipose-derived mesenchymal stem cells (ADSC-exo) and explore the therapeutic potential in IUA rat models. In IUA model, treatment with ADSC-exo maintained normal uterine structure, promoted endometrial regeneration and collagen remodeling, and enhanced the expression of integrin-β3, LIF, and VEGF. An improved receptivity of the regenerated endometrium was confirmed. Their findings demonstrated that ADSC-exo promoted endometrial regeneration and fertility restoration. It suggested that topical administration of ADSC-exo in uterus could be a promising strategy for patients suffering severe intrauterine adhesions and infertility (Zhao et al. 2020).
Another studies on rat model of Zhang at al evaluated urinary bladder matrix in order to improve endometrial regeneration, receptivity and fertility (H. Zhang et al. 2020).
Another promising research of Zhang SS, based on the synergistic effect of the well-known E2 and the Heparin-Poloxamer Hydrogel, revealed that administrating E2-HP hydrogel to injured uterus had a positive effect on endometrium regeneration in rat model (S. Zhang et al. 2020).
In the only prospective study performed on humans by Santamaria et al. 16 women with IUA confirmed by hysteroscopy were treated with uterine intravascular infusion of bone marrow-derived stem cell (BMDSC). During the follow-up period, menstrual function returned to normal within 6 months after BMDSC infusion, with three spontaneous pregnancy and seven pregnancies after IVF and embryo transfer reported (Santamaria et al. 2016). These novel studies begin to open the door for further prospective research on human population.

4. Conclusions

Currently, there is no ideal method to prevent IUAs and it is difficult to standardize a therapy valid for all patients as IUAs is a heterogeneous syndrome with specific peculiarities.
Many devices, used alone or in combination, have been proposed to prevent IUAs formation after intrauterine procedures, but at present it is difficult to establish which approach is the best, due to the heterogeneity of the studies, the contrasting results reported, and the different outcomes investigated. To avoid the adhesions relapse, it would seem to be recommendable the use of balloon catheters and IUD with adjunctive estrogen therapy. The combination strategy that using physical barriers as the delivery carriers for therapeutics might provide new alternatives for the prevention of IUAs.
Recently several new methods have been patented to prevent IUAs but long-term results are not yet available. More research is needed to assess the best approach to prevent adhesions in order to increase reproductive chances and if pregnancy occurs to reduce obstetrics risk such as miscarriage, preterm birth, abnormal placentation, intrauterine growth restriction.
Perhaps there is the key to improving the outcome of IUAs: the personalization of therapy and the evolution of biocompatible materials that are increasingly adaptable to specific needs.

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Tracheobronchial Amyloidosis

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Abstract

Amyloidosis is a form of plasma cell dyscrasia of unknown etiology, pathologically characterized by the extracellular deposit of fibrils derived from the light chain of monoclonal immunoglobulin. The involvement of the airways is more common in primary amyloidosis and is classified into: tracheobronchial amyloidosis, nodular parenchymal, diffuse parenchymal. The tracheobronchial form is usually the most frequent and is characterized by the presence of multiple submucosal plaques or, more rarely, by pseudotumoral endobronchial masses. Symptoms in the initial phase may be silent, subsequently manifesting themselves with cough, dyspnea, hemoptysis.

Keywords: amyloid substance, amyloidosis L and A, pseudotumoral plaques or masses of amyloid substance affecting the trachea and bronchi.

1. Introduction

Amyloid must be understood as any substance that presents a green birefringence under polarized light, after Congo red staining, a fibrillar structure in electron microscopy. The deposit and infiltration of this substance constitutes Amyloidosis. Although at first it was believed that amyloid was a single substance, it is currently known that the proteins that constitute it are different, all similar to each other from a morphological point of view, but different from a biochemical point of view (Piacenza 1992). Various proteins of this type have been identified in various combinations (immunoglobulins). The most important are amyloid L (AL) and amyloid A (AA). L amyloidosis derives from light chain immunoglobulins and is therefore usually associated with an abnormal functioning of plasma cells (Prakash 1995), both localized in the lungs and as part of a systemic pathology such as multiple myeloma or macroglobulinemia. Amyloidosis A derives from an acute serum phase reagent (AAS) synthesized in the liver. The latter can form in various conditions, connective tissue diseases (in particular rheumatoid arthritis), chronic infections (in particular tuberculosis), bronchiectasis and some neoplasms (such as Hodgkin's lymphoma). Due to the great variety of clinical and pathological manifestations, amyloidosis has been classified above all in relation to its biochemical origin. The traditional classification provides for four main forms of disease: Primary amyloidosis, in which no associated pathology is recognized or there is a concomitant disorder of plasma cells (most often multiple myeloma); secondary amyloidosis, in which there is an underlying or identifiable chronic inflammatory disease, such as tuberculosis, bronchiectasis, rheumatic disease; hereditary amyloidosis, a relatively rare form that can be localized in a specific tissue such as a nerve; Senile amyloidosis which affects many organs and tissues and is usually found in people over seventy (Fraser et al. 2006). The involvement of the respiratory tract can be isolated or integrated in the framework of a systemic amyloidosis that involves all organs. The localized form is the most frequent. Respiratory amyloidosis can take three main and characteristic forms: tracheobronchial, nodular parenchymal (the nodules can be solitary located at the periphery of the lung or more often multiple), diffuse parenchymal (almost exclusively affects the interstitium and is characterized by an infiltration of the alveolar wall by the am-

yloid substance, especially around the capillaries). The tracheobronchial form is probably the most frequent. It manifests itself with the presence of multiple submucosal plaques in the lumen of the trachea and bronchi or more rarely with a pseudotumoral endobronchial mass of a friable consistency that is easy to bleed, with an irregular surface, generally of a pinkish-yellowish color (Piacenza 1992). Radiologically, the lesions of the respiratory tract are visible at the level of the trachea, the main bronchi and the lobar and segmental bronchi. They can be observed on standard radiological examination and better still on CT. They are characterized by a focal or diffuse thickening of the airways or they may present the appearance of multiple nodules that develop at the level of the tracheal wall, of the main, lobar, or segmental bronchi projecting into the lumen and can cause mild, moderate, or considerable entity. A rare and particular anomaly, called osteoplastic tracheopathy (characterized by diffuse or nodular ossification of the tracheobronchial mucosa) can be similar to tracheobronchial amyloidosis. As evidenced by some observations of amyloid deposits with histological studies of these tracheae, it can be said that osteoplastic tracheopathy is a late stage in the evolution of tracheobronchial amyloidosis (Grenier 1993).

2. Clinical Case

A 75-year-old woman, housewife, non-smoker, in good health until the age of 65 when, following the appearance of a symptomatology characterized by dry, persistent and resistant cough to antibiotic and anti-inflammatory therapy, she performed, upon request by a pulmonologist, a chest x-ray examination with a negative result. Bronchoscopy revealed a thickening of the bronchial mucosa at the level of the branches of the left lower lobe bronchus. Subsequently, in addition to the persistence of the cough, she presented recurrent episodes of productive cough (at times with the emission of blood-streaked sputum) she manifested fever and dyspnea of modest entity. In November 2010 she performed pneumological consultancy at the territorial Pneumo-physiology Service of Lecce, in that circumstance the specialist doctor requested chest x-ray and CT (Figure 1 and Figure 2). After these last examinations which revealed the presence of a left basal thickening, she was asked to perform fibrobronchoscopy. In the latter examination, the presence of nodular formations at the level of the tracheal part was found (Figure 5), occlusion of the left lower lobe bronchus due to the presence of a pseudotumoral mass (Figure 3), stenosis of the lingula and upper lore bronchus proper due to considerable thickening of the spur (Figure 4) and stenosis serrata of the middle lobar bronchus due to thickening of the mucosa (Figure 6). The biopsy examination was positive for tracheo-bronchial amyloidosis.

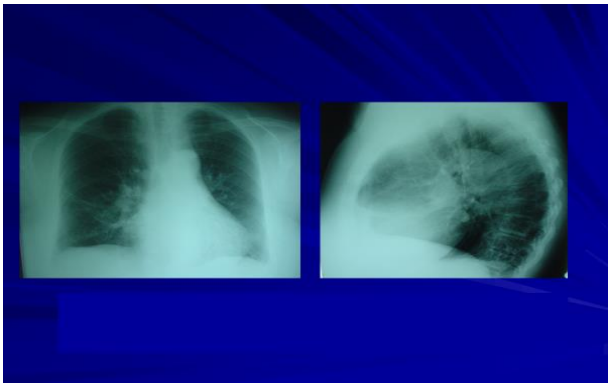

Figure 1. Chest X-ray. Left positive basal pulmonary thickening.

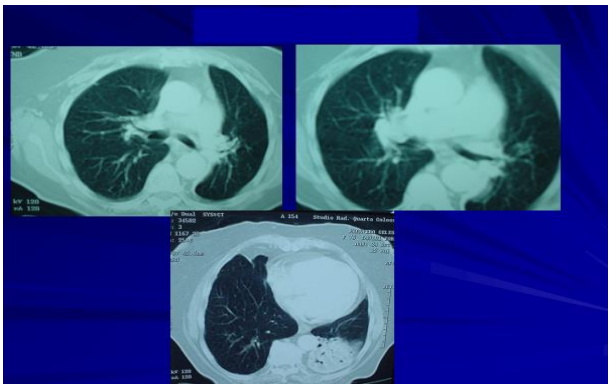

Figure 2. Chest CAT. Left lower lobe pulmonary thickening. Marked stenosis of the left lower broncho-lobar.

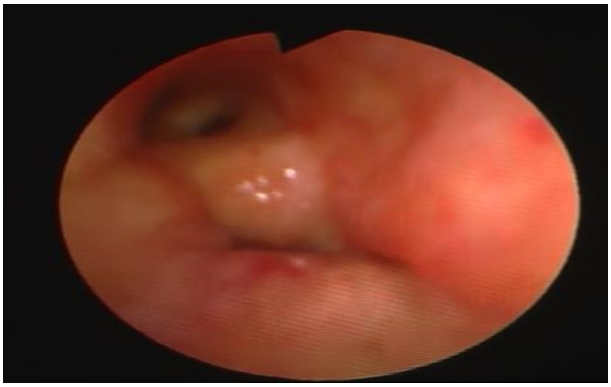

Figure 3. Occlusion of the left lower lobe bronchus due to marked thickening of the mucosa.

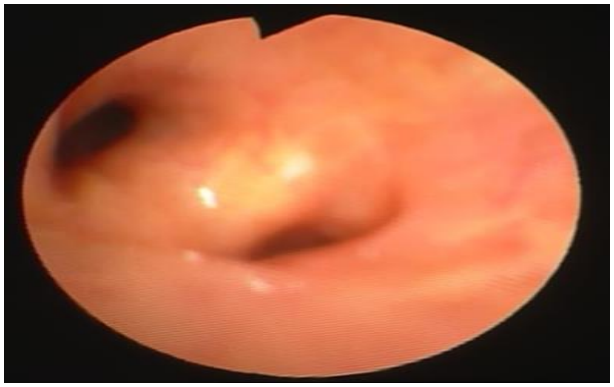

Figure 4. Stenosis of the left upper lobe bronchus and of the lingula due to marked thickening of the spur.

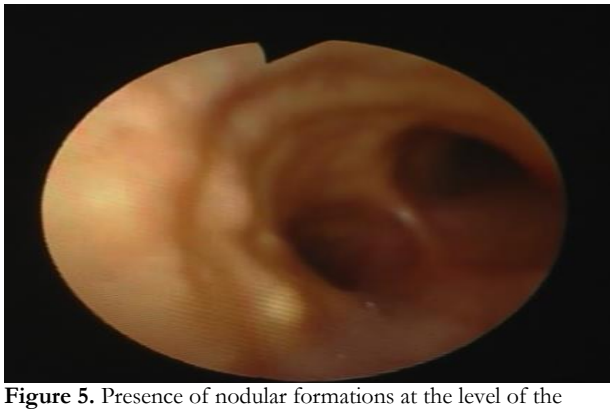

Figure 5. Presence of nodular formations at the level of the tracheal wall of amyloid substance.

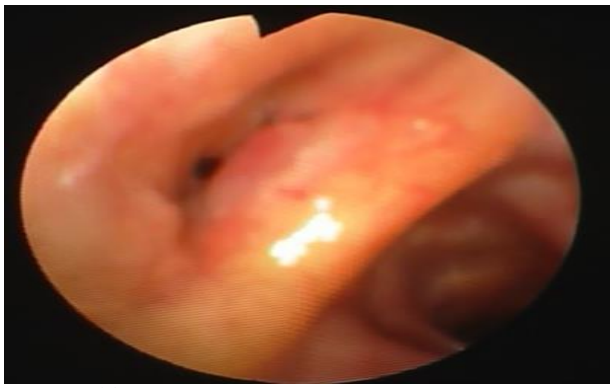

Figure 6. Tight stenosis of the middle broncho-lobar for notable thickening of the spur between the middle and lower lobe bronchus.

3. Therapy

The YAG laser treatment allows a resection of the amyloid pathology with satisfactory results. Recently it has been seen that in patients with tracheobronchial amyloidosis refractory to YAG or stending laser therapy, discrete results can be obtained with 20 GY external pulse radiation therapy which can be repeated 2/3 times.

4. Conclusions

This very rare pathology is characterized as we have seen from the endoscopic and radiological point of view by the presence of multiple nodules, plaques or pseudotumoral masses of easily bleeding friable consistency that develop at the level of the tracheobronchial wall, causing stenosis and sometimes occlusion of some bronchial branches. The symptoms in the initial phase can be silent or manifest with recurrent episodes of bronchial exacerbation. Subsequently, the cough becomes persistent and dyspnea and hemoptysis appear. The execution of radiological examinations (chest x-ray and CT) and in particular of the fibrobronchoscopy with biopsy (better if performed in the initial phase) allows to formulate the diagnosis and to perform appropriate therapy with good results.

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A Case of Retroperitoneal Fibroid and Literature Review

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Abstract

Uterine fibroids or leiomyomas are the most common benign female genital tumors, although this pathology can also manifest itself outside the uterus, as in the case we present, with a retroperitoneal development. In this article, authors showed a rare case of 81-year-old women, with a right pelvic mass and lower abdominal discomfort. Basing on a preoperative radiological imaging, clinicians oriented to a provisional diagnosis of mesenchymal neoplasm of an uncertain origin. During surgery in the retroperitoneal space, it was detected a huge mass close to the uterus, beneath the right broad ligament. After the opening of the retroperitoneal spaces, surgeons enucleated a well-demarcated tumor, measuring 12 x 7 cm in diameter and histopathological findings demonstrated a rare retroperitoneal uterine leiomyoma.

Keywords: Uterine leiomyoma, fibroids, retroperitoneal neoplasm, immunohistochemistry.

1. Introduction

Uterine fibroids or leiomyomas are the most common benign gynecological tumors, usually originating and included in the uterus. This is one of the most common female diseases and one of the most common cause of hysterectomies (Sparic et al. 2016). Generally, the retroperitoneal origin of a fibroid is very unusual.
Retroperitoneal fibroid has a marked morphologic similarity to uterine leiomyoma, by virtue of hyaline change end trabecular pattern of growth (Yüksel et al. 2020)
Nevertheless, a tumor in this retroperitoneal region with a leiomyomatosic appearance, has a differential diagnosis with a uterine leiomyoma extending posteriorly, a well-differentiated leiomyosarcoma, benign and a malignant gastrointestinal stromal tumor (GIST) (Barnaś et al. 2019).

This differential diagnosis can lead to make the misdiagnosis, or challenge the strategy of treatment of tumor, shifting towards very invasive and radical treatments.

2. Case presentation

We report the case of an 81-year-old woman, hospitalized for diagnostic investigation after incidental finding of a pelvic mass on ultrasonography and a successive computerized tomography (CT) imaging scan, assessing the presence of a wide solid mass of size 12 x 7 cm in the pelvic cavity.
At radiological appearance, this mass showed regular boundary, with isolated intralesional calcifications, inhomogeneous vascularity and hypodense areas peripherally. A CT guided mass biopsy was performed, with 3 samples of size 5 mm each. Those samples showed stromal frustules immunoreactive for smooth muscle actin (SMA) and negative for S-100 protein,

CKAE1/AE3 and CD34 so they were made of smooth muscle.

Thus, the entire mass was surgically enucleated in laparotomy and transported to the pathological anatomy unit for complete histological evaluation.

The morphological findings of the enucleated mass showed an irregular shape, with a compact, swirling and whitish cut surface (Figure 1). Hematoxylin and eosin staining revealed the intersecting fascicles of spindle cells (Figure 2), with no necrosis and mitotic activity. The immunohistochemical staining was positive for SMA and desmin (Figure 3) and negative for S-100 protein and CD117 (C-Kit). Therefore, the definitive diagnosis was a rare case of retroperitoneal fibroids or leiomyoma.

The patient' postoperative course was uneventful, with a discharging after seven days after surgery. No several adverse events occurred. Patients follow up showed no evidence of recurrent retroperitoneal leiomyoma, until now.

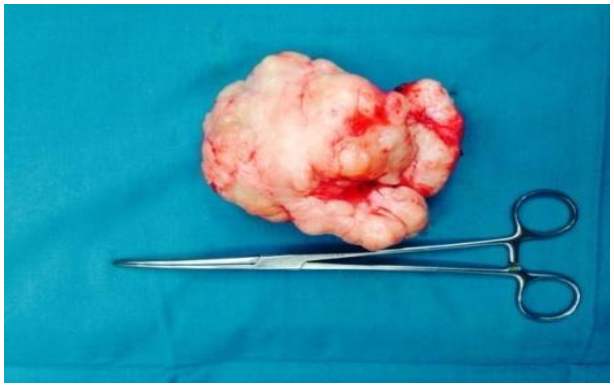

Figure 1. Grossly, it is well circumscribed mass, and the surface shows white whirling appearance.

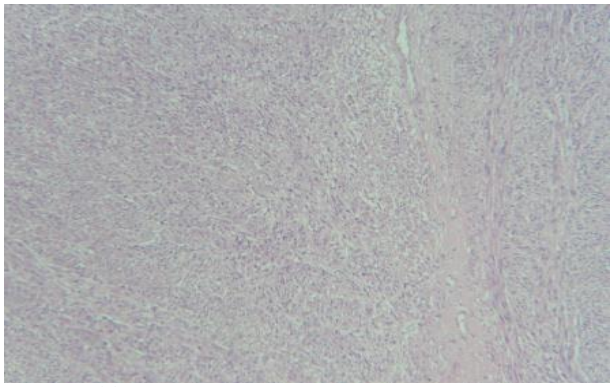

Figure 2. The tumor consists of intersecting fascicles of spindle cells (H & E, x100).

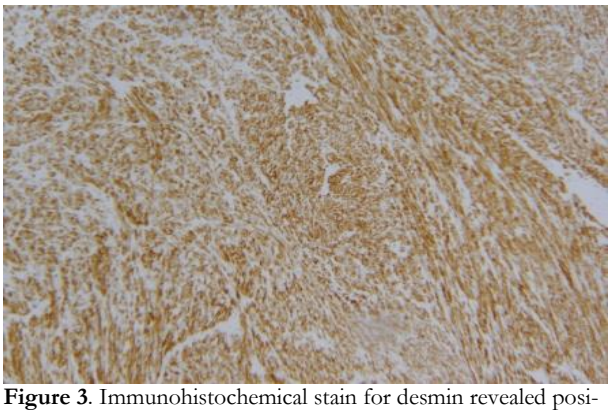

Figure 3. Immunohistochemical stain for desmin revealed positivity in the tumor cells, consistent with smooth muscle tumor (x100).

3. Discussion

This clinical report represents a rare case of retroperitoneal leiomyoma, which has a hard preoperative diagnosis, by radiological imaging. A complete surgical removal is necessary for pathological diagnosis and treatment (Mahendru et al. 2012).

Uterine fibroids are the most common gynecological benign tumors, accounting up to 25% of the reproductive aged women, usually involving uterine body, but they may occur in any site of the uterus (Sparic et al. 2016).

They have an unusual growth pattern and the incidence among primary retroperitoneal tumors has been reported as very low rate up to 1.2% (Naykı et al. 2014), located in the pelvis in the 73% of cases (Poliquin, Victory, and Vilos 2008). Retroperitoneal tumor is a rare condition, and the incidence of malignant retroperitoneal tumors is higher than benign tumors (Tantitamit et al. 2015). Dalen et al. (Dalen et al. 2001) reported that the incidence of malignant retroperitoneal tumors was 80% of all primary non-visceral tumors in the retroperitoneum and sarcomas such as liposarcoma or leiomyosarcoma comprised one third of retroperitoneal malignant tumors.

Several theories of the pathogenesis of extrauterine leiomyoma including retroperitoneal leiomyoma were suggested as followed: benign metastasizing leiomyoma, disseminated peritoneal leiomyomatosis, intravenous dissemination, parasitic leiomyoma, and so on (Barnaś et al. 2019). Of these theories, "parasitic" leiomyoma was first described by Kelly and Cullen (Howard Atwood and Cullen 1909) and it was defined as

completely separation of the pedunculated leiomyoma from uterus, with receiving their blood supply from another source.
Recently, as the increasing morcellation during myomectomy or hysterectomy, the theory of "iatrogenic" parasitic leiomyoma was suggested, as tumor growing by the fibroids' seeding during morcellation (Mynbaev et al. 2017).
Anyway, retroperitoneal parasitic leiomyoma is very rare condition. There are few reports of "parasitic myoma" and almost of these literatures are just case reports or small series.
Kho and Nezhat reported 12 cases of parasitic myoma in a single institution for 8 years. Of 12 cases of parasitic myoma, only 2 cases were found retroperitoneal space in this report (Kho and Nezhat 2009).
After a huge multidisciplinary clinical discussion on its origin, we thought that our reported case of retroperitoneal fibroid was consistent with a parasitic leiomyoma, since it had a separate blood supply, neither from uterine artery nor from ovarian artery. But patient had no evidence of concurrently uterine leiomyoma or no history of remote hysterectomy for fibroids or myomectomy, so the possibility of "iatrogenic" parasitic leiomyoma was clinically rejected.
Preoperative diagnosis of retroperitoneal leiomyoma can be very changeling, because of the rarity of this tumor. Common symptoms of retroperitoneal fibroids include abdominal discomfort, fatigue, backache, dyspareunia, and urinary and bowel complaints (Poliquin, Victory, and Vilos 2008).
About radiological preoperative diagnosis, pelvic magnetic resonance imaging (MRI) with contrast medium, is the most reliable technique for evaluating a retroperitoneal leiomyoma and for assess the anatomical location. But it could be difficult to differentiate a leiomyoma from a leiomyosarcoma basing on radiological imaging, such as pelvic CT scan or pelvic MRI alone (Karray et al. 2018). Some features of these retroperitoneal masses show an extensive central necrosis, invasive growth pattern, and heterogeneous appearance. They are helpful to differentiate a leiomyosarcoma from a leiomyoma (Mynbaev et al. 2020). In the literature there are cases diagnosed with fine needle aspiration biopsy [(DURSUN et al. 2005). The use of preoperative antigens, particularly Ca 125 and carcinoembryionic antigens, could be useful in patients with large tumors; in literature a case of CA-125 was reported to be high in leiomyomas 15 cm and above (Bischof et al. 1992).
Anyway, histomorphologic diagnosis is always mandatory for such cases, so as it is mandatory to preoperatively diagnose the retroperitoneal tumor as accurately as possible, since it can lead to an appropriate surgical method to remove the mass, as the problem is how to proceed, whether to radically remove the mass in laparotomy or to remove only the fibroid in laparoscopy (Tinelli and Farghaly 2018; Kondo et al. 2011). Moreover, preoperative radiological assessment of tumor vascularization is also necessary.
Surgery seems to be the only valid therapeutic option. Particularly, open surgery was the most used strategy in many reported cases. Large tumor size at the moment of diagnosis could be a contraindication to laparoscopic or robotic approach. Kondo (Tinelli and Farghaly 2018) reported a case of retroperitoneal fibroid where resection was done by laparoscopic approach. Age of the woman influences the therapeutic approach (hysterectomy vs leiomyoma resection).
Ultrasonography-guided or CT-guided fine-needle aspiration or biopsy may be histologically beneficial for the expectant management of asymptomatic patients refusing operation (Yüksel et al. 2020; L. Max et al. 2017).
Regular follow-up is mandatory because malignant transformation cannot be excluded (Jeong 2014; Paal and Miettinen 2001), but the prognosis of these patients is good.

4. Conclusions

The retroperitoneal uterine fibroid or leiomyoma is a rare condition, very difficult to diagnose preoperatively. This difficulty obviously also reflects on the surgical methodology to be applied in the removal: laparotomic radicality or minimally invasive surgery in case of fibroid (Billings, Folpe, and Weiss 2001).
A careful preoperative analysis of radiological imaging scan, by CT and MRI, or by intraoperative surgical and histological findings at frozen sections, may be helpful to diagnose accurately and to decide the strategy of treatment of retroperitoneal tumor.

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Habeas data and patient self-determination

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Abstract

In the digital era, the rising of new rights that redefine the very integrity of the person and legitimize their protection, especially in the field of health, calls for a reflection on the transition from habeas corpus to habeas data. The ancient habeas corpus, personal freedom understood as physical freedom, is now also a habeas data, in terms of digital freedom and the protection of personal information about the physical body. In this passage, the traditional legal culture clashes with the emergence of an information and knowledge society in which full and objective correspondence with constitutional concepts and rules is lacking. This is also happening in the health sector. Information in the medical field is an essential element, indispensable to be able to prepare the right treatment. The physician can collect, organize, and interpret patient data for the most correct diagnosis possible. Medical science, therefore, is information "from" the patient and "about" the patient, which is objectified through the computerised aggregation of the data of everyone undergoing medical treatment. Medical information becomes health data when it is processed, transforming it into a documental element of a digital nature. This article aims to give a theoretical contextualization of the concepts of habeas data, self-determination in the digital field and the issues related to informed consent and access to personal data.

Keywords: Habeas data, self-determination, information, access, informed consent

1. What is "habeas data"?

The cognitive analysis that moves from the right of habeas corpus of European legal culture to the constitutional guarantee of habeas data is one of the main innovations in the modern constitutions of Latin America, Africa and the former "satellite countries" of Eastern Europe (Acuña 2002). Although most of these rights were conceived and elaborated by European doctrine during the first half of the twentieth century, it is the "young" Constitutions established after the 1970s which represent a concrete example of legal production and guarantees which give importance to new rights such as: the right to data protection (as protection of the various rights of the individual which may be infringed by the laws of the Member States); the right to protection of personal data (as the power of the individual to obtain from public authorities, the defence of those rights violated or threatened by access, transmission, transfer, etc. . of one's own personal data); freedom of information (understood as the right to the informative self-determination of the person, i. e. the right to determine the when, how and quantum of a personal information subject to communication to third parties); freedom of information (as the personal guarantee to know and access personal information existing in databases, in electronic format, to control their content and therefore to be able to modify them in case of inaccuracy or undue storage or processing, and finally to decide on their circulation or transmission). Another new element foreseen in all modern constitutions of Latin American countries concerns the establishment of the constitutional guarantee of habeas data, according to which people have the right to claim that the image (even digital) that others have of them corresponds to the exact reality (Preite 2007). The

term habeas data has been proposed, therefore, to indicate a new and specific instrument of protection, symmetrical with respect to the pre-existing and traditional habeas corpus, precisely to protect the privacy and liberty of the citizen against computer abuse, a need that arises and develops with the new forms of interpersonal and also inter-institutional communication typical of the digital era (development of computer and information technologies, interconnection of world networks, development of new digital communication channels, telematic management and transmission of data). An important example in this area is the Constitution of Brazil, which contains declarations and principles not found in European Constitutions. In 1988 the Constituent provided for this new instrument of the citizen's freedom suitable for its safeguard against information technology even if, until the issuance of specific norms on the procedure of habeas data, the Brazilian jurisprudential practice continued to apply the procedure of "amparo", which takes the name of "mandado de segurança", a kind of special "amparo" of preventive type (to avoid the collection of information, mismanagement or treatment of the same) or of repressive or corrective type (to annul, rectify information or personal data that is false, incorrect or incomplete) with priority over all judicial acts except for the amparo itself and the habeas corpus (Acuña 2002). Unlike the Constitution of Brazil, in the Constitution of Paraguay the institution of habeas data has a much broader content as it includes access to information relating also to personal property, moreover it allows not only the rectification of data, but also their destruction if they are wrong or simply compromise other fundamental rights in an illegitimate manner. Every person has the right to know how the information will be used and what the purpose is. These are the substantial differences from the Brazilian Constitution, differences that offer more guarantees and broaden the object of protection of this right. In the State of Peru, the insertion of the institution of habeas data in the Constitution has taken place in a "contractual" form insofar as the right to the rectification of personal data is not contemplated, but the rights against the violation of which recourse is permitted are specifically regulated by reference to articles of the Constitution. In Ecuador, the 1997 Constitution, after the section on habeas corpus rights, includes a section on habeas data. It is not by chance that the paragraph is placed in this section of the Constitution entitled "Guarantees of Rights". As for the Constitution of Brazil, here, the insertion of the institution of habeas data was intended for the protection of particular "levels" of freedom of the citizen regarding personal information from other inmates. In addition to the possibility of correction and rectification of the data, their cancellation is also permitted. Other Latin American States, in addition to the traditional habeas corpus, included in the Constitutions for the protection of freedoms, contemplate the right of access to information in some articles of the relevant charters, without further specification and without indicating the possibility of making a habeas data appeal, as is the case in the Constitution of Guatemala in which there is a specific article regulating access to State archives and records.

2. Digital self-determination in health institution

The principle of digital self-determination, affirming itself as a social phenomenon through the passage from a process of "affirmation" of the person to an effort of "denial of the exclusivity of others", assumes the meaning of an unsuccessful attempt to preserve what remains most dear: «the fetish of a free will» (Frosini 1991). Being unable to assert himself, the subject can only limit external influences, not eliminating them, but reducing their scope and consistency to an acceptable level of tolerability. The development of information and communication technologies (ICT) and their use in all fields of human activity has represented a significant turning point in the application and interaction of computer knowledge. For example, the strategic use of these technologies in the health sector has led to the implementation of an eHealth model that is embodied in the combination of information technology, medicine, administrative science, and law, with the aim of affirming the centrality of the patient and his care, but which is counterbalanced by the problem of the use of his data. The data of each in-

dividual undergoing health treatment thus becomes an object of use and study (Preite 2014). Also, in the field of health, therefore, there is the passage from habeas corpus to habeas data, that is, from the protection of personal freedom in a merely physical sense to the protection from "any other restriction of personal freedom". Information in medicine is an essential element, indispensable to be able to prepare the right treatment. It is up to the doctor to collect, organise and interpret patient data for the most accurate diagnosis possible. Medicine, therefore, is information from the patient and the patient, which is objectified by the computerized aggregation of the data of each individual subject to medical care. Medical information becomes health data when it is observed to be humanly handled and processed, which transforms it into a document, even in electronic form, and creates a burden on the healthcare provider to protect new rights, including the right to privacy. Personal health data acquire not only scientific but also economic value, and it is precisely from this characteristic that derives a danger to which the protection of the patient must correspond (Izzo 2000). The use of electronic devices as a support for healthcare began with the creation of healthcare and administrative back-offices, mainly in healthcare companies, where it was created as an aid to take care of external relations with patients, providers, other companies, to systematize the overall information flows of the healthcare system. It is the task of the attending physician to contribute to this flow of information to allow the identity of the person concerned to be traced for administrative checks, for epidemiological and research purposes or to verify the correctness of medical prescriptions (Buccoliero, Caccia, and Nasi 2005). In the medical field, however, there is a difference and a different extension of the concepts of confidentiality and professional secrecy. The secret is non-specific and subjective and can only be defined in negative terms: it is secret everything that one wishes not to be brought to the knowledge of others. Confidentiality (e. g. sensitive or identifying data) has its own defined subject of protection, i. e. data leading to personal identification, health, sexual orientation and so on. In the forensic field, therefore, the different scope of the concepts of secrecy and confidentiality is relevant. The secrecy, however protected, does not give full guarantee of confidentiality. The disclosure of secrecy may be deemed lawful, and not sanctioned, for just cause of law and, in any case, only concerns the express nature of the subject matter of the secrecy; confidentiality is something else and must be protected within the framework of the individual's right to self-determination in all his or her free exercise of personality. Since the 1990s, the scope of confidential documents has been considerably reduced, leaving room for the category of documents accessible to those with an interest in them. Secrecy has become an exception, justified by the protection of values, to the right to information. Today, the right to information is an essential right for everyone and makes it possible to protect certain spheres of knowledge. This right is an important obstacle to abuses, mismanagement, corruption and, at the same time, facilitates the trust of the citizen who participates in the decision-making process of administrative and management apparatuses that govern and operate according to the principles of administrative transparency. Freedom of information is now beginning to be widely recognised in international law. There are numerous treaties, agreements and declarations of regional and international organizations that oblige or encourage states to adopt laws in this area. Many states around the world have now adopted laws on freedom of information and access. Specific laws guarantee the right of access in certain fields, such as health, the environment and consumer protection. Much of the legislation on the right to information has been adopted over the last 20 years and the new legislation adopts an innovative process to improve access to information. However, the evolutionary path does not end here, as many states remain trapped in the culture of state secrecy and the law is nothing but the mirror of societies that need to evolve on several fronts. The benefits of freedom of information include democratic participation and citizen awareness in public management. In medical science, information is the heart of treatment; in other words, information in many ways coincides with treatment. Medicine is therefore, first and foremost, information from the patient, whether understood in a subjective or objective sense. Every diagnosis presupposes and implies a flow

of data that the doctor must be able to collect, organize and interpret. Moreover, medicine is also (and above all) information on the patient: it becomes such when the physician shares the collected data in order to receive specialist responses aimed at integrating the diagnostic picture, that is, it allows to reduce the relational complexity level of clinical processes, determining the fundamental role that the timely transfer of medical information plays in the perspective of the provision of a treatment that appears to be more and more the complex product of a network work (Aydin 1989). The information thus shared (the patient's clinical history, symptoms, therapeutic treatment, and outcomes) can be archived and made accessible to other physicians, thus becoming "experience" for the scientific community. Once the information on the patient has become a "case", it is objectified, aggregated, and validated according to epidemiological and scientific canons, to become new knowledge to be used for diagnostic and therapeutic purposes. With the meta-analysis procedure of statistical evaluation of aggregate data, Western science seems to approach the potential of the inductive method for the first time. This represents a relevant fact that this revolution in the epistemological method followed by Western medicine, connected to the Cartesian deductive method, could only develop thanks to the advent of ICT. The consolidation of meta-analysis in the medical field, as a method of statistical processing and reading of the results of individual studies, is today the most evident indication of the value that the aggregation of data represents in the development of medical knowledge (Goodman 1999; Trimarchi 2003). One example is preventive medicine. In many international and national health policy documents and directives, prevention means collecting and studying information to quickly delineate the epidemiological development of diseases, and at the same time disseminating information about the care and preservation of health. Prevention means, therefore, guaranteeing the best accessibility, usability, timeliness, completeness and accuracy of information, information "to" the patient "for" the patient. But even when the primary objective is not prevention, but the individual seeking medical care and assistance, information is still an integral part of treatment. This is the profound ethical and social significance underlying informed consent and its recognition as a legal principle coessential to the treatment of the patient and to the respect of his or her subjectivity in the face of care. In the legal field, information on medical activity assumes a key role in ensuring the implementation of patient rights. A role that becomes evident when the evaluation of the health service received by the latter transits through a courtroom. This is the moment in which medical information assumes (or at least: should assume) documentary forms suitable to satisfy the needs of certainty and authenticity required by law. In fulfilling a function other than the one for which it was collected and produced (e. g. clinical), medical information is relevant as documentary data (or set of data) subject to precise rules, which must meet formal requirements aimed at certifying the integrity and completeness of the information contained therein, even when this conflicts with the need for promptness and speed related to the therapeutic task that the information itself, first and foremost, serves to perform.

3. Access to information and informed consent

The right of access to information is not a new concept because it appeared for the first time in the eighteenth century, in the middle of the "Enlightenment" phase. The French Declaration of 1789 refers to the right of access to information in the provisions concerning public contribution: "Every citizen has the right to decide, personally or through his representatives, on the necessity of state contribution, in order to recognize it freely and to know the purposes for which it is used". Since then, several states have taken measures to regulate access to public information. Today, public administrations produce large quantities of documents containing data and information of all kinds. Almost all political and economic information documents are of public source (laws, judgments, economic planning documents, studies and research by public bodies, statistical data, scientific reports, etc.). Public information is therefore an integral and essential component of modern democracies and an indispensable element in feeding

public opinion. Over time, the scope of confidential documents has been considerably reduced, leaving room for the category of documents accessible to anyone with a legitimate interest. Secrecy has therefore become an exception to the right to information and is justified only in special cases and situations provided for by law. The right to information is an essential right and enables certain spheres of knowledge to be protected. Freedom of information is now widely recognized in international law; there are numerous treaties, agreements, and declarations by governmental or supranational organizations that oblige or encourage states to adopt laws on the subject. In medicine, information is at the heart of care and coincides with it. Medicine is therefore, first and foremost, information "from" the patient, both in the subjective and objective sense. Every diagnosis presupposes and implies a flow of data that the doctor must know how to collect, organize, and interpret. In addition, medicine is also information "on" the patient when the doctor shares the data collected to receive specialist feedback aimed at supplementing the diagnostic picture, i. e. it allows to reduce the level of relational complexity of clinical processes, thereby determining the crucial role that the timely transfer of medical information plays in the provision of care, which is increasingly becoming apparent in the context of the provision of care. The complex product of a network work (Fiori, Bottone, and D'Alessandro 1999). The information shared in this way (the clinical history, the symptoms, the therapeutic treatment of the patient and its outcomes) can be treated, stored, and made available to other physicians, thus becoming an experience for the scientific community. This reflection is propaedeutic to the medical practice of "informed consent", which was born in the context of a renewed social culture on the way to understand the doctor-patient relationship, the same that has also influenced the jurisprudence, which has firstly acknowledged and then considered as fundamental the compulsoriness of informed consent. It is no coincidence that an increasing number of patients have taken legal action on the (presumed) professional negligence of the doctor, based in many cases on imprudence and negligence in making the diagnosis or on the failure to carry out in-depth diagnostic tests, as well as on the lack of information and acquisition of consent, thus considerably increasing the number of disputes on this delicate subject. Informed consent is, in fact, the right of the patient to choose, accept or even refuse the treatment (diagnostic-therapeutic) offered to him, after having been fully informed (unless the patient expressly waives) about the diagnosis and expected course of the disease, the treatment options (including their refusal) and their consequences (Preite 2014). However, the issue becomes complex when analysing the effects of telemedicine on informed consent, which also extend to the possibility that the patient receives a benefit derived from the knowledge of other physicians via telematics. The question is whether and to what extent computer technologies applied in the medical and clinical (e-health) fields can improve the cognitive processes by which patients receive the explanatory information that is the subject of informed consent. In the United States, computer-based dissemination systems have long been on the market, which can be delivered by the doctor to the patient to facilitate the learning of the contents of the information accompanying the patient's decision to undergo a particular therapeutic or diagnostic procedure. These systems guide the patient to understand the information received and measure the actual degree of it through test grids, the computer support documents at the end of the path the results of the cognitive process followed by the patient. Moreover, digital technology envisages the possibility of implementing new tools suitable for protecting the patient's self-determination. It can already be assumed that the implementation of digital health cards can provide anyone with the possibility of making their decisions regarding the therapeutic scenarios following a sudden event knowable, with a margin of certainty and security, as well as with a functional versatility in the critical context in which these decisions must be made known to the health authorities, which is completely unknown to traditional paper documents. With reference to informed consent, therefore, e-health represents a further possibility to offer answers to the problem of the uncertain distribution of the burden of proving in court whether (and in what way) informed consent has been given. In the background of the ques-

tion, there is an antagonism between a penalist approach which ends up placing the burden of proof on the doctor (Riz 1990; Nannini 1989) and a contractual approach which produces opposite effects, opening to the patient the difficult experience of proof of a negative fact entrusted to testimonial discussions. Hospital practice has reacted pragmatically to this problem by providing for the use of information forms which must be read, accepted, and signed by the patient. E-health certainly facilitates decision-making between doctor and patient when initiating a treatment or an invasive diagnostic procedure, a decision which can be institutionalised at a different level from what it seems to be today, because of a practice which relies exclusively on the legal value of a signature. Informing a patient is the exclusive task of the practice in modern medicine and cannot be reduced to the simple acquisition of a signature, rather it is necessary to institutionalize and take care of the relationship between the parties involved in the process and thus the moment of doctor-patient communication (Schuck 1994).

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