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# *Case report as a challenge in clinical practice and research*

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***Prof. Asoc. Dr. Voltisa LAMA***

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*Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. Without clinical expertise, practice risks becoming tyrannized by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. –*

**David Sackett<sup>1</sup>**

The clinical case report has a long-standing tradition in the medical literature and despite the recent tendency toward a reduced acceptance of case reports in some high impact journals as more advanced research methods have gained ground, the genre still appears popular. It is a valued part of the different research methods, especially since it complements other approaches (2). Clinical cases provide a very useful tool by which clinicians can share their experience and may be considered as decisive evidence if they are well designed and accurately presented.

A case report consists most often of one case or even two cases; while the case series report usually consists of three to ten patients. Case reports and case series reports are descriptive studies based on single or multiple observations made during the patient assessment. Case reports describes the rare and atypical issues and it is an unique approach to present unusual and uncontrolled observations regarding the symptoms of the patient, the clinical and lab findings, the side effects of medications, the course of illness, complications of interventions, etc. In short, anything that is rare or has never been observed from the clinicians previously might be noteworthy for the medical community and ought to be published<sup>2</sup>.

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<sup>1</sup> David L Sackett, William M C Rosenberg, J A Muir Gray, R Brian Haynes, W Scott Richardson (1996). Evidence based medicine: what it is and what it isn't. British Medical Journal; 312:71-72

<sup>2</sup> Trygve Nissen, Rolf Wynn (2014). The clinical case report: a review of its merits and limitations. BMC Res Notes;7:264, DOI: 10.1186/1756-0500-7-264

The clinical case is unique in taking care of the detailed study of the individual patient. A detailed description of the history, examination findings, special investigations and management are crucial to the interpretation of the case. The case report allows emphasis on the narrative aspect, especially in the field of psychology and psychiatry. The objective is not generalizable knowledge, but an understanding of the meaning and intentionality for an individual or individuals, which is really important in the medical field. Relevant examples are Sigmund Freud's breakthrough case study of the patient "Anna O", by which Freud discovered the unconscious root of her disease and how to treat her somatization symptoms or Hans Asperger publication in which he described children with different wired cognitive style, and together with Kanner study of a similar group of children brought to the discovery of what today is called the "autism spectrum disorder". In medical field the patient symptoms or findings should be described meticulously, making it possible for other medical doctors to detect cases with similar clinical picture.

There are various advantages and also some disadvantages to the case study approach as a research method. Case reports have proved useful in the identification of adverse and beneficial effects, the recognition of new diseases, unusual forms of common diseases, and the presentation of rare diseases. From a single patient or case series report new hypotheses could be formulated. These hypothesis could then be tested with another type of study that is designed to contest or confirm the hypotheses. Case reports are considered the lowest level of evidence, but they are also the first line of evidence, because they are where new issues and ideas emerge. They can help in the identification of new trends or diseases. Still the method is unable to deliver quantitative data and there is a lack of ability to generalize, no possibility to establish cause-effect and bias of over-interpretation. The major challenges to case studies are based on generalization, validity and longevity of the case. Case reports should explore and infer, not confirm, deduce, or prove.

The editorial policies of the journal will influence the format of publication. Compared with other study designs case reports provide a lower level of evidence and case reports are less cited, which may adversely affect a journal's impact factor. We have published in the previous *Medicus* journals 1-2 cases per issue. Although high-impact journals have reduced the number of case reports and case series published per issue, these types of study continue to have a unique importance in the field of health sciences<sup>3</sup>, indicating that they still carry weight in the scientific medical literature. The proficiency and judgment that clinicians acquire through clinical experience and clinical practice is reflected in more accurate diagnosis and in their clinical decisions.

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<sup>3</sup> Keyse Loyanne Batista da Silva; Samara Maria Douets Vasconcelos Cunha Dias; Rivadávio Fernandes Batista de Amorim (2018). Case report and case series: is there room for them? *Geriatr Gerontol Aging*. 12(1):4-7. DOI: 10.5327/Z2447-211520181700085

# *Metastatic renal cell carcinoma to the thyroid gland*

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## **Background**

The thyroid nodules are frequent in general population. The nodules are more prevalent in women and the prevalence of thyroid nodules increased with age and detection are increased in people who underwent thyroid ultrasound, even for diagnostic imaging unrelated to the thyroid. (1)

Most thyroid nodules are benign and around 5 % of all nodules are cancer. Approximately 90 % of thyroid cancer are differentiated thyroid cancer. Metastasis to thyroid are rarely observed in the clinical practice. The incidence of metastasis to thyroid gland is 0.36 % in all thyroid malignancies. (2)

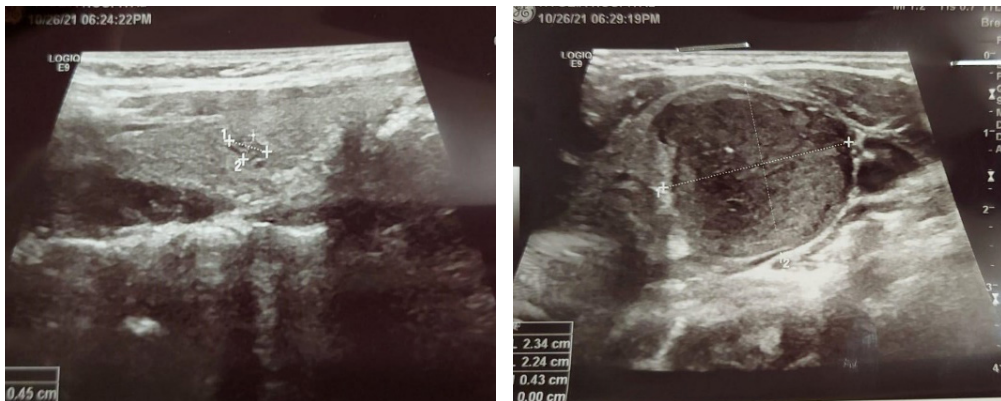
## Case Presentation

A woman 42 years old present to the consultation, because she had noticed an increase of left lobe of the thyroid gland for the last months. She hadn't known history for thyroid disease. She hadn't fever, no pain or tachycardia.

During physical examination nodule around 2 cm in the left lobe of thyroid was detected during palpation. Clinically the function of thyroid was normal. Laboratory test confirmed normal values of serum thyroid –stimulation hormone (TSH) and FT4 (Free thyroxine) and increase values of anti –thyroid peroxidase (TPO) antibodies.

The ultrasound of the neck was performed and an oval shaped hypoechoic solid nodules with dimensions 2.34 x 2.24 cm in the left lobe of thyroid was diagnosed and one nodule below 1 cm to the right lobe of thyroid. The nodule had well-defined smooth margin without calcification and increased vascularity. No suspicious lymph node was detected to the neck.

**FIGURE 1-** Thyroid ultrasound (A, B)



A. An oval hypoechoic solid nodules with dimensions 2.34 x 2.24 cm in the left lobe of thyroid

B. Right lobe of thyroid with a nodule 0.45 x 0.29 cm

Her past medical history: The patient referred than eight years before she underwent surgery: Left nephrectomy for a renal cell carcinoma.

During follow up, she denied know metastasis from renal carcinoma, but last follow up was performed three years ago, and the positron emission tomography (PET), wasn't performed before. The patient was advice to performed FNA – Biopsy. The result of biopsy was suspicious for malignancy. Based on result of FNA-Biopsy the patient underwent surgery- total thyroidectomy.



The pathology findings were consistent with a solitary metastasis most compatible with a clear cell carcinoma from her previous renal carcinoma and the chronic lymphocytic thyroiditis.

The immunohistochemistry findings ruled out primary thyroid cancer: CD-10 positive, EMA positive, Thyroglobulin negative, HBME-1 negative.

1.5 months after thyroid surgery the positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose ( $^{18}\text{F}$ -FDG) was performed where focal  $^{18}\text{F}$ -FDG uptake was seen in the thyroid bed, but didn't find other metastasis. The ultrasound of the neck, doesn't detected thyroid tissues and without pathological lymph node.

The lab results (after surgery): TSH = 5.9 m UI/ml (normal range 0.17-4.2); Ac TPO antibodies = 90 UI/ml (Normal range < 70), Thyroglobulin <0.2 ng /ml (Normal range 0-5); Thyroglobulin antibodies = 32 UI/ml (Normal range < 70).

The patient after surgery was treated with levothyroxine and continue the follow up by oncologist.

## Discussion

Thyroid nodules are frequent findings on thyroid ultrasound and the increased use of imagin studies has increased the frequency of thyroid nodules. The incidence of thyroid cancer has been increased faster last years, but this has been referred as an overdiagnosis of low risk thyroid cancer and identification of subclinical disease (3, 4).

Papillary carcinoma is the most common subtype of primary malignancies of thyroid cancer. Thyroid metastasis is uncommon, the incidence of thyroid metastasis ranges from 0.15 to 6 %, depending on the study. Usually the metastasis to the thyroid gland originates from renal cell carcinoma, lung cancer or breast cancer (5).

The incidence of renal cell carcinoma increased with age. Renal cell carcinoma is the most common cancer of the urinary system. Most of renal cell carcinoma are detected during screening test, but distant metastasis may be seen frequently even years after detection of primary tumor (6, 7).

Clinically there is no difference between primary and metastasis cancer of the thyroid gland. There is no difference even on radiological data's and sometimes even fine needle aspiration biopsy can't differentiated primary tumor from metastasis (8). Now days the immunohistochemical studies help the right diagnosis (9). After detection of isolated metastasis to the thyroid gland, thyroidectomy is recommended. The survival rate after thyroidectomy may prolong after aggressive treatment for solitary thyroid metastasis (10).

## Conclusion

Thyroid metastasis from renal cell carcinoma is uncommon finding. Renal cell carcinoma can metastasize to distant organs even many years after detection of primary cancer. If the patient had only isolated metastasis to the thyroid gland, thyroidectomy is recommended to improve the prognosis of the patient.

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# Knowledge, attitudes and behaviors of the community about palliative care

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## Abstract

*Background: Although cancer is the disease for which people need palliative care the most, the number of diseases and conditions requiring palliative care has increased and will continue to grow. Palliative care improves health, reduces unnecessary hospitalization as well as overuse of health services. There are several barriers to palliative care access and the main are those related to the public such as: lack of public awareness on palliative care, on their benefits; cultural and social barriers.*

*Aim: Assess the current level of knowledge, attitudes, and behaviors of the community on palliative care*

*Methodology: This is a descriptive study that collects information from a representative sample of 712 subjects from Lezha, Mirdita and Shkodra districts, through a semi-structured questionnaire. SPSS statistical program was used for data analysis.*

*Results: 77.5% of participants had never heard of palliative care. The majority of respondents, 66.3%, did not know services that provide palliative care in Albania, or in their area of residence. 58.8%, do not recognize any of the rights of palliative care patients. There are incorrect and fatalistic attitudes towards diseases that require palliative care.*

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*Most preferred to receive palliative care services in private clinics (42.7%) or abroad (20.1%). Over 2/3 of them, 67.9%, have not seen/heard/read any information on palliative care and only 4.6% mention the medical staff as a source of information.*

*Conclusions: There is a lack of information, misunderstandings and fatalistic attitudes on many issues related to palliative care. The subjects did not have information on the services that provide palliative care in Albania and in their residential areas as well as on the rights of palliative care patients. Medical staff has been a minimal source of information on palliative care issues. The findings of the study were significantly related to the educational level of the subjects in the study and the residence without obvious differences between the districts included in the study.*

**Keywords:** *palliative care, community, attitude, knowledge, misconception*

## **Introduction**

According to the WHO, palliative care is an approach that improves the quality of life of patients facing life-threatening illness-related problems, as well as their families by preventing and alleviating physical, psychosocial, or spiritual suffering [1].

Today's concept of palliative care is much broader than caring only for cancer patients. It is needed for a very wide range of diseases and includes care for patients with other diseases such as end-stage chronic disease, acute trauma, cardiovascular disease, neurological disease, dementia, severe burns, extreme weakness of old age [2]. Evidence shows that the need for palliative care is constantly increasing as the reasons that lead to this - life expectancy (population aging), incidence and prevalence of chronic diseases, as well as people's interest in improving the quality of life - are increasing. [3].

Although cancer is the disease for which people have most need for palliative care, the number of diseases or other conditions that require palliative care has increased. There are over 20 diseases that require palliative care support including HIV, dementia, cerebrovascular disease, congenital malformations, malnutrition, musculoskeletal disorders, etc [4]. Globally, by 2060, deaths with serious health-related suffering will increase in all regions, most rapidly among people aged 70 years or older [5]. Considering that the burden of non-communicable diseases is increasing and as result of the ageing of populations, the global need for palliative care will continue to grow.

The WHO has focused a global response on palliative care and the 2014 World Health Assembly resolution urges all member states to include palliative care as a key part of their health systems. Integrating palliative care at all levels of the health

care system is essential to be accessible to anyone in need of palliative care as well as to achieving the Sustainable Development Goal (3.8: Universal health coverage) [6]. But despite this, currently lack of access to palliative care continues to be a public health problem worldwide. Thus, every year, it is estimated that about 40 million people need palliative care and only about 14% of them currently receive it [2] and 45% of countries do not have access to palliative care [7]. Palliative care improves health by avoiding suffering and thus constituting an indicator of high-quality health systems and generating economic benefits [8]. Early palliative care reduces unnecessary hospitalization as well as overuse of health services [9].

Globally, there are several barriers to insufficient access to palliative care. Among the main barriers to access to palliative care are those related to the public such as: lack of public awareness on palliative care, on the benefits it offers; cultural and social barriers (beliefs about death and dying; misunderstandings) is only for cancer patients, the use of opioid analgesics leads to substance abuse, etc [2]. Low level of awareness can have consequences for palliative care service, leading to negative perceptions resulting in the quality of care provided for palliative care services [10,11]. Palliative care is most effective when considered early in the disease. Early initiation of palliative care improves the quality of life for patients, reduces unnecessary hospitalization and over-use of health care services [2].

In Albania, cancers cause more than 18% of all deaths, ranking second among the causes of death, after cardiovascular disease. It is estimated that cancer rates in Albania will increase in the next decade due to population aging, declining fertility rates and some lifestyle factors. Palliative care in Albania has been established since 1993. Palliative care in the public sector is provided only in one center in Tirana, in-house oncology service (SOB) and in six districts by several non-governmental organizations. The National Cancer Control Committee, the National Cancer Control Program has been set up and the National Cancer Control Strategy, 2011-2020 has been approved. Terminal patients and their families are uninformed and confused about the level of service they need to address their health needs in the terminal stage [12].

**Aim:** Assess the current level of knowledge, attitudes, and behaviors of the community on palliative care

## Methodology

This is a descriptive study that collects information from a representative sample of 712 entities from the community of Lezha, Mirdita and Shkodra districts. The sample size was selected in proportion to the size of the population number. The

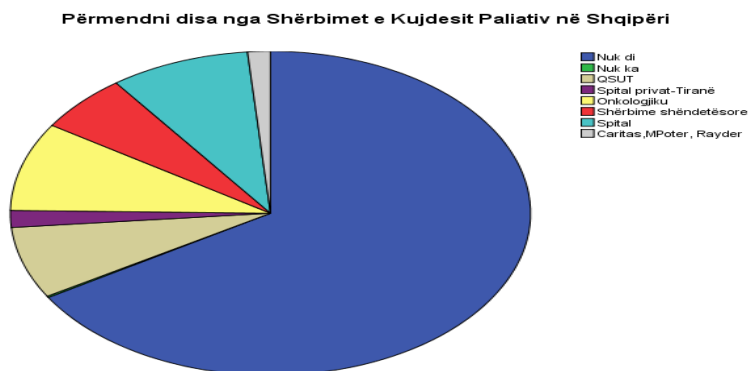
subjects in the study were stratified by districts, then by villages within each district. Within each layer, random selection was strictly observed, simple and proportional to the size of the respective stratum. A semi-structured questionnaire was used for data collection which was tested and then the final version was drafted. The staff who conducted the interviews were trained in advance in the field for the specifics of this study. The subjects selected by sampling were initially explained the purpose of the study, assured of confidentiality, informed oral approval obtained, and encouraged to give the most honest answer possible. All of these were reflected on the first page of the questionnaire. SPSS statistical program was used for data entry and analysis.

## Results and discussion

A total of 712 questionnaires were analyzed: Lezha 172 subjects, Shkodra 404 subjects and Mirdita 136. Out of 712 subjects participating in the study, 57.4% were female and 42.6% male with a wide age range, from 20 to over 65 years old. Of these, 28.7% lived in urban areas and 71.3% lived in rural areas. Data on the education of the respondents showed that 31% of them had higher education, 43.3% had secondary education, 24.9% had 8-year education and 0.8% had primary education.

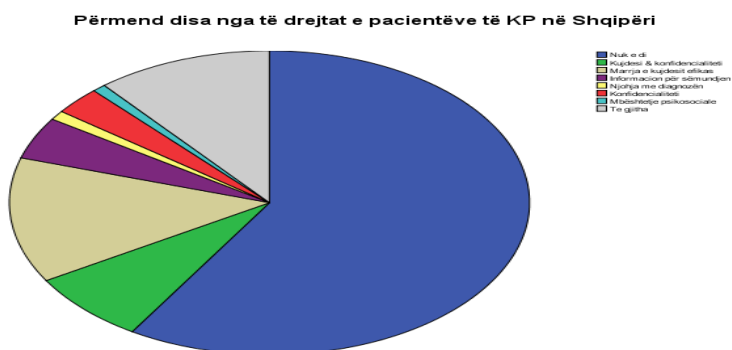
A large number of participants (77.5%) had never heard of palliative care. But even those who claimed to have heard of palliative care when asked the in-depth question “what is palliative care?” defined it as: care for the person with AIDS, care for the person with bed diseases. Most of the respondents (66.3%) did not know services that provide palliative care in Albania, while 67.7% of them do not have information about the existence of these services in their area. Data on knowledge on services providing palliative care in Albania are presented in Chart 1 below.

**GRAPH 1. Knowledge of palliative care services in Albania**



More than half of the respondents (58.8%) did not recognize any of the rights of palliative care patients and only a small number (11.0%) knew more than one of these rights. Specifically, receiving efficient care was recognized by 13.3% of participants, receiving palliative care and confidentiality, recognized by 7.6%, receiving information on the disease by 4.5%, maintaining confidentiality by 2.9%, getting acquainted with the diagnosis by 1.0 % and psychosocial support from 0.8% of respondents. Data on the knowledge of the subjects in the study, on the rights of palliative care patients in Albania, are presented in Graph 2.

**GRAPH 2.** Knowledge on the rights of palliative care patients in Albania

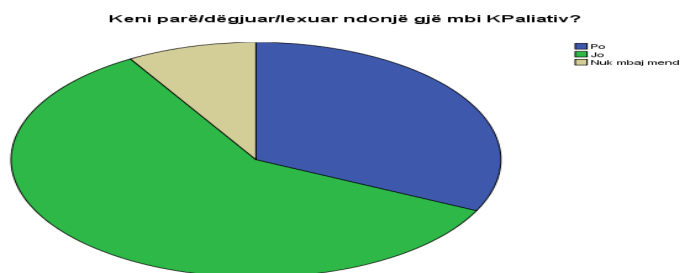


There are incorrect attitudes on many of the issues related to palliative care. Incorrect attitudes about continuing care for a patient until the end of life were identified in 4.9% of respondents. They think that if the patient is at the end of life, care for him should be stopped. Data analysis also showed that issues related to palliative care continue to remain taboo and there are still fatalistic attitudes towards diseases requiring palliative care. Thus, 14.2% of the respondents would not want to discuss their problems with anyone, if they were palliative care patients, while 15.6% of them would not want to provide services to palliative care patients.

The analysis of the data shows a preference for the use of private sector services, which indicates a lack of trust in public health services. Thus, when asked “where would you prefer to receive services if you needed palliative care?”, Only 31.6% of them refer to a doctor at a health center. The rest answered that they would prefer clinics and a private doctor, 42.7%, in clinics abroad 13.1%, and to the best service without defining 7%. An issue of interest due to its importance was the information on the deposit of opioid / analgesic drugs that remain in cases where the patient loses his life. More than 2/3 of the subjects, 69.2% of them, did not know how to deal with them in these situations. About 13.6% of them reported that they should be thrown in the trash, 9.3% answered that they are buried and only 5.4% of them answered that they should be handed over.

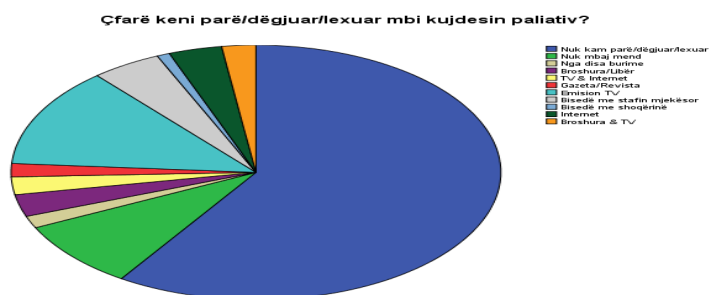
A variety of answers were taken from the question “what do you think are the problems / needs of palliative care patients”, where two of the most mentioned needs were economic and psychological. Other problems that were identified were: lack of medicines, expensive medicines, lack of 24-hour service, delay in receiving services, lack of paliative care services, lack of paliative care center in their areas, lack of psychosocial staff, lack of confidentiality, lack of necessary equipment for this patients, etc. The subjects in the study were asked the question “have you seen / heard / read any information related to palliative care”?, only about 1/3 of the subjects (32.2%) reported that they have seen / heard or read information related to paliative care. Others, 59.3% have not seen / heard / read any information and 8.6% do not remember this. Data on the information on the palliative care, are presented in graph 3.

**GRAPH 3.** Have you seen / heard / read any information on palliative care



Regarding the source of information on palliative care issues, television is mentioned the most by 12.6% of respondents. The Internet was mentioned by 3.5% of respondents, followed by brochures and books, 2.8%, newspapers and magazines 1.7%, society by 0.8% and 1.5% claimed to have received information from several sources. Medical staff is mentioned as a source of information by only 4.6% of the subjects in the study. Data on the source of information on palliative care are presented in graph. 4 below.

**GRAPH 4.** Data on the source of information on palliative care





One of the main goals of the study was to identify communication channels for the delivery of health messages, as part of the assessment, before initiating a communication intervention to change behaviors. Based on this, participants were asked about their preferences for receiving information on palliative care. Primary preference for receiving information on palliative care was health staff, reported by 36.1% of respondents, television by 7.3%, internet by 16.2%, brochures/magazines/books by 7.0%, and 18.1% of respondents considered all sources of information listed in the questionnaire

## Conclusions

There is a lack of information, limited information and misunderstandings on many of the issues related to palliative care by the community. The subjects did not have information on the services that provide palliative care in Albania and in their residential areas. There is also a lack of information on the rights of patients in need of palliative care. Issues related to palliative care and terminal diseases in particular, continue to remain taboo and there are fatalistic attitudes towards diseases that require palliative care. Respondents reported a number of problems related to palliative care such as lack of 24-hour service, lack of a palliative care center in their areas, lack of psychosocial staff, lack of confidentiality, lack of necessary equipment, etc. Our study also found that health staff has been a very minimal source of information on PC issues. Television and radio have been reported as among the main sources of information on palliative care. Almost all the findings of our study were significantly related to the educational level of the subjects in the study, and residency. Subjects residing in urban areas and with a higher level of education demonstrated better knowledge than their counterparts residing in rural areas and with a lower level of education. There were no obvious differences in the knowledge, attitudes or behaviors of the subjects when compared between the districts included in the study.

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# *Secondary antiphospholipid syndrome at a young male*

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## Abstract

*Background: Antiphospholipid syndrome (APS) is an autoimmune disease characterized by recurring venous and/or arterial thrombosis and the presence of circulating antiphospholipid antibodies. APS occurs as a primary condition or secondary to other autoimmune disorders, mainly systemic lupus erythematosus (SLE). The diagnosis of APS is made on the basis of suggestive clinical findings and the presence of one or more of the following antiphospholipid antibodies (LAC, aCL antibody or a $\beta$ 2GPI antibody present on two or more occasions, at least 12 weeks apart). A clinically significant aPL profile has been detected in approximately 30 % of patients with SLE.*

*Case presentation: We are presenting a rare case of a 23 years old male with complaints of dyspnea, retrosternal discomfort, fatigue, general weakness, joint pain over a period of 3 months. The patient reported a single syncopal episode, 3 months prior to admission as his first clinical manifestation. He was at first diagnosed with Thrombocytopenia in 2007 and Systemic Lupus Erythematosus (SLE) in 2020. During his hospitalization, the patient experienced recurrent headaches, dizziness and episodes of elevated blood pressure (170/100 mmHg), as well. Moreover, laboratory and imaging examinations showed bilateral pulmonary thromboembolism and positive Anticardiolipin antibodies, positive ANA, positive SSA & SSB.*

*Conclusion: Given the lack of typical clinical findings in the early stages of the disease, establishing a diagnosis of APS can be challenging. Although APS is one of the most common thrombocytophiliias, unfortunately, it remains underdiagnosed. Clinicians should investigate for the presence of antiphospholipid antibodies, as early diagnosis may influence the course of the disease.*

**Keywords:** Antiphospholipid syndrome, SLE, Male

## Background

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by a state of hypercoagulability potentially resulting in thrombosis of all segments of the vascular bed [1].

The syndrome is characterized clinically by recurrent venous and/or arterial thromboembolic events, or pregnancy morbidity. In addition to these clinical manifestations, the sine qua non for the syndrome is the persistent presence of a unique collection of autoantibodies that target specific phospholipid-binding proteins [2]. Antibodies against  $\beta$ 2-glycoprotein I (a $\beta$ 2GPI) and cardiolipin (aCL), together with the functional assay lupus anticoagulant (LAC), are the three

laboratory tests considered in the revised criteria for the diagnosis of the syndrome [3].

Currently, we use the classification criteria for antiphospholipid syndrome (APS) formulated during the consensus conference in Sapporo and revised in Sydney [4].

The classification criteria for definite APS are met when at least one clinical criteria (thrombosis or pregnancy morbidity) is present in association with one laboratory criterion (LAC, aCL antibody or a $\beta$ 2GPI anti- body present on two or more occasions, at least 12 weeks apart), and thrombosis should be confirmed by objective validated criteria [3, 5].

However, there are several clinical manifestations not included in the classical revised criteria of APS such as thrombocytopenia, hemolytic anemia, cardiac valve disease, renal microangiopathy, livedo reticularis, neurologic disturbances, leg ulcers and amaurosis fugax [6] that are common features in APS patients and as stated by Miyakis et al., they can be classified as “non-criteria features of APS”.

Prevalence of the aPL in the general population ranges between 1 and 5%. However, only a minority of these individuals develop the APS. Some estimates indicate that the incidence of APS is around 5 new cases for 100,000 persons for year and the prevalence around 40–50 cases for 100,000 persons [7].

Although the ontogeny of these pathogenic antibodies has not been fully elucidated, some evidences suggest the involvement of both genetic and environmental factors. The ability of aPL to induce a procoagulant phenotype in APS patients plays a central role in the development of typical arterial and venous thrombotic manifestations of the disease. Inflammation serves as a necessary link between this procoagulant phenotype and actual thrombus development. Recent evidence indicated a role for abnormal cellular proliferation and differentiation in the pathophysiology of APS, especially in those patients with pregnancy morbidity and other more atypical manifestations that have no identifiable thrombotic cause [8].

The APS can be found in patients with no clinical or laboratory evidence of another definable condition (“primary” APS), or it may be associated with other diseases (“secondary” APS).

Renal involvement in primary APS is primarily characterized pathologically by noninflammatory occlusion of a broad spectrum of renal blood vessels, ranging from glomerular capillaries to the main renal artery and vein [9,10,11-14].

Involved arteries and arterioles often have a thrombotic lesion, resulting in reactive intimal mucoid thickening, subendothelial fibrosis, and medial hyperplasia [9].

Affected glomerular capillaries reveal thrombi with associated mesangiolysis, mesangial interposition along the glomerular capillary wall, and electron lucent areas in the subendothelial space.

Focal atrophy of the cortex in association with interstitial fibrosis may be observed, presumably resulting from tissue ischemia.

Renal disease in antiphospholipid syndrome associated with systemic lupus erythematosus — Patients with lupus and aPL commonly have a history of systemic thrombosis, fetal loss, neurologic disorders, and thrombocytopenia [15,16,17]. In patients with lupus, the principal laboratory features that correlate with the presence of high titers of immunoglobulin G (IgG) aPL are thrombocytopenia, the presence of a false-positive Venereal Disease Research Laboratory (VDRL) test for syphilis (fluorescent treponemal antibody [FTA] negative), and a prolonged activated partial thromboplastin time (aPTT) [15,10,18]. Renal disease in this setting may result from microthrombi and/or deposits of immune complexes.

Here, we describe a case of a young man who was diagnosed with antiphospholipid syndrome (APS) with early complex and unusual manifestations.

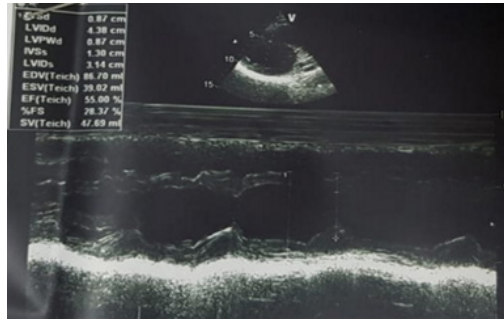
## Case presentation

A 23-years old man presented to the Emergency Department on September 2019 with a 3-month history of dyspnea, retrosternal discomfort, fatigue, general weakness and joint pain. His personal medical history was significant for a single episode of syncope 3 months prior to his presentation. In 2007 he was diagnosed with Thrombocytopenia, hospitalized for 1 week with a platelet count of 98,000/mm<sup>3</sup>. He was treated with a daily dose of Prednisone 10 mg, however he reported poor treatment compliance. In March 2020 he was diagnosed with Systemic Lupus Erythematosus (SLE) and was prescribed Hydroxychloroquine (HCQ) 200 mg/d p.os and Prednisone 5 mg/d p.os. He continued not to adhere to the prescribed therapy. He had no known allergies and his family history was unremarkable.

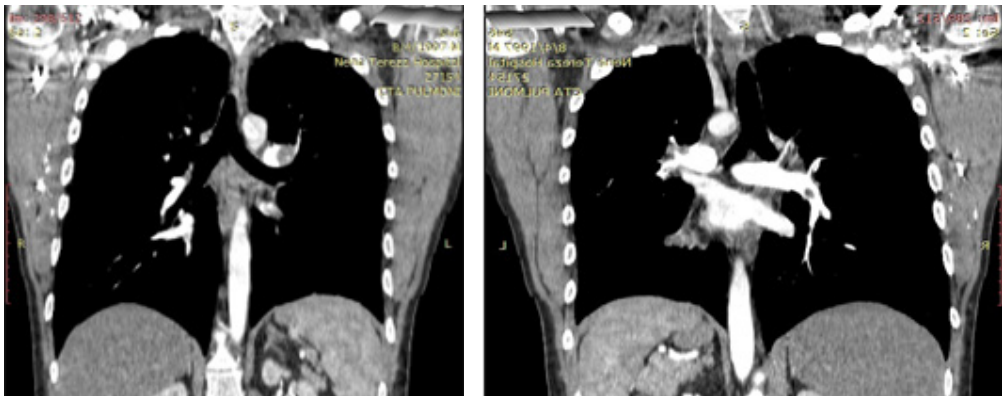
Following his admission to the Department of Internal Medicine, the physical examination showed:

- Normal body temperature,
- HR 91 per min & BP 170/110 mmHg
- Bilateral vesicular respiration, RR 26 per min, SpO<sub>2</sub> 96%
- No edema

Multiple imaging studies were scheduled. A transthoracic ultrasound and an abdominal ultrasound, were both normal. Subsequently, a chest CT revealed bilateral pulmonary embolism (PE).



**Echocardiography**



**Chest CT Angiography**

A Complete Blood Count analysis showed: WBC 8500/mm<sup>3</sup> (n.v 4000-10000), HGB 14.9 g/dl (n.v 11.0-16.5), RBC 4.99x 10<sup>6</sup>/mm<sup>3</sup> (n.v 4.2-6.1 x 10<sup>6</sup>), HCT 41.6% (n.v 35.0-50.0), MCV 83 (n.v 80-97), MCH 29.9 (n.v 26.5-33.5), PLT 154x10<sup>3</sup> (n.v 150-400);

Laboratory findings were as follows: prothrombin time (PT)— INR 1.1 (n.v. < 1.2), activated Partial Thromboplastin Time (aPTT) 87 (n.v. < 1.20), Amylase 108 U/L (n.v. 29–100), Alanine aminotransferase ALT 101 U/L (n.v. 0–45), Aspartate aminotransferase AST 68 U/L (n.v. 0–35), C-Reactive-Protein (CRP) 3.46 mg/L (n.v. 1.1-8), Serum Urea 19 mg/dl (n.v 10-43), Creatinine 0.8 mg/dl (n.v 0.5-1.2), Potassium 4.8 mmol/l (n.v 3.5-5.1), Sodium 138 mmol/l (n.v 136-146), Chloride 108 mmol/l (n.v 101-109), Blood glucose 84 mg/dl (n.v 74-106), Bilirubin 0.8 mg/dl (n.v 0.5-1.2),

Lipid profile: Cholesterol 280 mg/dl (n.v 140-220) and Triglyceride 154 mg/dl (n.v 50-150); Ferritin 213.1 ng/ml (n.v 22-275).

Urine analysis: Albumin 25 mg/; RBC 1-2/mm (0-5); WBC 2-3mm (0-5);



Proteinuria 1.2 g/day.

Microbiological tests (i.e. Manthoux, Quantiferon, CMV, EBV, HIV, HBV, HCV, VDRL) were all negative.

Neoplastic markers: CEA 0.89 (n.v <5); AFP 1.2 (n.v <20); CA 19-9 25.1 (N);

Workup for autoimmune diseases revealed elevated levels of IgG Anti-Cardiolipin 75.5 u/ml (<10), IgM Anti-Cardiolipin 10.1 U/mL (<10); ENA Screen 8.8 (<0.8), RF 20.6 UI/ml (<20) with positive Antinuclear antibody (ANA), Anti-RO 52, Anti-SS-B and Anti-SS-A, whereas, Anti ds-DNA was negative.

## Treatment

The patient was put on bed rest and was started on anticoagulation therapy with Enoxaparin 6000 UI bid initially, along with Prednisolon 25 mg/d IV, Perindopril/Amlodipine 4/10 mg/d and Atorvastatin 20 mg/d. Two days later, he was switched to Warfarin 3 mg p.os, followed up with INR. On the 6th day, INR was 2.3, so Enoxaparin was discontinued. Hydroxychloroquine (HCQ) 200 mg/d p.os was added to his regimen, in addition to the anticoagulation therapy with Warfarin.

In a 3 month follow-up, the patient was asymptomatic. During the physical examination, HR 91 bpm, BP 120/75 mmHg, bilateral vesicular respiration, SpO2 96%, were noted. Maintenance therapy with oral anticoagulation and hydroxychloroquine was continued.

## Discussion and conclusions

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the occurrence of venous and/ or arterial thrombosis and the presence of circulating antiphospholipid antibodies [19]. Single or multiple thrombi in veins, arteries and the microvasculature may give rise to a diverse clinical picture. While deep vein thrombosis, particularly of the lower limbs, is the most frequently reported clinical manifestation (39%), thrombocytopenia (30%), livedo reticularis (24%), stroke (20%), pulmonary embolism (14%), heart valve lesions (10%), epilepsy (7%), myocardial infarction (6%), leg ulcers (5%) and amaurosis fugax (5%) may also occur and they are classified as “non-criteria features of APS” [20].

The average age of primary APS patients has been reported to be about 35–40 years and the disease is more common in women than in men. In this report we describe a rare case of a young male who presented with a 13 year history of a wide spectrum of clinical manifestations involving multiple organs, in whom a diagnosis of APS was initially missed.



Dyspnea and syncope were presenting symptoms. In patients with pulmonary embolism of the main or lobar pulmonary arteries, dyspnea or tachypnea occurred in 92% of cases. Conversely, acute PE may be a frequent finding in patients presenting with syncope (17%), even in the presence of an alternative explanation. [21].

In APS, pulmonary embolism disease occurs in approximately 14% of the patients [22]. The pathogenesis of pulmonary embolism in APS may show wide variability, but common complications of the pulmonary system involve pulmonary thromboembolism and its associated sequelae, such as infarction and PH. [23] aPLs are associated with thrombosis; a 2GPI antibodies are not only a marker of thrombophilia, but moreover contribute to hypercoagulability. PE may be the first manifestation of APS. Cervera et al. [24] prospectively examined the morbidity and mortality in 1,000 APS patients over a 10-year period. They found that 14.1% of patients had PE at initial diagnosis and incidence of new PE was 3.5% over the 10-year follow-up. PE-associated mortality occurred in 5.4% of the patients. [24]

The mainstay of treatment for acute thromboembolism in a patient with antiphospholipid syndrome (APS) is anticoagulation. Typically, this involves heparin overlapped with warfarin followed by indefinite warfarin therapy in most patients. The rationale for indefinite anticoagulation therapy is the high rate of recurrent thrombosis, although the number of risk-stratified studies is limited. Following initial interventions for an acute thrombosis, we suggest anticoagulation with warfarin rather than a direct oral anticoagulant (DOAC; eg, apixaban, dabigatran, edoxaban, rivaroxaban) based on the lack of data regarding efficacy and safety of the DOACs in APS patients. Due to its autoimmune nature, immunomodulatory agents for the treatment of APS have been proposed [25]. However, there is a lack of high-quality data to guide practice and there is no good-quality evidence to support the use of specific immunomodulatory agents. We often add hydroxychloroquine (HCQ) and statins for patients with recurrent thrombosis despite adequate anticoagulation and we often use rituximab for patients with hematologic manifestations of APS (eg, thrombocytopenia) or a thrombotic microangiopathy (TMA) picture. (See 'Thrombocytopenia' above.) Statins can be used as an additional treatment in difficult-to-treat APS patients. Limited data suggests that statins may have a beneficial effect in APS patients by reducing proinflammatory and prothrombotic markers [25-29]. However, there is insufficient data to recommend the routine use of statins in patients with APS in the absence of hyperlipidemia.

Based on the patient's medical history, laboratory and imaging findings, an autoimmune disorder was among the top differential diagnosis. The autoimmune profile revealed the presence of  $\beta$ 2GPI antibodies, aCL antibodies and LAC. In these circumstances, due to the presence of multiple specific "non-criteria features

of APS”, namely thrombocytopenia, and bilateral pulmonary embolism (Bilateral PE), along with the persistence of elevated levels of aPL 3 months apart and the presence of an associated autoimmune disease (LES), a diagnosis of secondary APS was made.

Thrombocytopenia, as a primary manifestation of APS, has a prevalence of approximately 20 to 40% [30]. It has been suggested that antiphospholipid antibodies bind to the phospholipids in the platelet membrane, thus participating in the process of platelet destruction, that ultimately leads to thrombocytopenia. However, the specific role the aPL plays in this process, is yet to be proven. Immunosuppressive therapy appears to be effective in patients with APS-associated thrombocytopenia [31]; indeed, a short cycle of intravenous prednisolone resulted in a significant increase in platelet count in our patient.

Considering his age, sex and unspecific symptoms our patient presented a diagnostic challenge. Though APS is one of the most common thrombocytophiliias, its often goes undiagnosed. The lack of prophylactic measures, puts patients in a significant risk of serious complications including pulmonary embolism, infarction and pulmonary hypertension, that can turn out to be fatal.

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# *Rehabilitation on Cervical Spondylosis*

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## **Abstract**

*Introduction: Cervical Spondylosis (SC) is the most common disorder of the cervical spine. Intervertebral discs can degenerate as a result of natural aging. Other degenerative changes include osteophyte formation, facet joint hypertrophy, longitudinal ligament calcification, and ligament flava thickening.*

*Aim: The aim of this study is to show the different methods of physiotherapy used for the rehabilitation of cervical spondylosis and to compare among them the combined methods to see which of the methods is most effective in terms of relieving the main symptoms of cervical spondylosis.*

*Methods: In this study we investigated 33 studies that have used different treatment methods of patients with cervical spondylosis. The elected studies ranged from 2002 to 2020. For this review articles have been taken from official sources like PubMed, Google Scholar, Medscape and Cochrane library.*

*Results: During the analysis it was observed that the combination of different therapeutic methods is more effective than a single method. Combining exercise therapy with other methods seems to be the most effective program for relieving the symptoms that come from cervical spondylosis.*

*Conclusion: We concluded that exercise therapy combined with other methods is one of the most effective methods in the rehabilitation of cervical spondylosis.*

**Key words:** *cervical spondylosis, cervical spondylosis with radiculopathy, rehabilitation, exercise, cervical traction, manual therapy.*

## Introduction

Spondylosis belongs to the group of osteoarthritis and is related to injuries at the level of the articular cartilage and is associated with destructive and constructive phenomena (osteophytes).

Spondylosis can develop in different parts of the spine and according to the affected part gets the following names:

- Cervical spondylosis at the C1-C7 level
- Thoracic spondylosis at the level of Th1-Th12
- Lumbar spondylosis at the L1-L5 level
- Lombo-sacral spondylosis at level L5-S1-S2 (1)

## Etiology

Cervical spondylosis (SC) is the most common disorder of the cervical spine. Intervertebral discs can degenerate as a result of natural aging. Other degenerative changes include osteophyte formation, hypertrophy of the facet joints, calcification of the longitudinal ligament, and thickening of the flava ligament. (2) These articular changes can lead to stiffening and narrowing of the segments and loss of physiological cervical lordosis.

SC presents in three symptomatic forms such as neck pain, cervical radiculopathy and cervical myelopathy. Neck pain and cervical radiculopathy (involvement of nerve roots) can be acute, subacute, or chronic resulting in various stages during the degenerative cascade. (3) Symptoms of SC include one, or a combination of: numbness; weakness and tingling in the neck and / or arms; neck and / or arm pain; stiffening of the neck; headache; symptomatic compression of the spinal cord (myelopathy) (4) or nerve roots (radiculopathy) (5); a combination of both (myeloradiculopathy), or a problem with bladder function from cervical myelopathy. (6,7).

## Epidemiology

The prevalence of SC is the same for both sexes, but the degree of severity is higher in men. (8-10). In about 10% of patients, SC is due to congenital bone abnormalities, blocked vertebrae and lamina malformation that placed under stress on adjacent intervertebral discs. (11) SC involves 2% of hospital admissions. It is the most common cause of spinal cord dysfunction in patients older than 55 years. Based

on radiological findings, 90% of men older than 50 years and 90% of women older than 60 years have degenerative changes in the cervical spine (12).

## **Methodology**

For the realization of this study, the method of reviewing the latest literature for the rehabilitation of cervical spondylosis was used. 44 studies were found and from these 33 studies were selected for further review which were in line with the inclusion and exclusion criteria. Selected studies ranged from 2002 to 2020.

### *Inclusion criteria*

- Females and males aged 18-75 years
- Diagnosed with cervical spondylosis based on physical examination and radiography
- Cervical spondylosis with radiculopathy
- Subacute and / or chronic stage of cervical spondylosis

### *Exclusion criteria*

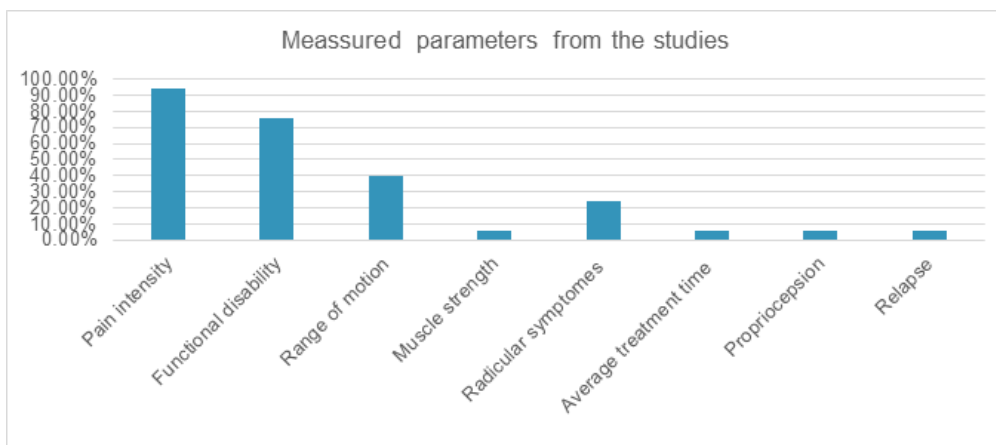
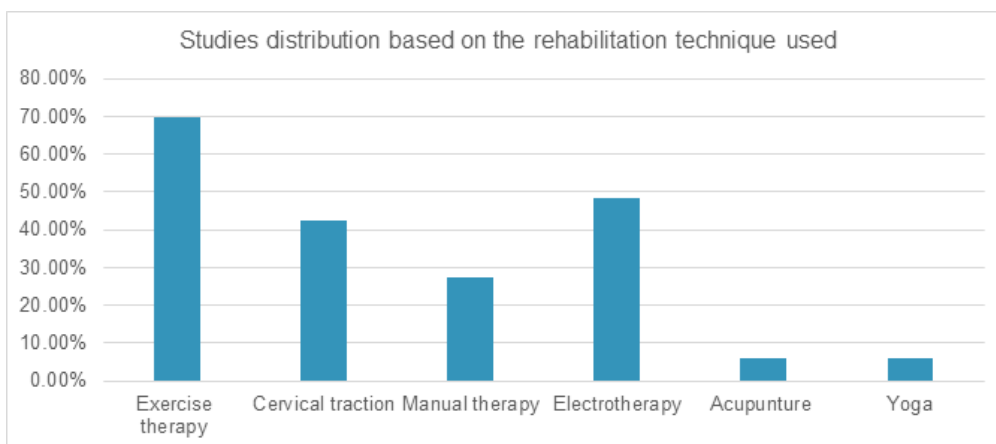
- Cervical spondylosis with myelopathy
- Acute stage of cervical spondylosis
- Spinal canal stenosis in the cervical region
- Red flags (tumor, osteoporosis, fracture, prolonged history of steroid use, rheumatoid arthritis)
- Pregnancy
- Ankylosing spondylitis

## **Results**

The reviewed articles focused on different aspects of physical rehabilitation which included:

1. Combining exercises with electrotherapy (13)
2. Combination of exercise therapy with cervical traction and electrotherapy (14)
3. Combination of exercise therapy with deep transvers massage, stretching and electrotherapy (15)

4. Combination of exercise therapy, electrotherapy and kinesiotaping (16)
5. Manual therapy techniques (17)
6. Combination of manual therapy with exercise therapy (18)
7. Combination of exercise therapy with cervical traction (19)
8. Combination and comparison of cervical traction and manual therapy (20)
9. Combination of cervical traction and electrotherapy (21)
10. Combination of manual therapy, exercise therapy and cervical traction (22)
11. Electrotherapy (23)
12. Acupuncture (24)
13. Yoga (25)



According to the results, the most encountered therapy is exercise therapy combined with other therapies and the main parameters measured are pain intensity and functional disability.



Physiotherapeutic rehabilitation in persons with cervical spondylosis should combine different methods to obtain the maximum possible results.

From the above analysis it is clear that the combination of different therapeutic methods is more effective than a single method. Combining exercise therapy with other methods seems to be the most effective program for relieving the symptoms coming from cervical spondylosis. Also, cervical traction is a very effective method when combined with other methods, especially for relieving radicular pain. Other methods such as manual therapy, electrotherapy, acupuncture and yoga should not be left out which also have beneficial effects in improving the symptoms.

## Discussion

Exercise therapy combined with other methods is very effective in relieving symptoms. It is thought that training the muscles of the cervical region, especially the deep flexors of the neck is an effective and safe method for improving pain, disability and muscular strength. According to Saleh MSM et al., (2018) (26) in a study conducted for training of deep cervical flexors (DCFs), DCFs training was more effective, comfortable and safe for improving proprioception, pain, muscular strength of dizziness severity neck and dizziness handicap (DHI) inventory points. In a study conducted by Wani S. et al., (2013) (27) the effectiveness of cervical retraction exercises (McKenzie) with or without biofeedback pressure for the treatment of pain in cervical spondylosis was compared. The study concluded that the group that used biofeedback pressure cervical retraction exercises (group B) experienced more pain reduction and functional disability associated with cervical spondylosis than the group that used biofeedback pressure cervical retraction exercises. Telci EA and Karaduman A. (2010) (28) in their study comparing the effect of different conservative methods of treating cervical spondylosis found that the results for pain, disability, quality of life, psychological state and patient satisfaction were higher in the groups receiving combination therapy than in the drug treatment group. These results indicate that individualized use of regular exercise for patients with neck pain provides long-term improvements in function and quality of life. To maximize the benefits exercise therapy can also be combined with manual therapy. Various methods of manual therapy are effective in treating cervical spondylosis. Langevin P. et al., (2015) (29) comparing 2 manual therapies and exercise protocols for cervical radiculopathy has concluded that manual therapy and exercises are effective in reducing the pain and functional limitation associated with cervical radiculopathy. Neck pain has a major impact on society, due to its long duration, the disability it causes and reduced productivity. Exercise therapy combined with electrotherapy can be a beneficial solution for relieving

pain. Electrotherapy has the best effect if used in combination. The many benefits of electrotherapy are widely known especially for the rapid relief of pain. In a study by Venosa M. et al., (2018) (30) it was found that high-intensity laser therapy plus exercise was more effective than ultrasound / TENS plus exercise in terms of functional improvement. High intensity laser therapy can be promoted and used in this pathology with positive results.

When treating patients with degenerative changes, pain relief therapy is recommended based on indirect treatment and with active patient participation. It is useful to work with PNF models that mimic the activities of daily functional life. According to the study conducted by Maicki T. et al., (2017) (31) it was demonstrated that rehabilitation of patients using PNF and manual therapy had a statistically significant impact on reducing pain and improving the performance of daily life activities. women with cervical back pain. However, the PNF method proved to be more effective in the short term (after 2 weeks) and in the long term (after 3 months). Evidence-based cervical spondylosis physiotherapy management is also part of cervical traction. Essentially the cervical traction pulls the head from the neck and creates space between the vertebrae to eliminate compression. This is especially important for cervical spondylosis with the presence of radiculopathy. Combining cervical traction with other methods is thought to be effective. This is supported by a study conducted by Sanduja A. (2010) (32) whose results imply that mechanical cervical traction is a useful physiotherapeutic tool for reducing neck pain and consequently neck disability. Also according to Qayyum S. et al., (2017) (33) mechanical traction has been proven to be more effective than manual therapy in patients with radicular pain from cervical spondylosis at the C5-C6 level. Singh A. and Rastogi A. (2018) (34) in their study demonstrated that intermittent cervical traction with hot packs and exercises is more effective in managing cervical spondylosis than just hot packs and exercises. This suggests that increasing cervical traction may provide additional effects. But not all authors think so. Regarding the combination of cervical traction, exercise therapy and manual therapy, some authors think that increasing cervical traction does not bring additional benefits. According to Young I. A. et al., (2009) (35) the addition of mechanical cervical traction to a multimodal treatment program of manual therapy and exercise exhibits no significant additional benefits for pain, function, or disability in patients with cervical radiculopathy. In contrast to the above study Cleland JA et al., (2005) (36) noted that 91% of patients with cervical radiculopathy treated with multimodal treatment of manual physical therapy, strengthening exercises, and intermittent cervical traction had reduced pain and improved function after completion of treatment and after 6 months follow-up. Acupuncture is another treatment method used for cervical spondylosis. It is an ancient Chinese medicine based treatment. For the treatment of cervical spondylosis it is often

used alone, but can also be used in conjunction with movement therapy. In both cases it is effective. Luo B. and Han J. (2010) (37) in their study demonstrated that acupuncture plus movement therapy and conventional acupuncture were similar in the treatment of cervical spondylosis, but the former was superior to the latter in short-term treatment and fewer points used.

## Conclusion

From the above reviews it was concluded that exercise therapy combined with other therapies such as manual therapy, cervical traction and electrotherapy is one of the most effective methods in the rehabilitation of cervical spondylosis. Exercise therapy contributes to pain relief, improved muscle strength and quality of life in these individuals. Also important finding is that cervical traction combined with other therapies like manual therapy, exercise therapy and electrotherapy, is effective in relieving neck pain, radicular pain and disability coming from cervical spondylosis. The use of manual therapy techniques has more benefits for relieving the symptoms of cervical spondylosis if used in combination with exercise therapy, cervical traction and electrotherapy. This combination helps reduce pain and improve function. Acupuncture alone or in combination with movement therapy is effective in rehabilitating cervical spondylosis in the short term. During the rehabilitation of patients with cervical spondylosis, the additional application of yoga as exercise therapy has an effect on improving the effectiveness of treatment.

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# *Psychoanalytic view of neurotic forms of love object choice* \_\_\_\_\_

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The way of building relationships and choosing a partner in life can not be something random between two people who decide to spend part of their lives together. Of course, many of our experiences in life lead us to certain choices.

Sigmund Freud, the founder of psychoanalysis, goes further when he says that partner selection is determined by the early relationship between child and parent. Even Freud in his essay “On some neurotic mechanisms in jealousy, paranoia and homosexuality” (1922) says that “these jealousies take root in the depths of the unconscious, take back the earliest movements of infantile affectivity and originate from the Oedipus complex” (p. 217). The roots for this are found in the triangle of the child-mother-father relationship and the phallic stage where the child shows the most pronounced closeness to the parent of the opposite sex (all this a necessary and indispensable process). The way of expressing love between parents and consequently the expression as triumphant in front of the child with the word “I took mom/dad” can affect that in adulthood, the individual develops pathological behavior. Every behavior, from what we explained to the choice of the object of love, has its roots in early relationships.

Freud in his essay ‘On Narcissism’ (1922) (p. 76-104) talks about two ways of selecting the object of love:

- 1 - Choosing the object of love according to the narcissistic type:
  - a - A person who is like us.
  - b - A person who is like us in the past.



- c - A person who represents an idealized image of himself in the future.
- 2 - Choosing the object of love according to attachment:
  - a - A woman who cares for and nourishes her.
  - b - A man who protects.

According to Freud, the narcissistic type of partner selection in life is more common in women and refers to the search for a partner, a fulfillment or fulfillment of self-love (p. 89, On Narcissism). This, according to Freud, explains why women constantly need to express love to them, or in other words, they want to be loved more than they want to be. Based on this we can say that women are looking for a partner who is less narcissistic than them and is willing to invest from his libido, energy towards their object which is himself, so they are attracted and look for a partner who pays attention to him and shows him him. The demand for representation in the presence of other individuals may have other unconscious roots related to the child-mother-father triangle. An unresolved issue in childhood due to love for the father and jealousy for the mother, may be the impetus for women to show pathological desire to look 'chosen'.

"The selection of the object of love according to the form of attachment is based on the fixation on the figure of one of the parents during the infantile period of development." This, according to Freud in "Three Essays on Sexuality" (1922) is more prevalent among men who try to seek the mother or part of the infantile experience experienced in childhood, in every woman they have in life" (p.151,152 Three essays on sexuality (1922). By searching for the elements of the first infant relationship experienced in childhood, we understand the effort to fulfill the image of the mother through the elements of care, unconditional love, child care within them, acceptance to be weak and small in moments certain. However, the woman they have selected loses its importance when it starts and acquires the characteristics of a mother with elements such as restrictive, reprimanding, punishing and, most importantly, not showing love. Based on this, we can say that what men are looking for is: to be forgiven by their partner despite their shortcomings and above all what they are looking for is a kind of hidden instinctual desire to gain the partner's pride which is based on the relationship infantile with the mother and compliments with the desired attention of the mother in infancy. This also explains why men suffer criticism from their partner in a relationship, criticism which can be perceived by the man as the end of the partner's love for him.

The relationship with the mother is essential for each of the sexes in the infantile stage of development. For women it is very important how love is treated towards the object of love, which at an early age is the father and how rivalry with the mother is treated. In the pre-oedipal stage, girls enjoy a deep connection with the mother, which serves as a form of internalization of the values, characteristics



and image of the woman whom she will project later in life. The Oedipus phase is then characterized by a rivalry and hatred towards the figure of the mother as an attempt to defeat the competition and replace it in the love for the father. Parental behavior and treatment at this stage is very essential in building the character of the child. Typical behaviors which were mentioned above, such as: expression of love in the couple by making children jealous, can cause a stagnation in the phallic stage precisely in the Electra complex. This can prompt individuals to project pathological behaviors driven by an unresolved element during this phase of life. We base this argument on what Freud says: “The pre-Oedipal connection phase is decisive for the future of the woman because during that period preparations are made for the acquisition of the characteristics with which she will fulfill her role in society” (p. 168, Introduction to Psychoanalysis). Just as the pre-Oedipal phase is important for the acquisition of feminine characteristics by the mother, so the post-Oedipus phase with hostility and rivalry towards the mother enjoys invaluable importance and serves as a prerequisite for a happy future marriage, elements which are preserved in it the unconscious. But as Freud points out, “any relationship will experience moments when the enmity and rivalry carried by the infant relationship between mother and daughter is projected onto the spouse at a certain stage of life. For Freud, if this is experienced in the beginning of the relationship, it is likely that the second part of the relationship will be happy. There is also a phase of calm that is reached after the birth of the first child where the female learns to share the object of love, now not orienting everyone towards herself. By directing it towards the child, the female somehow gives up her narcissism. (p.168, Introduction to psychoanalysis). In cases where the first child is male, the female manages to feel a fulfillment after the replacement of what is called the conflict of the Oedipus complex in childhood. Now the woman has what she did not have as a child, a man has been born, whose roots stem from the desire to have a penis. This means a release of the relationship after the birth of the first child, especially if the gender of the child is male.

Annie Reich in the article “Narcissistic object choice in women” while talking about the narcissistic choices of the object of love by women explains that: love (partner)”. Based on this I can say that women who have not had enough appreciation and attention during infantile intercourse may develop unhealthy forms of relationship building in adulthood. Given what Annie Reich pointed out that women who approach partner selection from an extreme addiction attribute to him the characteristics of fantasy experienced during childhood, we can hypothesize that these individuals during childhood may have experienced a underestimation of the fact that they are female, may have had a brother who was overestimated for the fact that he is male and has a penis, may have always felt incapable of receiving the object of love from the mother, despite their efforts.

Sometimes we can find women who during childhood, in that important infantile experience have developed a form to get the attention of the object of love (in that case the father), for example: through flattery, complaints, excessive femininity, etc., this form is also projected in adulthood as they choose the partner in life. Women who approach the choice of the object of love from an extreme addiction generally have a magnificent ideal ego or a weak ego, which both enjoy an exaggerated sense of self-criticism and inferiority, I think because they failed to master the object of love, inferiority which can only be fulfilled by an overrated partner. As a result of the inability to express her aggressive feelings, the woman in these cases sublimates them into masochistic behavior by easily accepting submission, even demanding it. It is by surrendering to a partner that dominates it, it is in these cases that the female manages to fulfill her inferiority, and separation from such an object can cause trauma up to conversion or psychotic disorders. To stop this, we encounter cases in which women who persistently seek dominance to the point of excessive display of masculinity by their partner, either admitting to being a second choice or admitting to being betrayed. In these cases these women suffer less because the event that happened in the present is not a feeling unknown to them. Praying for submission makes them feel valued, and only in this way do they gain importance in a relationship.

Before relating the elements to the above wording, it is necessary to clarify what is found to be healthy in attractions through partners in a relationship. Based on the Freudian premise: "in so many years of study I do not know what a woman wants", so that a woman does not know what she wants and at the same time wants many things she does not want. This is for a woman the strongest instinctive weapon that activates in the partner two very important elements: a) the masculine ability of being programmed to be complementary to the needs of the partner and b) promotes the display of masculine features through occasional outbursts aggressive. By activating the latter in the partner, the female displays her ability to calm her partner through her femininity, showing in a form the dominance, but not only, emphasizing once again her narcissism. It seems like a struggle for dominance (which the female just does not love anymore) but no, it is such a magical spiral rooted within both sexes as complementary to each other and two incomplete halves separately. This is found to be a healthy form of relationship building between a couple.

The aspect that we will relate to is through what we have clarified so far, the form of selection of the partner in life, ie the object of love, by women, and the tendency to choose a category of men who present certain characteristics which we will try to we clarify. In order to have a clearer mention of the mentioned categories of men, we can refer to them with names such as: strong, those who feel nothing for you, thugs, gangsters, those who deal with dirty work, etc. We will relate this

to what Freud refers to as male motivators: power, power, sex. What we see today in building relationships based on therapeutic experience but not only, from the numerous conversations in the auditorium, as well as from many focus groups realized, I can say that I find a pathological form of selection of the object of love by both sexes. Of course this was not discovered and did not develop now, but the current social conditions affect their highlighting and why not have influenced their formation.

The tendency to attract the category of men we labeled above comes as a form of acceptance of submission, i.e. a masochistic form of relationship building by accepting and seeking submission. Based on what Annie Reich has emphasized about the selection of the object of love based on an extreme form of addiction, as well as the overestimation of the object of love, we find women who select as object of love exactly the men we labeled above. Focusing on the elements of male power, power and perceived sexual ability, is nothing else and does not go beyond the pathological form of selection of the object of love, labeling this selection absolutely as pathological where there is essentially only acceptance of submission. , or as Annie Reich pointed out, masochistic. A stagnation in the phallic stage, an unquenchable desire for the male genital organ, a lost fight with the mother in infancy, a pronounced lack of attention to her needs, etc., foster and form the dependent character and pronounced tendency in the search for a male to overestimate it, as the only form of reliving its non-existence during the phallic phase. In this form, only by being ignored, by being oppressed do they feel worthwhile?

This can also be understood in other forms. We pointed out above that the female form of love is more pronounced than the narcissistic form, something that connects them to themselves or that they are the object of love, to be needed more than they want. The wrong tendency in choosing the object of love is observed in those relationships where women feel proud of their husband's power / sexual ability and promote this as a narcissistic form of saying that they are the ones who deserve it, but also as a form of saying that they are the chosen ones and the others are "mom". This goes even further in the reasoning given to the importance of male dominance over them in a relationship, overshadowing the importance of communication and compromise as a healthy form of relationship development. Doing so, thus appreciating dominance, is the only form from which they can feel valuable because earlier in the early stage of development, only by acknowledging submission have they been important in the family. I reiterate, the search for validity in the manifestation of the partner's instinctive aggression, be it through "shouting, restraint, persistent search for jealousy on the part of the partner, the pathological desire for him to be desired by others but chosen to be you again, or even the manifestation of sexual aggression; they are nothing but pathological

forms of experiencing a relationship, the roots of which we must persistently seek in what is experienced in the phallic stage of development.

The tendency to appear in front of an audience marked as more seductive women, as a form of challenging other women so that the position in the partner's arms is not threatened, is explained by the motive of the fear of substitution that the woman may have experienced during childhood age. The roots of this incorrect display of relationship building are again in the incorrect mother-daughter relationship and stagnation in the phallic stage, precisely in what we call the Oedipus and Electra complex, where the child has constantly experienced the fear of losing position as father's favorite from mother's risk. The tendency to be seductive is just a form of expression, other forms of expression are those mentioned above: flattery, excessive femininity, flattery, tendency to be dominant, complaints, attraction, etc. Each of these forms can be used as a form to attract a partner in life, but which all lie within the boundaries of the unhealthy form of choosing the object of love.

It is culturally unacceptable for women to act casually and based on what they feel they are doing. Given this very simple premise, and making the connection with the narcissistic form of the selection of the object of love by women, that one of the forms was the selection based on an idealized image of oneself in the future (above, point c), we note a tendency to pathologically select the object of love when its actions are generally instinctive and well thought out, or to be more precise, they feel attracted to those actions which are a manifestation of id, which for the woman has been unacceptable during childhood because she was not a boy and did not enjoy the 'magnificent attribute' of having a penis.

To continue with a detailed analysis of how men choose the object of love we will start from what Freud (1909-1910) spoke about the psychic impulses that push a neurotic man to select the object of his love at "A special type of choice of object made by men" on his book "Three essays on sexuality".

Freud points out that such psychic impulses are often encountered even in persons with normal mental health.

**1 - Rivalry: The existence of an injured party.** A man would never choose as a partner a woman who is free and has no interest in him, but only the one through whom he would realize the right of domination as a husband.

Some relationships can start from scratch, where no one expects something to happen between two individuals, this is due to some impulses which are completely unconscious. A category of men whom Freud described as neurotic in choosing the object of love may begin to feel attracted to a woman for whom they have not previously agreed, just because someone else is interested in it. This falls into the category of "rivalry or existence of an injured party". Based on this root of the unconscious, we find through observations and therapeutic work

such an approach to building relationships by men. Also due to the unconscious impulse of rivalry we see men who show a pronounced need for the partner to be attractive as a condition for building the relationship, so that others talk about it or see it constantly, as a form of showing in persistently dominating other men. An unresolved issue in the Oedipus complex and a strong childhood feeling that the child experienced growing up that the mother belongs to someone else (the father) and that he finds it impossible to receive her love, lead to the formation of this neurosis in men. In this way, the selection of the object of love based on rivalry, complements in men the feeling of the injured third party.

**2 - Jealousy:** A woman who is rumored to be: “A woman who is chaste and whose reputation is pure is never an attraction to be able to raise her to the status of an object of love”, but only a woman whose fidelity and credibility is open to doubt.

Improper explanations for the nature of sexual intercourse between parents, open intimate relations between partners in the eyes of parents, keeping children in the bedroom until a great age of their development, can promote in children the formation of this neurosis which appears in adulthood. For children, but also for every adult, the mother is a symbol of purity, honesty and chastity. Children facing experiences that can damage this image of the mother in their mind, for example through the thought: “my mother also has sex like everyone else”, or “kisses, explicit sexual hugs”, can lead to formation of this neurosis. Expressions of love between partners should be oriented more towards the values of respect, courtesy, care, etc. than clear manifestations of actions of a sexual nature but without neglecting the latter. The appearance of sexual acts in the eyes of children is important in conveying the message to male children to build the idea that the mother is the father and thus activates the Oedipus complex, during the pre-Oedipal stage the male child will assimilate the values of the father so to be the mother’s favorite, and at this point the need arises to display caring and respectful behaviors in order for the child to acquire these values. The Oedipal stage where the child displays feelings of rivalry with the father helps him project love to another woman outside his circle, which coincides with the latent and then genital stage where the first pleasures begin.

**3 - Uninterrupted compulsive repetition:** In these love relationships the character of a man is formed, which in a way adapts to any occasion of falling in love. Such links are repeated with the same qualities in different stories as copies of each other.

Cultural approaches with a very strong deterrent and moralistic tendency towards the relationship between the male child and the mother when he shows feelings of affection, love or physical closeness to the mother, influence the

formation of this neurosis. Numerous expressions such as “leave your mother because you are already an adult; enough to kiss the mother; how the boy sits on mom’s lap” etc., can influence the male child to repress the instinctive desire which later in life is projected in love directed only in an emotional and affective aspect. These men in the genital stage of development feel that they can form relationships with any woman which offers them emotional affection. The roots of this lie in the fixation created on the figure of the mother. Generally, these men tend to choose partners who are lower in status than they are, which would ensure the affection and love of the partner.

**4 - Salvation fantasies:** The man is convinced that she needs him, and that without him she would lose all moral control and quickly sink to a miserable level.

It often happens to see a man mature in life and profession, falls in love with a suffering woman or whose social status may be put at risk. The man feels a strong need that the woman needs him and in case he will not save her, she will fall into a miserable condition. In most cases, these men do not manage to fall in love or feel attracted to women who appear self-confident or who may have a built-in career, which conveys the lack of need to get rid of it.

During the phallic stage of development in the early infant relationship, rather than losing the war in trying to win the love of the parent of the opposite sex, for a child, whether girl or boy, leaves irreversible traces (as early as the next day) may have pathological consequences), if he/she (child) mistakenly perceives that \* same-sex parent is not worth fighting \* and directs to him/her feelings of pity, pain, or care. The primary conflict with the same sex is essential in the acquisition of values, norms and characteristics by the child, this as a mechanism to appear “liked” in the eyes of the parent of the opposite sex. These likes that in the genital stage of development, are projected externally on the partners we choose in life!

“I would not have wanted anything more in life than protecting my father,” says Freud. For the man, a weak father, who is not worth fighting to get the mother’s love is the main impetus in the formation of this neurosis in men. This category sees the father as powerless to please the mother and consequently does not fight for him. By not activating rivalry for the father in the struggle for the mother’s love, the male child is not encouraged to take from the father his values and characteristics in order to be the mother’s favorite in her eyes. Thus the male child during the infantile stage of development directs towards the mother the feelings of the fantasy of salvation, which he must bring to the mother god since the father is not enough and he must save her from that condition, and if it is not him, the mother will be with a partner who is not worth it, does not protect her, is weak, is not masculine enough, etc. In these cases we can have reports where the father may be completely indifferent to the partner, not present, does not show love, does not show protective and caring skills towards the partner, etc.



At the end of this part, which is absolutely not exhausted, I can say that whether thoughtfully or even unconsciously, there is a tendency to encourage Albanian youth to act instinctively, as a form of expression of complete freedom, which as we tried to clarify, this freedom often times leads us to various pathologies that we do not always have the willingness and comfort to understand.

What I think is that people are more easily managed through instinct and chaos than through order, and this is known by those who may have certain interests in influencing the culture of a country. To destroy a superego, one must give unconditional freedom to the id, motivating what it portrays as something publicly accepted, promoting it in the media, making it socially acceptable. Wrongly, although nothing goes wrong, the manifestations of the id have now turned into a new superego, and those impulses which the id conveyed hitherto and caused the necessary conflict for the existence of the ego, are no more, and the id must produce other desires, which will certainly be more pathological than the previous ones.

To put it more into practice and to make it more tangible, what until yesterday was socially unacceptable, ie part of the morals of the superego, today is considered something socially desirable and sought after by most young people forming thus a new social “morality” for the generation in which we live. Once this is internalized, the id will produce again and continuously new impulses which have the sole purpose of achieving momentary satisfaction, which is achieved but does not provide stability and guarantee, ie does not fulfill. So the id will continuously produce dark pulses because according to the pleasure principle, the impulses that the id transmits the moment they are met, they widen and deepen the threshold and so the next time the id will transmit a pulse, it will have to be deeper and greater than the former in order to feel the momentary fulfillment. This becomes more difficult the moment we replace the superego, cultural, religious, legal morals, etc.; with elements that id himself has dictated to us.

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# *Impact of physiotherapy in patients with Hemophilia A*

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## **Abstract**

**Introduction:** Hemophilia is a congenital X-ray disease associated with bleeding in which blood does not clot. It is categorized as a hemostasis problem. Hemostasis, the cessation of blood flow as a result of damage to a blood vessel, is normally divided into two processes, primary hemostasis and secondary hemostasis. In hemophilia, the secondary hemostasis (which results in the formation of a clot in the fibrin) is in this case broken. So, low coagulation is due to an abnormal protein plasma clotting abnormality in factors VIII and IX that are involved. **Aim:** The aim of this study is to show that combined rehabilitation based in exercises is more effective just a simple therapy to improve hemophilia and reducing the symptoms. **Methods:** In this review study 30 studies were obtained which have used different physiotherapeutic methods in the treatment of hemophilia A. The elected studies ranged from 2001-2019. The literature is based on official sources as Cochrane library, Pubmed, MEDLINE, DOAJ, Medscape, Clinical trial.gov and some articles like is Official Journal of WFH , BMJ Open. **Results:** During the study it was observed that the combined physiotherapeutic rehabilitation had more efficiency than a simple treatment method. **Conclusion:** A physiotherapeutic rehabilitation with combined methods based on exercises gives better and positive results in the treatment of hemophilic patients.

**Key words:** hemophilia A, manual therapy, electrical stimul, laser, ultrasound, hematoma, ergo metric bicycle, PNF, arthropathy, yoga, hydrotherapy, kinesio taping.



## Introduction

People in ancient times wrote about blood and bleeding problems. They could see that many people had different bleeding problems. But they knew very little about blood clots. [1]

Patients with mild hemophilia have little spontaneous bleeding and heavy bleeding in cases of severe trauma, patients with moderate hemophilia show severe bleeding after minor trauma, while patients with severe hemophilia are characterized by severe spontaneous bleeding or after a minor trauma. [2]

Although effective treatment has resulted in recent decades, hemophilia has been known since antiquity. A modern description is attributed to Dr John Conrad, who described hemophilia as an inherited tendency of men to bleed. [3]

Hemophilia A and B are recurrent disorders associated with X chromosome. Females carry the mutated gene while the disorders manifest entirely in males. [4]

Hemophilia is a congenital disease of the X chromosome that is associated with bleeding in which the blood does not clot. It is categorized as a problem of homeostasis. Homeostasis, the blockage of blood due to damage to a blood vessel, is normally divided in two processes: primary homeostasis and second homeostasis. In hemophilia, the secondary homeostasis (which results in the formation of a fiber clot) in this case is impaired. So the low coagulation is due to an abnormality of the functional plasma clotting protein of factors VIII and IX that are involved. [5]

Hemophilia A (or classic hemophilia) affects about 80% of cases.

Hemophilia B (or Christmas disease) affects about 15% of cases. [6]

The severity of hemophilia A can be described as:

- Mild hemophilia
- Moderate hemophilia
- Severe hemophilia. [6]

## Epidemiology

The worldwide incidence of hemophilia is approximately 1 case for 5000 men, 1/3 of the affected individuals have no family history. The prevalence of hemophilia A varies by reporting site with a range of 5.4 -14.5 cases for 100000 males. In the USA, the prevalence of hemophilia A is 20,6 cases for 100000 men. In 2016 the number of people with hemophilia in USA was about 20000. [12]

### **Statistical data of Hemophilia A in Albania:**

A total of 200 patients with Hemophilia A have been registered:

- 152 adults patients >14 years old
- 48 pediatric patients < 14 years old

### **Hemophilic A patients grouped by age:**

- 0-4 years old: 7 patients (3.5%)
- 5-13 years old: 41 patients (20.5%)
- 14-18 years old: 28 patients (14%)
- 19-44 years old: 86 patients (43%)
- >44 years old: 38 patients (19%)

### **According to the severity of the disease (factor level) are:**

- 98% adults with severe hemophilia (factor level <1%)
- 30 adults with moderate hemophilia (factor level 1-5%)
- 24 adults with mild hemophilia (factor level 5-40%)

### **48 pediatric patients are registered:**

- 26 patients with severe hemophilia (factor VIII level <1%)
- 19 patients with moderate hemophilia (factor VIII level 1-5%)
- 3 patients with mild hemophilia (factor VIII level 5-40%) [14]

## **Etiology**

Blood coagulation factors VIII and IX are found on the X chromosome causing a disorder on the X chromosome and making hemophilia a rare disease for women. Since women have two chromosomes X they are hemophilic when both X chromosomes are affected. Men will always be affected by hemophilia when they carry an affected chromosome. 2/3 have a prominent family history while 1/3 of cases come from a spontaneous genetic mutation. [7]

Hemophilia A binds to a recessive pattern that binds to the X chromosome. The gene for factor VIII is located on the long arm of the X chromosome in the q28 band. The factor VIII gene is one of the largest genes containing about 0.1% of the DNA on the X chromosome that is 186 kilo base long. The mature protein contains 2332 monoacids and has a molecular weight of 300 kb. It includes 3 domains A, 1

domain B, 2 domains C. The intron 22 of the factor VIII gene contains two other genes. The first gene is transcribed in the opposite direction to that of the factor VIII gene itself. The second gene is transcribed in a direction similar to the factor VIII gene. Homologous recombination of the factor VIII gene by inversion and cross linking results in a division in the factor VIII with two parts directed in opposite direction. This causes an interruption in the normal factor coding sequence with an inability to transcribe the complete protein resulting in loss of function. [8]

Combined factor V and VIII deficiency is an autosomal recessive disorder, with clinical manifestations in both males and females. This disorder is caused by mutations in one or two genes, the LMAN1 binding protein or by the lack of coagulation factor MFC2 which encodes the proteins involved in the intracellular transport of factor V and VIII the coagulation factors themselves are normal. [10]

## **Study Method**

### *Purpose*

The purpose of this study is to show that combined exercise based rehabilitation is more effective than just a combination therapy in improving the treatment of hemophilia and reducing symptoms.

## **Objectives of the study**

### *General objectives*

The main objective of this study is to show the effectiveness of each method as combined and not combined in reducing symptoms and improving the quality of life in hemophilic patients. To demonstrate the impact of an exercise program on increasing joint ROM and muscle strength on improving the lives of hemophilic patients. To demonstrate the effectiveness of combined kinesio taping therapy with exercises. To find out which combination of modalities is most effective in treating hemophilia. To demonstrate the psychological and physical effects that come from Yoga or other specific methods in improving the activities of daily living. To compare the effectiveness of hydrotherapy and ground exercises with each other. To find the most efficient and least costly method in rehabilitating hemophilia.

## Methodology

To realize this study work the method of reviewing was used the latest literature according to the current guidelines for hemophilia from WFH. 38 studies were reviewed of which 8 of them were eliminated due to small number of subjects, leaving between treatments or not completing the study for various reasons and from these 30 studies were selected. Patients underwent a rehabilitation or combined rehabilitation and the effectiveness of each treatment method was monitored. The literature was obtained from official sources such as: Cochrane library, Pubmed, MEDLINE, DOAJ, Medscape, Clinical trial.gov and much information was obtained from various journals such as Official Journal of WFH, BMJ Open. The studies obtained are from the years 2001-2019. Keywords used are: hemophilia A, manual therapy, electrical stimulation, laser, ultrasound, acupuncture, hematoma, PNF, ergo metric bike, arthropathy, yoga, hydrotherapy. These studies can not be conducted here due to small samples taken in the study and conditions not applicable in Albania, lack of qualified staff and intervention methods.

## Criteria

Inclusive criteria	Exclusive criteria
Men Mild, moderate, severe hemophilia With or without factor and prophylactic treatment Age 6-65 Hemophilic arthropathy Pain Literacy skills	Von Hillenbrand disease History of fracture or trauma of the limbs Orthopedic surgical intervention Brain damage, STROKE, other paralysis Other diseases such as cardiovascular, hepatitis B and C Age >70 Serious psychological problems

### Survey Instrument

HJHS questioner

FISH questioner

VAS scale

## Results

**A. Eid et al. (2013)** [44] in his study demonstrate that resistance training and aerobic exercises are effective in increasing bone mineral density and improve muscle strength and functional ability. In the study were taken 30 hemophilic boys selected in two groups. Control group I did physical therapy program with stretching exercises 115 min and aerobic exercises in form of a routine 30 min 1

hour 3 times a week for 3 months. Group II did the same program but additional treatment program with resistance in form of ergo metric bicycle 20 min and resistance with weight 20 min lasted 1 hour 40 min 3 times a week for 3 months. Changes were seen in the study group before and after treatment ( $p < 0.05$ ) while the control group had no significant changes before and after treatment ( $p > 0.05$ )

**Rubén Cuesta-Barriuso PhD et al. (2016)** [45] in his study saw the effectiveness of combining a physiotherapeutic education with an exercise program at home. 20 hemophilic patients were randomly selected. The experimental treatment group received education 60 min every 2 weeks and in parallel received a 15 week exercise program. Control group didn't take education or an exercise program. Educational intervention based on physiotherapeutic exercises improves quality of life and disease behavior and this improvement comes after 6 months of follow up with Gilbert scale examination.

**Necati Muhammed TAT (2019)** [46] investigates the effects of Kaltborn method manual therapy on a simple home exercise program at the level of functional hemophilia independence, kinesio phobia functional level, ROM pain of hemophilic patients with arthropathy.

*According to the results supported by the above studies we see that exercises therapy combined another manual method like Kaltborn or ergo metric bicycle are positive in the effects they bring to hemophilic patients.*

**Alaa R Morgan (2018)** [47] makes a comparison in the effects that pulsed ultrasound brings against low level laser in hemophilic patients with knee swelling. According to the study the author concludes that US is more effective than LLT in reducing swelling and increasing ROM in patients with hem arthritis of the knee. ( $p < 0.005$ )

**Manuel Gomis et al. (2009)** [48] study determines the changes that occur from electrically stimulated treatment. The electrical stimulation in muscle in hemophilic patients was effective in increasing muscle strength combined with exercises. 30 subject, group A with severe hemophilia, group B without hemophilia. Group A performed an electrical stimulation program  $f = 45\text{Hz}$  10 sec for 8 weeks. Group A had significant changes in diameter increase. ( $p < 0.01$ ), strength ( $p < 0.05$ ), EMG activities ( $p < 0.05$ )

**Behrouz Parhampour et al. (2013)** [49] study estimates that treatment with short term resistance and electromagnetic impulse is effective in improving bone formation and joint activity in severe hemophilia A with osteoporosis. 48 randomly selected patients where training resistance  $n = 13$ , training resistance combined with electromagnetic pulse  $n = 12$ , electromagnetic pulse  $n = 11$ , control group  $n = 12$ . Through the Colorado Questionnaire there was significant improvement in RT group and RTPMF compared to PEFM and control gr.

**Mohamed Khawaji et al. (2010)** [50] describes the intensity and duration of physical activity with early long term prophylaxis concluding from the information

gathered from the assessment with HJHS that hemophilia treatment strategies including treatment early general, primary prophylaxis was successful in reducing the frequency of bleeding and preventing chronic diseases of the joint.

**Mazloun V et al. (2014)** [51] study compares the impact of conventional exercise therapy with hydrotherapy concluding that the use of hydrotherapy in addition to routine rehabilitation may be beneficial in joint pain and ROM. And that hydrotherapy is quite effective in reducing pain.

**L. VALLEJO et al. (2010)** [52] study concludes that after the proposed training program significant changes were seen in the increase of aerobic and mechanical capacity and that aquatic therapy had positive effects on motor performance and improved aerobic and mechanical capacity without causing further complications.

**Mehdi Kargarfard et al. (2013)** [53] in his study showed the importance of water therapy in hemophilic patients improvements that brought in muscle strength and articular ROM compared to gr who did not attend any physical therapy. 20 men were selected 10 of them in experimental gr and 10 in control gr. The changes were made with Biodex test. ( $p < 0,01$ )

**De la Corte-Rodriguez H et al. (2013)** [54] in his study show the role that both physical and drug therapies have in hemophilic patients and concludes that both therapies are quite effective in reducing the impact of injury and bleeding and increase the quality of life in these patients. Performing physical examination and performing measurements according to HJHS and Gilbert scale. Drug therapy reduces pain, bleeding in the joints and muscles while physical therapy brings better physical abilities and increase strength in ROM.

**Chan Yuan-Chi et al. (2015)** [55] in his study were seen the effects that kinesio taping has on hemophilic patients in functional activities and balance skills compared to the group who didn't receive kinesio taping treatment. 30 participants were selected randomly and in the group who did physical therapy including kinesio taping were seen significant changes that in the other group with physical therapy only.

**LAMBING et al., (2012)** [56] included 9 subjects in his study. Some of them received treatment with 15% coagulation factor replacement and some others who did not receive this treatment but perform about 14 acupuncture treatments. 6 of 9 subjects reported improvement in pain by 50 % points. 7 of 9 had an improvement in quality of life. Assessment were made with QOL SF-36 and VAS scale. As a result none of the patients treated with acupuncture had any episodes of bleeding, bruising or tanning of the skin, and studies suggested acupuncture as an effective and safe therapy for hemophilic patients.

**Patricia Ribeiro Pinto et al. (2017)** [57] in his study appreciates the effect that two psychological therapies like cognition therapy and hypnosis bring on the management of pain and emotions by increasing well being and quality of life and

enabling these patients to learn to live with this disease. Functional assessment was measured with Peterson Scale and Gilbert Score while psychological assessment was measured with A36Hemophilia-Qol.

**Noushin Beheshtipoor et al. (2015)** [58] in his study about Yoga we look at the effects that brings on the quality of life in children and adolescents with hemophilia which are very positive and Yoga is a therapy that not only brings improvement in the quality of life but also reduces bleeding episodes. According to Friedman test results there was a significant change in QOL before and after treatment ( $p < 0.001$ ). A significant reduction in bleeding was seen ( $p < 0.001$ )

**Bak, Won-Sook et al. (2012)** [59] in his study shows that having Tai Chi in a program of its own in hemophilic patients improves joint movement, strength and psychological condition.

**Matthew Slattery et al. (2001)** [60] in his study shows the effects that functional orthosis of the foot brings as a great help in reducing pain and increasing the ability of movements performed by the sole of the foot. But the authors said that we have to make others studies in the future for the real effects of the orthosis.

**Reza Mahdavinejad et al. (2012)** [61] in his study showed that correctly physical activities and psychological activity can improve physical and psychological activities in hemophilic patients. 20 male with hemophilia A were chosen and after completing the formulary the therapy began and were seen significant changes in the group that the therapy were combined. ( $p < 0.05$ ).

**S. HARRIS et al. (2006)** [62] according to his study it was included that the group that performed an exercise program had further reduction of joint destruction compared to the group that did not perform exercises and the exercises performed regularly are the best solution in hemophilic patients.

**L M González et al. (2011)** [63] in his study compared physical activity versus sedentary behaviors between hemophilic and healthy patients and concluded that physical activity has positive effects not only on hemophiliacs but also on healthy individuals and should be encouraged as healthy children spend more time making sedentary rather than active in a sport. A total of 41 patients with hemophilia A and 25 healthy patients included the study. Differences were found between the total amount of physical activity ( $p < 0.001$ ) and energy expenditure between the two group ( $p < 0.001$ ) for the group of hemophilic patients performing exercise therapy such as walking, climbing, cycling etc.

## Discussion

In this review study we will focus mostly on the various combined physiotherapeutic methods where the main basis are exercises where physical therapy is an important component in the management of hemophilia symptoms. About 50 years of drug treatment of hemophilia has evolved giving physiotherapeutic treatment safety and



importance resulting in effective prevention of bleeding episodes. To support these various studies have been found which have combined methods based on exercises that share the same thoughts as the authors above as there may be contradictions.

**T. HILBERG et al., (2003)** [64] in his study evaluated the safety of two physiotherapeutic programs that combine manual therapy with exercises at home with educational session in hemophilic patients concluding that treatment with manual therapy improved articular ROM and movements and reduced pain.

**D. CZEPA et al. (2012)** [65] evaluates the effects of surface electrical stimulation on the quadriceps muscle concluded that the group doing electrical stimulation and exercise had an increase in strength in the stimulated leg and results showed that the surface electrical stimulation poses no risk to the patients health and is used for therapeutic purposes.

**Ruth Mulvan et al. (2010)** [66] examine the feasibility and safety of a 6 week individualized exercise program in hemophilic patients concluding that an exercise program according to the requirements of each hemophilic individual had positive effects on improving symptoms by being safe and professionally supervised.

**Ruben Cuesta-Barriuso et al. (2018)** [67] evaluated the safety of two physiotherapeutic programs that combine manual therapy with exercise at home with educational sessions in hemophilic patients with elbow arthropathy concluding that treatment with manual therapy improved joint ROM and reduced pain.

in his study showed the effects brought by the combination of modalities with exercises and only one exercise treatment where the treatment of manual therapy with traction, passive stretching, proprioception, isometric exercises, thermotherapy and local krio therapy improved muscle perimeters and pain impact.

These 4 studies confirm even more and support the studies mentioned above the effectiveness and importance of exercises in hemophilic patients versus a physical sampling.

**F. QUEROL et al. (2006)** [68] evaluated the effects of superficial electrical stimulation on the quadriceps muscle concluded that the group performing electrical stimulation and exercise had an increase in strength in the stimulated leg and the result showed that the superficial electrical stimulation poses no risk to the patients health and is used for therapeutic purposes.

**A. CEPONIS et al. (2013)** [69] in his study evaluated painful episodes in hemophilic patients by rapid skeletal muscle US where it demonstrated that the fast high resolution MSKUS is a valuable point of care image tool to distinguish whether episodes of articular pain is related to bleeding or not.

**R. CUESTA-BARRIUSO et al. (2013)** [70] in his study showed the effects brought by the combination of modalities with exercises and only one exercise treatment where the treatment of manual therapy with traction, passive stretching, proprioception, isometric exercises, thermotherapy and local cryotherapy improved muscle perimeters and pain impact



Looking at these studies and based on the above studies we understand that modalities are an important therapy in the treatment of hemophilia combined with an exercise program to give more compromising effects and that US is one of the modalities that has more effective result in the treatment of hemophilic patients.

**Matthew Alexander et al. (2012)** [71] conclude that although the use of a prophylactic treatment will still have bleeding episodes in hemophilic patients but prophylactic treatment plus modern treatment will significantly reduce the rate of bleeding episodes compared only to prophylactic treatment.

**Rasha A. Mohamed et al. (2014)** [72] concluded that the combination of a routine aerobic exercise treatment with routine apparatus EN Tred is more effective than treatment with ergo metric bicycle alone. Aerobic exercise in a form of a routine treatment in children with hemophiliacs an excellent supplement to the regularly planned physiotherapeutic intervention.

Even this is a study that supports combined physiotherapeutic methods like the above authors who argue that exercises combined with ergo metric bicycle or other apparatus are more effective than just ergo metric bicycle.

**M. K. GARCIA et al. (2009)** [73] demonstrated the overall articular improvement of movement in hemophilic patients when subjected to an active movement in warm water and investigate how it happens looking the physiology of immersion, hydrostatic pressure to compare the results came to the conclusion that active free movement exercises in a hot water pool represent an approach of great importance in order to gain the amplitude of movement in the leg and knee joint preventing dysfunctions arising from hemorrhage predisposing the joint for the functional activities and facilitating muscle strengthens.

## Conclusion

Combining the exercise program with different physiotherapeutic methods is more effective in the treatment of hemophilia A.

Hydrotherapy has a positive effect combined with the ground exercise program.

Sports therapy and continuous activity of patients with hemophilia brings many benefits increase muscle strength and quality of life.

## Recommendations

Medical treatment is only part of good health. From this review literature study we can give some recommendations for improving life and developing activities in daily life in hemophilic patients:

Exercise and stay in shape  
 Wear protective suitable sport for activity  
 Perform regular medical checkups including examination of muscle and joints.

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# *Chronic Lead Poisoning Problems – A literature review*

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## **Abstract**

*Poisoning due to lead occurs mainly by ingestion of food or water contaminated with lead. However accidental ingestion of contaminated soil, dust or lead based paint may also result in poisoning. Lead is thought to be quickly absorbed in the blood stream and is believed to have adverse effects on certain organ systems like the central nervous system, the cardiovascular system, kidneys, and the immune system.*

*Lead is a common environmental pollutant. Exposure to lead occurs mainly at occupational sites, production of lead-acid batteries or pipes, metal recycling and foundries.*

*In cases of chronic exposure, lead often sequesters in the highest concentrations first in the bones then in the kidneys. According to the US Centre for Disease Control and Prevention and the World Health Organization, a blood lead level of 10 µg/dL or above is a cause for concern. However there is no threshold value below which lead*

*exposure can be considered safe. It has been found to impair development and have harmful effects even at lower levels.*

*Organic lead poisoning is now very rare around the world because of withdrawal of organic lead compounds as gasoline additives. Nevertheless, such compounds are still used in industrial settings. Organic lead compounds cross the skin and respiratory tract easily and quickly, affecting predominantly the central nervous system.*

*Pregnant women who have elevated blood lead levels are at a risk of premature birth or of babies with a low birth weight. The foetus may be adversely affected at blood lead concentrations well below 25 µg per deciliter.*

**Key Word.** *Saturnism, PB, Chronic poisoning with Lead.*

## **Background**

Lead poisoning, also known as 'saturnism', is a type of metal poisoning caused by lead in the body. The brain is the most sensitive. Symptoms may include abdominal pain, constipation, headaches, irritability, memory problems, infertility, and tingling in the hands and feet. It causes almost 10% of intellectual disability of otherwise unknown cause and can result in behavioral problems. Some of the effects are permanent. In severe cases, anemia, seizures, coma, or death may occur.

Chronic Overexposure Effects - Chronic overexposure to lead may result in severe damage to blood-forming, nervous, kidney and reproductive systems. Some common symptoms of chronic overexposure include loss of appetite, metallic taste in the mouth, anxiety, constipation and nausea.

Unfortunately, there is no cure and exposure cannot be fixed. But the effects can be reduced by removing the lead source, getting early intervention, and eating a diet high in iron and calcium. If lead levels are very high, x-ray or chelation therapy may help to remove some of the lead out of the blood.

## **Causes of Poisoning with Lead (Pb)**

- Water, mainly due to older lead tubes and use of lead connector.
- Soil contaminated with lead or benzene paint, perishable lead paint, leaded gasoline residues, used engine oil, tire weight or past pesticides, contaminated landfills or industries close as foundries
- Exposure of the profession to mines, smelters or production facilities involving lead
- Imported ceramics and ceramics used for dinner



- Lead crystal is used for decanted liquids or for food storage
- Ayurvedic and folk remedies, some of which contain lead for “curative” benefits and others which are contaminated during production
- Imported toys, cosmetics, candy and household products produced in countries without lead restrictions
- Paints and varnishes for paintings
- Industry of production of bullets and fuses
- Lead-contaminated opium

Lead poisoning occurs especially when inhaled vapors or lead-containing powders, for example, during the processing of lead-based paints. But lead can also enter the body through contact skin or food. For example, lead-containing ointments used in beauty care can cause lead poisoning (1, 2).

**Periodic Table of the Elements** www.elementdatabase.com

1 Hydrogen

2 Helium

3 Lithium

4 Beryllium

5 Boron

6 Carbon

7 Nitrogen

8 Oxygen

9 Fluorine

10 Neon

11 Sodium

12 Magnesium

13 Aluminum

14 Silicon

15 Phosphorus

16 Sulfur

17 Chlorine

18 Argon

19 Potassium

20 Calcium

21 Scandium

22 Titanium

23 Vanadium

24 Chromium

25 Manganese

26 Iron

27 Cobalt

28 Nickel

29 Copper

30 Zinc

31 Gallium

32 Germanium

33 Arsenic

34 Selenium

35 Bromine

36 Krypton

37 Rubidium

38 Strontium

39 Yttrium

40 Zirconium

41 Niobium

42 Molybdenum

43 Technetium

44 Ruthenium

45 Rhodium

46 Palladium

47 Silver

48 Cadmium

49 Indium

50 Tin

51 Antimony

52 Tellurium

53 Iodine

54 Xenon

55 Cesium

56 Barium

57 Lanthanum

58 Cerium

59 Praseodymium

60 Neodymium

61 Promethium

62 Samarium

63 Europium

64 Gadolinium

65 Terbium

66 Dysprosium

67 Holmium

68 Erbium

69 Thulium

70 Ytterbium

71 Lutetium

72 Hafnium

73 Tantalum

74 Tungsten

75 Rhenium

76 Osmium

77 Iridium

78 Platinum

79 Gold

80 Mercury

81 Thallium

82 Lead

83 Bismuth

84 Polonium

85 Astatine

86 Radon

87 Francium

88 Radium

89 Actinium

90 Thorium

91 Protactinium

92 Uranium

93 Neptunium

94 Plutonium

95 Americium

96 Curium

97 Berkelium

98 Californium

99 Einsteinium

100 Fermium

101 Mendelevium

102 Nobelium

103 Lawrencium

Legend:

- Hydrogen
- alkali metals
- alkali earth metals
- transition metals
- post-transition metals
- metalloids
- nonmetals
- noble gases
- halogens

## Physio-Pathology of the spread of Pb in the body

Organic lead poisoning is now very rare, because countries across the world have phased out the use of organic lead compounds as gasoline additives, but such compounds are still used in industrial settings. Organic lead compounds, which cross the skin and respiratory tract easily, affect the central nervous system predominantly.

Exposure occurs through inhalation, ingestion or occasionally skin contact.

Lead may be taken in through direct contact with mouth, nose, and eyes (mucous membranes), and through breaks in the skin. Tetraethyllead, which was a gasoline additive and is still used in aviation gasoline, passes through the skin; however inorganic lead found in paint, food, and most lead-containing consumer products is only minimally absorbed through the skin. The main sources of absorption of inorganic lead are from ingestion and inhalation. In adults, about 35–40% of inhaled lead dust is deposited in the lungs, and about 95% of that goes into the bloodstream. Of ingested inorganic lead, about 15% is absorbed, but this percentage is higher in children, pregnant women, and people with deficiencies of calcium, zinc, or iron. Infants may absorb about 50% of ingested lead, but little is known about absorption rates in children.

Chronic lead poisoning in adults occurs when an amount of lead of about 500 nanograms or more is swallowed. 95% of the lead that enters the blood is bound to erythrocytes (red blood cells) and proteins in the blood.

- Lead then travels through the bloodstream to organs such as the brain, liver and lungs, where it has a half-life of 20 days.
- While some bullets are secreted, some are also deposited in teeth and bones. There, the half-life is 5 to 20 years.
- If the bone substance is degraded to a greater extent, the level of lead in the blood can increase even without the new lead being supplied from outside the body.
- Because lead also crosses the placenta, lead poisoning can be passed from mother to unborn child (<https://mjekesor.com/pulmon-poisoning-causes-treatment-of-symptoms/>).
- Lead can also enter the body through contact skin or food. Exposure occurs through various routes such as absorption, ingestion or skin contact
- Human exposure to lead occurs in lead-related professions, from gasoline, ceramics, shipbuilding, lead-based painting, battery recycling, metal recycling, and book printing, to name a few.
- One of the main causes for lead pathology is that it interferes with the activity of an essential enzyme called delta-amino levulinic acid dehydratase, or ALAD (see image of enzyme structure), which is important in heme biosynthesis cofactor found in hemoglobin. Lead also inhibits the enzyme ferro chelatase, another enzyme involved in heme formation (3).

## How humans are exposed to chemicals in the environment and their effect on human health

Acute lead poisoning occurs only when very large amounts of lead or lead components are ingested once. In adults, for example, a Dose of 5 to 30 grams of lead salt lead acetate, which is easily soluble in water, has a lethal effect.

K Chronic poisoning in contrast, daily intake of 1 microgram, e.g. through food, after a longer period of time.

Health world organization estimates risk-free daily oral intake of an average of about 100 to 500 micrograms.

Pharmaceutical companies give the maximum daily dose of Pb up to 1.0  $\mu\text{g} / \text{g}$ , but prolonged daily intake with this dose is dangerous for humans (4).

- Various organs of the human body are affected by lead poisoning as SNQ, Bone marrow where blood is formed, Gastro-intestinal tract, Gonads (testicles and ovaries), Skin, Kidneys.
- Long-term exposure can lead to problems with mental and physical development, and in severe cases can result in coma or death.



## **Pb intoxication in children**

In children as well as adults, the nervous system is most exposed to lead toxicity. Children up to the age of six are, however, particularly vulnerable to lead poisoning because of their rapid rate of growth and development (6).

- Developmental delays
- Learning disabilities cause behavioral problems
- Abdominal pain
- Loss of Appetite
- Laziness or fatigue - children who look like Lazy.
- Pica- is an eating disorder in which people eat things that have no nutritional value like paint or plaster, and 'Pb intoxication'.
- Anemia
- SNC - Encephalopathy and coma
- Along with bones, teeth, and blood, many other tissues store lead, such as the brain, spleen, kidneys, liver, and lungs (7).

Women who were exposed to lead before or during pregnancy have it stored in their bones. According to the World Health Organization (WHO), during pregnancy, lead is restored to the bloodstream, exposing the fetus to premature birth or a low birth weight (<https://sq.thomson-intermedia.com/10-symptoms-of-lead-poisoning-in-children-2058>).

## **Symptoms of Acute and Chronic Poisoning**

Symptoms of lead poisoning are often subtle and difficult to identify. In some people, there may be no symptoms. Most often seen:

- Irritability. Fatigue
- Headache
- Loss of concentration
- Short-term memory deficit
- Dizziness and loss of coordination.
- Unusual taste in the mouth
- A blue line along the gum (known as the Burton line)
- Tingling or numbness (neuropathy)
- Abdominal pain
- Decreased appetite

- Nausea and vomiting
- Diarrhea or constipation e Clumsy speech

Occupational exposure to lead increases the risk of cardiovascular disease, in particular: stroke and high blood pressure (8, 9).

## **Symptoms in Children**

Children who have lead poisoning may have poor appetite and may lose weight. They may also have stomach pain, constipation and vomiting. In addition, they can be very tired and nervous.

Caregivers may notice that the child is very pale, which occurs as a result of anemia. Children with lead poisoning may also experience learning difficulties.

## **Symptoms in Adults**

Adults exposed to too much lead may experience headaches, memory loss, mood swings, stomach aches and fatigue. They may also have tingling, numbness, or pain in the hands and feet. Men may have a lower than normal sperm count and the sperm may be abnormal. Women exposed to too much lead while pregnant may experience a miscarriage or premature birth.

Acute lead poisoning is characterized by:

- Headaches, limb pain, severe abdominal pain, and silence. In severe cases, coma and circulatory failure can occur with death. Spastic ileus (intestinal obstruction) is also possible.

Acute lead poisoning can be treated with gastric lavage. However, chronic lead poisoning is more insidious (10).

- Long-term lead contamination can lead to a variety of symptoms. Since heavy metal has an inhibitory effect on blood formation, so-called lead anemia develops in chronic lead poisoning. Like all forms of anemia, this leads to fatigue and reduced physical and mental performance.
- A layer of gray-gray to black lead sulfur is deposited in the gums. the cardiovascular system is damaged due to vasodilator hormones released by lead.

- Cardiac arrhythmia, heart failure and myocardial infarction may occur. Furthermore, due to damage to the brain nervous system, symptoms such as disorientation, headache, aggression, hyperactivity, insomnia or apathy occur.
- Severe cases of nerve damage are characterized by delirium, coma or convulsions, which can lead to death from circulatory failure
- Furthermore, numbness and sensory disturbances in the extremities,
- As well as motor deficits are possible. Finally, kidney damage can also develop in the long run over a certain lead concentration in the blood.

## **Chronic Poisoning. Effects on children**

As lead safety standards become more stringent, fewer children in the US are found to have elevated lead levels.

A pregnant woman who has elevated blood lead levels is at greater risk of a premature birth or with a low birth weight. Children are more at risk for lead poisoning because their smaller bodies are in a continuous state of growth and development. Young children are much more vulnerable to lead poisoning, as they absorb 4 to 5 times more lead than an adult from a given source. Furthermore, children, especially as they are learning to crawl and walk, are constantly on the floor and therefore more prone to ingesting and inhaling dust that is contaminated with lead.

The classic signs and symptoms in children are loss of appetite, abdominal pain, vomiting, weight loss, constipation, anemia, kidney failure, irritability, lethargy, learning disabilities, and behavioral problems. Slow development of normal childhood behaviors, such as talking and use of words, and permanent intellectual disability are both commonly seen. Although less common, it is possible for fingernails to develop leukonychia striata if exposed to abnormally high lead concentrations (11).

On July 30, 2020, a report by UNICEF and Pure Earth revealed that lead poisoning is affecting children on a “massive and previously unknown scale.” According to the report, one in three children, up to 800 million globally, have blood lead levels at, or above, 5 micrograms per deciliter ( $\mu\text{g} / \text{dL}$ ), the amount at which action is required

Chronic or acute poisoning occurs, depending on the severity and duration of lead exposure

Chronic poisoning usually presents with symptoms that affect multiple systems, but is associated with three main types of symptoms: gastrointestinal, neuromuscular and neurological.

The central nervous system and neuromuscular symptoms usually come from intense exposure, while gastrointestinal symptoms usually come from exposure for longer periods. Signs of chronic exposure include short-term memory or concentration loss, depression, nausea, abdominal pain, loss of coordination, and numbness and tingling sensation in the extremities. Fatigue, sleep problems, headaches, dizziness, slurred speech and anemia are also found in chronic lead poisoning. “A” lead color “of the skin with pale and / or livid is another feature. A blue stripe along the gums with a bluish black tip on the teeth, known as the Burton stripe, is another indicator of chronic lead poisoning. Children with chronic poisoning may refuse to play or may have hyperkinetic or aggressive behavioral disorders Visual disturbance may present with blurred vision that progresses gradually as a result of central scotoma, caused by toxic optic neuritis (12, 13).

## Diagnostic

Diagnosis of lead poisoning is best done by a Blood Test, but can also be done by analyzing urine, hair or teeth.

In urine, however, lead can be dispersed irregularly due to the body’s not necessarily using fluids, so measurement inaccuracies in lead poisoning cannot be ruled out.

Lead poisoning is the accumulation of lead in the body, which usually develops over months or years. While lead poisoning is common in the developing world, causing over 800,000 deaths a year, it can also affect US households.

Blood lead concentration is measured in micrograms ( $\mu\text{g}$ ) per deciliter (dL) of blood. The current acceptable range is (blood lead level (BLL):

- Less than 5  $\mu\text{g}$  / dL for children
- Less than 25  $\mu\text{g}$  / dL for adults

For this, your doctor may order non-invasive X-ray fluorescence (XRF), essentially a form of high-energy X-ray that can assess how much lead is in your bones and detect areas of calcification that indicate long-term exposure (14).

## Complications

Chronic lead poisoning should be suspected if a person feels constantly stressed for no apparent reason, complains of widespread headaches and abdominal pain, and shows signs of anemia.



- Typical symptoms also include a yellow discoloration of the skin and the so-called lead fringe, a blue-black stain on the gums. Anyone observing such symptoms should see a doctor immediately.
- Lead poisoning usually causes fatigue, nausea and vomiting immediately. In the long run, improper treatment of poisoning can cause further complications.

In children, even a small amount of lead can cause permanent physical and mental damage. The main complications are developmental disorders, hearing problems, concentration coordination difficulties.

In addition, behavioral problems such as aggression and hyperactivity may occur. Typical physical complications of lead poisoning include kidney damage and during illness rarely lead poisoning can lead to life-threatening sepsis with severe consequences. Higher amounts of lead also pose a risk of kidney failure, which can also be fatal if left untreated.

Chronic lead poisoning reduces overall well-being and is associated with loss of appetite, fatigue, headache, abdominal pain constipation. In addition, because lead reduces the formation of red blood cells, the risk of anemia increases. Furthermore, permanent kidney damage and other complications can develop.

The extent of the symptoms depends mainly on the amount of lead ingested and the composition of the affected person; prompt treatment significantly reduces the risk of permanent damage and usually leads to a complete recovery of the patient.

## Treatment

Lead poisoning is preventable. This includes individual efforts such as removing lead-containing items from the home, workplace efforts such as improved ventilation and monitoring, state laws that ban the use of and national policies such as laws that ban lead in products such as paint, gasoline, ammunition, wheel weights, and fishing weights reduce allowable levels in water or soil, and provide for cleanup of contaminated soil. Workers' education could be helpful as well. [The major treatments are removal of the source of lead and the use of medications that bind lead so it can be eliminated from the body, known as chelation therapy. Chelation therapy in children is recommended when blood levels are greater than 40–45 µg / dl. Medications used include dimercaprol, calcium disodium edetate, and succimer (15).

In 2016, lead is believed to have resulted in 540,000 deaths worldwide. It occurs most commonly in the developing world

Therapy can be given either orally or intravenously. Chelation therapy is indicated in people with severe lead poisoning or signs of encephalopathy. It can



also be considered for anyone whose BLL is above 25 µg / dL. Chelation therapy has less value in chronic cases below this value.

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- Therapy can be given either orally or intravenously. The most common agents include:
  - Bal in oil (dimercaprol) u Calcium disodium
  - Chemet (dimercaptosuccinic acid) u D-penicillamine
  - EDTA (ethylene diamine tetra-acetic acid)
- Side effects may include headache, fever, chills, nausea, vomiting, diarrhea, shortness of breath, irregular heartbeat, and chest tightness. In rare cases, seizures, respiratory failure, kidney failure, or liver damage have occurred.
- In acute lead poisoning, the fluid used for gastric lavage consists of three percent sodium sulfate solution. Activated charcoal is administered at the same time, which causes lead components - converted to lead sulfate, which is more difficult to digest - to bind to activated charcoal.
- If the lead has already passed beyond the stomach and entered the body, the patient is administered drugs such as penicillamine, which bind the lead to his body and thus make it harmless, so that the heavy metal can be secreted back through the kidneys. .
- Treatment of iron, calcium and zinc deficiency, which are associated with increased lead absorption, is another part of treatment for lead poisoning.
- If lead encephalopathy is present, anticonvulsants may be given to control seizures, and treatments to control brain swelling include corticosteroids and mannitol.

- Administration of dimercaprol, DMSA (Succimer) or DMPS before calcium EDTA is necessary to prevent redistribution of lead into the central nervous system.
- At this point, blood provides an ideal means of monitoring whether therapy is working as desired. Antispasmodics (antispasmodics) are used to treat abdominal pain.
- If kidney damage has occurred, blood washing may be required temporarily or even permanently. It is imperative that the patient avoid any further contact with the heavy metal bullet (17).

To do this, however, it is necessary to clearly identify the source of the lead poisoning.

## Prognosis

The prognosis for lead poisoning depends on the amount of lead in the body and the duration of exposure. The earlier lead poisoning is identified and treated, the better the prognosis is (18).

Addition to abdominal pain, brain damage can occur in children, making their prognosis less favorable and requiring even faster action. Chronic lead poisoning will lead to death after a while if left untreated. Nerve and kidney damage in particular plays a role here, as they ultimately make the affected person unable to live. However, even severe cases of chronic lead intoxication can be treated with complexing agents and chelation therapy. However, organ damage that has already occurred at a structural level cannot be reversed with this, so the affected persons will continue to live with post-therapy limitations (19). Chronic lead intoxication can also recur in the affected person and lead to symptoms if the source of the damage cannot be found.

## Prevention

Meanwhile, to further reduce your family's risk:

- Make sure everyone washes their hands often.
- Teach children not to put their hands or fingers in their mouths. To give everyone a daily supplement of iron and calcium. . Vacuum and wet wash frequently.
- Encourage children to play on the ground around the house if the exterior paint is raw or deteriorating.

- Place an entrance inside and outside the entrance to your home.
- Encourage everyone to take off their shoes before entering.
- If you work in a factory or factory where there is a risk of lead exposure, take a shower and change your clothes before going home.

Lead poisoning can be prevented primarily by avoiding the release of lead. The use of many lead-containing materials is restricted or prohibited. Remaining lead-containing materials (e.g., in old car batteries) are disposed of separately (20).

Water pipes that still contain lead, which can contaminate leaded drinking water to a considerable extent, need to be replaced. Pregnant women and young children in particular should avoid drinking lead-containing water.

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# *The application of the fractal analysis in oncopathology*

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## **Summary**

*Fractal analysis is an objective approach that in oncopathology is one of the important fields of application. In this study is present fractal methodologies at histological level that have been successfully applied to characterize pathological features and able to perform differential diagnosis and prognosis in oncopathology. The basic principles and prospects of fractal geometry in pathology are promising. In particular, fractal analysis is emerging as a powerful tool to perform differential diagnosis and prognosis of the patients in cancer and other malignancies as well to improve the effectiveness and safety of patient care. All fractal objects have Fractal Dimension FDs, commonly calculated with box counting. Morphometry, the measure of shapes of the structures, can be added to every imaging technique in order to obtain objective indexes. In this field, fractal analysis has been applied to histopathology, cytopathology, and electron microscopy with great success. Performing fractal analysis of tissue samples, it's possible to make differential diagnosis between the early stage of tumours and flogosis, or among the different types of Basal Cell Carcinoma, and different grade of Invasive Bladder Carcinoma, well as to investigate the subtle alterations of the nuclear patterns in human breast tumours, or to evaluate other tumours. Fractal analysis shows a high ability for automatic classification of cancer cells in urinary smears, as well as to identify prostate cancer cells, has been able to distinguish*

*diagnostic/prognostic classes in the invasive bladder carcinoma and myelodysplastic syndromes. In the future, fractal analysis may help with the diagnosis, understanding of pathogenesis and management of the lesions.*

**Keywords:** *Fractal analysis, fractal dimension, oncopathology, differential diagnosis, prognosis.*

## Introduction

The first work using the concept of fractal geometry in cell biology was done by Paumgartner, Losa and Weibel which examined mitochondrial and reticulum membrane surface densities and found fractal behavior. <sup>[1, 2]</sup> Subsequently, in histology, fractal geometry has proved usefulness in describing the shape of neurons, glial cells, convolutions of the brain surface, retinal vasculature and in other tissues. <sup>[1, 2, 3, 4]</sup> In effect, living structures may be described as being in a self – organizing, fluctuating steady – state far from equilibrium. Self organization and a state far from equilibrium are characteristics of chaotic structures. Chaotic structures present fractal geometry, so is not too astonishing that the branching pattern of the airways in the lung, or the arterial vascular pattern of the cardiovascular system <sup>[5, 6, 7]</sup>, colorectal polyps <sup>[4]</sup> anal intraepithelial neoplasia <sup>[16]</sup> and in the more tumour pattern as mycosis fungoides, basal cell carcinoma, urothelial carcinoma <sup>[8]</sup>, breast cancer <sup>[12]</sup>, brain tumours <sup>[13]</sup> etc, have been described with fractal properties.

Like coastlines a tumour examined by light microscopy has a complex, irregular border and retains a similar level of complexity over a range of magnifications. <sup>[4, 5, 8, 11, 12]</sup> Euclidian morphometric measurements were found to be invalid outside precisely defined conditions of resolution and magnification. <sup>[2, 3, 5, 12]</sup> Fractal analysis was used by the authors as a numerical method of describing the irregularity of the epithelial – connective tissue interface, in an attempt to provide an objective means of classifying the irregularity of the interface. So, moderate/severe dysplasia and squamous cell carcinoma were significantly distinguished by the fractal dimension values, from the normal epithelium and mild dysplasia. <sup>[4]</sup> Cross and co-workers <sup>[4]</sup> also applied fractal analysis to evaluate colorectal polyps. Studying 359 cases colorectal polyps the authors demonstrated that all the examined polyps had a fractal structure and the fractal dimension between these categories.

In this study, its applied fractal dimension analysis to study human tumours at light and ultrastructural levels, and presenting data obtained studying the epithelial – connective tissue interface in basal cell carcinoma of the skin, the boundaries of invasive bladder carcinomas (urothelial neoplasia), and the lymphocytic nuclear membrane in mycosis fungoides and chronic dermatitis.

Mandelbrot's concept of fractal geometry [1] is a powerful approach in order to precisely

## Material and methods

The material of this study was derived from a series of 147 cases of basal cell carcinoma of the skin, (BCC), and 27 cases of invasive bladder carcinomas (IBC) were analysed.

### *Histopathology*

**A. Basal cell carcinoma (BCC).** Haematoxylin and eosin-stained paraffin sections of each case of BCC were reviewed by a single pathologist and assigned to three diagnostic categories:

1. Circumscribed basal cell carcinoma (CBCC) are tumours composed of large islands (one or more) of basaloid cells, aggregated in cohesive clusters bound together by fibrovascular stroma. The tumour margins are convex and the neoplasm grows expansively with regular front of the invasion.

2. Infiltrative basal cell carcinoma (IBCC) are tumours that lack central cohesive mass of basal cell islands as seen in solid BCCs, consisting of elongated islands and cords that are widely separated spatially.

3. Mixed basal cell carcinoma (MBCC), are tumours that have a mixture of solid and infiltrative growth pattern.

Five - micron - thick sections were stained with monoclonal antibodies against human cytokeratins and used for image fractal analysis.

**B. Invasive bladder carcinoma (IBC).** Haematoxylin and eosin-stained paraffin sections of each case of IBC were reviewed by a single pathologist and assigned to diagnostic categories and histological grade. Histopathological diagnosis of 27 cases, presented 12 cases resulted as a low grade, 8 cases Papillary Urothelial Neoplasm of Low Malignant Potential (well-preserved cell pattern, cells with increased and uniform size, fine and even chromatin, papillary and loose cluster cell arrangement); 4 cases are Low Grade Papillary Urothelial Carcinoma, while 15 cases of IBC areas high grade: High Grade Papillary Urothelial Carcinoma (cells with increased and polymorphic size, coarse and uneven chromatin, isolated and loose cluster arrangement).

### *Fractal analysis*

Was performed by using the box-counting method, using software Visual Basic 3.0. Briefly, each image was converted with a net of square boxes (4 to 100 pixel),

and the number of boxes containing any part of the outline was counted. A log-log plot of the reciprocal side length of the square against the number of outline – containing squares was performed. The slope of the best linear segment of the best linear segment of the graph represented the fractal dimension of the image.

To perform computerized image analysis and to obtain morphometric fractal indices, the first challenge is the tissue/cell segmentation, to separate noise and biological features. The second step is the feature selection to isolate the tissue, the cells, or the nuclei of interest. The last important challenge is the system of evaluation, e.g. the log-log plot in order to determine the fractal dimension of the skeletonized tissue/cell/nucleus, being the fractal dimensions the exponent of a log-log plot, meaning the self-similarity of the biological structure. In a possible approach, images are digitized, while aperture settings and conditions of illumination and magnification are kept constant. Single pixel outlines of the contours of the image are automatically obtained by using grey-level threshold segmentation. x 40 magnification may be suitable to evaluate tissue, x 100 magnification to analyze the distribution of nuclei. Image analyzer can be used to obtain the skeletonized images.

## Results

Linear discriminant analysis was applied by a Wilks'lambda statistic, and the results summarised in a confusion matrix, in order to evaluate the predictive significance of fractal dimension with respect to the qualitative classification of basal cell carcinoma: none of the cases of circumscribed basal cell carcinoma was placed in the infiltrative basal cell carcinoma group. The percent of correct classification was 74 %, with  $p < 0,001$ . (Table 1)

Variance analysis was used to analyze the samples of invasive bladder carcinomas of different histological grades: 12 cases as a low grade (Figure 1), 8 cases Papillary Urothelial Neoplasm of Low Malignant Potential; 4 cases are Low Grade Papillary Urothelial Carcinoma; while 15 cases of IBC are High Grade Papillary Urothelial Carcinoma (Figure 2).

The lowest histological grade resulted in the lowest value of fractal dimension ( $p < 0,05$ ), while

the cases with high grade resulted in high values of fractal dimension ( $p < 0,05$ ). (Table. 2)

Fractal dimension value statistically differs between low grade (well preserved cellular pattern), respectively with high grade (low-preserved cellular pattern with pleomorphic cells and coarse chromatin).



**FIG. 1.** Papillary Urothelial Neoplasm of Low Malignant Potential



**FIG 2.** High Grade Papillary Urothelial Carcinoma.



**Table 1.** Fractal dimension of histological outlines of basal cell carcinoma tissue, confusion matrix between actual and predicted group membership, after discriminant analysis.

Group <sup>a</sup>	Predicted Group Membership <sup>b</sup>			
	Number of cases	1	2	3
CBCC	60	51 (85 %)	9 (15 %)	0 (0 %)
MBCC	39	12 (31 %)	21 (54 %)	6 (6 %)
IBCC	48	3 (6 %)	9 (19 %)	36 (57 %)

<sup>a</sup> CBCC – circumscribed basal cell carcinoma; MBCC – mixed basal cell carcinoma; IBCC – infiltrative basal cell carcinoma.

<sup>b</sup> Present of cases correctly classified = 74 %;  $p < 0,001$ . Mean value  $\pm$  standard deviation.

**TABLE 2.** Fractal dimension of histological outlines in two different histopathological type of Invasive Bladder Carcinoma (low grade, high grade).

Low grade	High grade	
IBC = 1, 35 ± 0, 20. n = 12	IBC = 1, 50 ± 0, 17 n = 15	p < 0, 05

IBC – infiltrative bladder carcinoma.

Note: Mean value ± standard deviation

## Discussion

Lowered cost and increased power of computer system, have recently brought image analysis into many histological laboratories. Image analysis in oncological pathology is a powerful tool to isolate important discriminating factors useful in the diagnostic decision.

A lot of morphometric measurements have been performed to discriminate between different diagnostic classes, examples include the measures of nuclear diameter, perimeter, area and respective form factor. [1, 3, 4, 5, 6, 7, 8]

Fractal dimension gives an objective number that is able to characterize quantitatively a lesion close to a 100% correct classification. In effect, since many years, neoplasms in organs have been studied by fractal analysis for demonstrating differences between normal, dysplastic and neoplastic cells and tissues [2, 3, 5, 7], also estimating angiogenesis [10, 13], analysing monocytes in diabetes [10] for detection of prostate cancer on histopathological samples [17], evaluating the response of anticancer therapy as well as in order to determine the prognosis of the patient, in the squamous cell carcinomas of the larynx, the first work that used fractal dimension to perform prognosis [21], studying the fractal characteristics of chromatin observed in light and electron microscopy [10], or studying glioma tissues, being the fractal indexes able to differentiate the malignant grades of that tumour, [13] as well in radiomic approaches in order to predict pathological response after chemo-radiotherapy in rectal cancer [16]. Also in our hands, fractal analysis has been very able to distinguish among diagnostic classes linked to prognosis in cancer, studying bioptic samples in mycosis fungoides [8] as well in and myelodysplastic syndromes [19]

However, all these Euclidian parameters present many problems when applied to the highly irregular histopathological structure, for example, all are dependent on scale or, in other words, on the magnification. [3, 9, 10, 11, 12]. In the recent years, in the field of oncological pathology same works on concerning diagnosis and prognosis of patients. [17, 18, 19, 20, 21, 22]

Here we present our original data concerning the great capacity of fractal analysis to distinguish among diagnostic classes in the study of tumours. Fractal analysis, performed with box-counting method, has revealed the ability of this approach to distinguish between circumscribed and infiltrative pattern of basal cell carcinoma of the skin, thus originating a non subjective method to analyze that type of malign neoplasms. Using the box-counting technique over the tissue outlines in order to evaluate the geometric complexity <sup>[3,10,12, 15, 17]</sup> or the entropy <sup>[9, 14]</sup> of the sample. Also, fractal analysis has allowed us to obtain an index that distinguishes between urothelial carcinoma low grade, with urothelial carcinoma high grade.

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# *Screening for cervical cancer as an organized or opportunistic challenge* \_\_\_\_\_

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## **Abstract**

*Pap test is already part of the successful examinations in the early detection of cervical cancer. The objective of this 1-year retrospective study (2019-2020), is to assess the importance of periodic Pap tests, the distribution of squamous and glandular anomalies, as well as determining the predominant categories for each anomaly, in 4123 cases of Hygeia hospital, in Albania. The age group 60-69 years was with the most anomalies. 72.8% of women included in the study tested negative for intraepithelial lesion or malignancy. There was an increase in the positive percentage of Pap tests with epithelial cell abnormalities with increasing age group up to the age of 70 years ( $p < 0.001$ ). With epithelial cell abnormalities 97.7% of them were of squamous origin (ASC-US 86.2%) and 2.3% of them were of glandular origin.*

*The Pap test should be a routine test for all sexually active young women, for early precancerous detection of the cervix. It is a valid, inexpensive, uncomplicated, non-invasive screening test for the detection of premalignant and malignant lesions of the cervix<sup>7</sup>. The American Cancer Society recommends that all women should begin screening for cervical cancer 3 years after the onset of coitus. It is also recommended*

*that every 1-2 years, women who have passed the age of 30 and have had 3 consecutive normal pap results can be examined after 2 years<sup>11,12</sup>. Pap test cytology should be initiated in all women aged 21 years<sup>11,13</sup>*

**Key words:** Pap Smear, Young women, Hygeia hospital

## Introduction

Cervical cancer currently ranks second globally, among the types of cancer in women. Intraepithelial cervical neoplasms and cervical cancer remain significant health problems worldwide with high morbidity and mortality in the case of advanced lesions<sup>1,2,11</sup>. The Pap test is widely recognized as one of the most successful examinations in the early detection of cervical cancer. The Bethesda system is widely used worldwide and has almost completely replaced the Papanicolaou numeric system (a simple and very effective procedure for detecting premalignant cervical lesions)<sup>3,4</sup> for Pap test reporting. According to this system pre-invasive cervical lesions are classified into 2 groups: high-grade squamous intraepithelial lesions and low-grade squamous intraepithelial lesions<sup>5</sup>. Pap test is a cytological test designed to detect abnormal cervical cells from the transformed cervical area<sup>6</sup>. The cervical cytology screening process has reportedly reduced female mortality in the US and Canada by about 70% in the last 50 years. However today there are still women who lose their lives from cervical cancer<sup>1,2</sup>. For this reason it is necessary and have been designed and organized accurate screening programs by specialist doctors to increase the evidence and reduce the incidence of morbidity and mortality from this disease and in our country by IPH.

## Objective

This is a retrospective study during the period 2019-2020, realized at Hygeia Hospital which had in its focus the Pap test, determining the importance of performing this examination periodically as a method of preventing the development of cervical cancer.

## Material and Method

For a period of 1 year, 4123 Pap tests were evaluated on women of the age groups 19-70 years old, performed at Hygeia Hospital in Albania and the results of

cytopathological examination were collected. We analyzed the age group of women with and without anomalies; we assessed the distribution of anomalies of squamous origin and those of glandular origin for each age group; as well as we determined the age group with the highest percentage of anomalies. These data were studied to detect any correlation between the type of anomaly and the age group.

Our patients were divided into two categories: women whose expenses were covered by insurance companies and women who paid their own expenses. Pap test results were evaluated for each category of patients and abnormalities were determined for each age group. These data were studied to reveal any correlation between the type of anomaly and age group as well as to assess any possible relationship between the way Pap test costs are covered and their results.

The interpretation of the Pap test by the anatomopathologist was based on the Bethesda system. The study included only patients who had doctor-interpretable swabs without pronounced inflammation or with a small number of cells.

Results

In 4123 Pap tests analyzed, 3100 cases were negative for malignant intraepithelial lesion or neoplasia while 1023 cases were epithelial cell abnormalities.

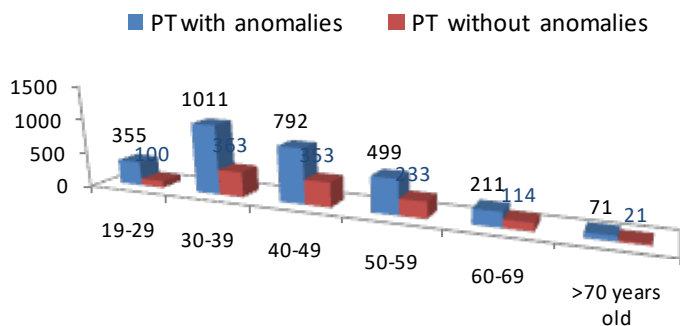
TABLE 1: Distribution of Pap tests with positive and negative results

Pap Test	Number	Percentage
No anomalies	3100	75.1%
With anomalies	1023	24.9%

The most common age group is 30-39 years old, which accounts for 33.3% of cases followed by 40-49 years old 27.8%; 50-59 years old - 17.8%, 19-29 years old - 11%. Women aged 60-69 years old and those aged 70 years old and over represented 7.9% and 2.2% of all women reported for age.

Pap test positivity increases significantly with age in examined women, from a positivity level of 22% in women aged 19-29 years old, 26.4% in 30-39 years old, 30.8% in 40-49 years old , 31.8% in 50-59 years old and reaching the peak in women aged 60-69 years old where the positivity of the Pap test is 35.1%, over 70 years old at 22.8%. These changes are statistically significant (P <0.001).

**GRAPH 1:** Distribution of Pap test results in relation to age group



Women who resulted in epithelial cell abnormalities on Pap test were divided into two categories; those with squamous cell abnormalities and those with glandular cell abnormalities and their percentage was calculated. Squamous origin was evidenced in 97.7% of women who tested positive for Pap test and glandular origin in 2.3% of them.

**TABLE 2:** Distribution of squamous and glandular abnormalities

Pap test with anomalies	Number	Percentage
Squamous anomalies	1390	97.7
Glandular anomalies	33	2.3%

## Categories distribution of squamous anomalies

In the group of women with squamous cell abnormalities 86.2% of them resulted in “ atypical of undefined nature” ASC-US, 0.1% resulted in squamous cell carcinomas, 1.2% with HSIL, 8.1% with LSIL, 4.3% with the status “can not to exclude HSIL ”and atypical squamous cells were detected in the remaining 0.1%.

**TABLE 3:** Distribution of categories of squamous anomalies

Squamous anomalies	Number	Percentage
ASC-US	1198	86.2
ASC-H	60	4.3
LSIL (CIN 1)	113	8.1
HSIL ( CIN 2dhe CIN 3)	16	1.2
Squamous cell carcinoma	2	0.1



## Distribution of glandular anomalies

Among women with abnormalities Pap test of glandular origin, 87.9% of them resulted in atypical endocervical glandular cells (AGC), endometrial, undetermined and the remaining 12.1% resulted in atypical glandular cells in favor of neoplasia.

**TABLE 4.** Distribution of anomalies of glandular origin

Glandular anomalies	Number	Percentage
Atypical cell	29	12.1%
Cell in favor of neoplasia	4	87.9%

## Relationship between funding status and Pap test results

It is noticed that there is a significant difference in the results of the Pap test with anomalies between women who are affiliated with insurance companies and those who pay the costs of their examinations themselves.

Thus, among women who are affiliated with insurance companies, Pap test resulted with anomalies in 21.7% of cases while among women who are not affiliated with insurance companies Pap test resulted with anomalies in 28.7% of cases. This difference is statistically significant ( $P < 0.001$ ).

**TABLE 5:** Relationship between funding status and Pap test results

Variable	Total n (%)	Connection with insurance companies		Value of P **
		No n (%)	Yes n (%)	
Results of Pap Test				
No anomalies	3800 (72.8)	2939 (71.3)	861 (78.3)	<0.001
With anomalies	1423 (27.2)	1184 (28.7)	239 (21.7)	

## Discussions

The Pap test represents an effective examination in the study of cervical epithelial cell abnormalities.

In our study, the age group with the highest screening was 30-39 years old, followed by 40-59 years old, probably related to the fact of information and

the highest level of awareness about cervical cancer and the possibility of its prevention<sup>7</sup>, while age 29 is more discouraged for screening, such interventions are not acceptable, in contrast age over 70 has less information<sup>11</sup>.

Pap test positivity followed an upward trend parallel to the increasing age group. HPV infection or other sexually transmitted infections are present shortly after sexual intercourse, the highest frequency of sexual intercourse and multipartnership at younger ages, the presence of CIN or precise lesions of cervical cancer are encountered for nearly a decade after the peak incidence of HPV <sup>7,8</sup>. This may explain why their percentage increases with age, as in our study.

From our study the squamous origin of epithelial abnormalities predominated by 97.7% compared to the glandular origin. Compared to studies in other countries in our study this incidence is much higher, as in Turkey study by the Turkish Cervical Cancer And Cervical Cytology Research Group (2009), 1.8%, in Saudi Arabia Jamal and Al-Maghrabi ( 2003) ranged from 1.7% to 29.9% <sup>9</sup>, Eastern Nigeria 12.2% evidenced by Ajah et al. (2015) <sup>10</sup>

Among squamous epithelial abnormalities ASC-US resulted in a higher frequency of 86.2% and in abnormalities of glandular origin predominated those with atypical cells (AGC) 86.7%. In studies in different countries have encountered different prevalence in this finding.

We noticed that insured women, whose expenses are paid by private insurance companies, have significantly lower results with epithelial cell abnormalities compared to women who pay for their own examinations; perhaps this is indicative of a more regular and periodic check-up of women associated with insurance companies, compared to women who pay for their own examinations.

## Recommendations

The Pap test should be a routine test for all sexually active young women, for early detection of cervical cancer. It is a valid, inexpensive, uncomplicated, non-invasive screening test for the detection of premalignant and malignant lesions of the cervix<sup>7</sup>.

The American Cancer Society recommends that all women should begin screening for cervical cancer 3 years after the onset of coitus. It is also recommended that every 1-2 years, women who have passed the age of 30 and have had 3 can be examined consecutive normal pap results after 2 years<sup>11,12</sup>. Pap test cytology should be initiated in all women aged 21 years<sup>11,13</sup>.

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