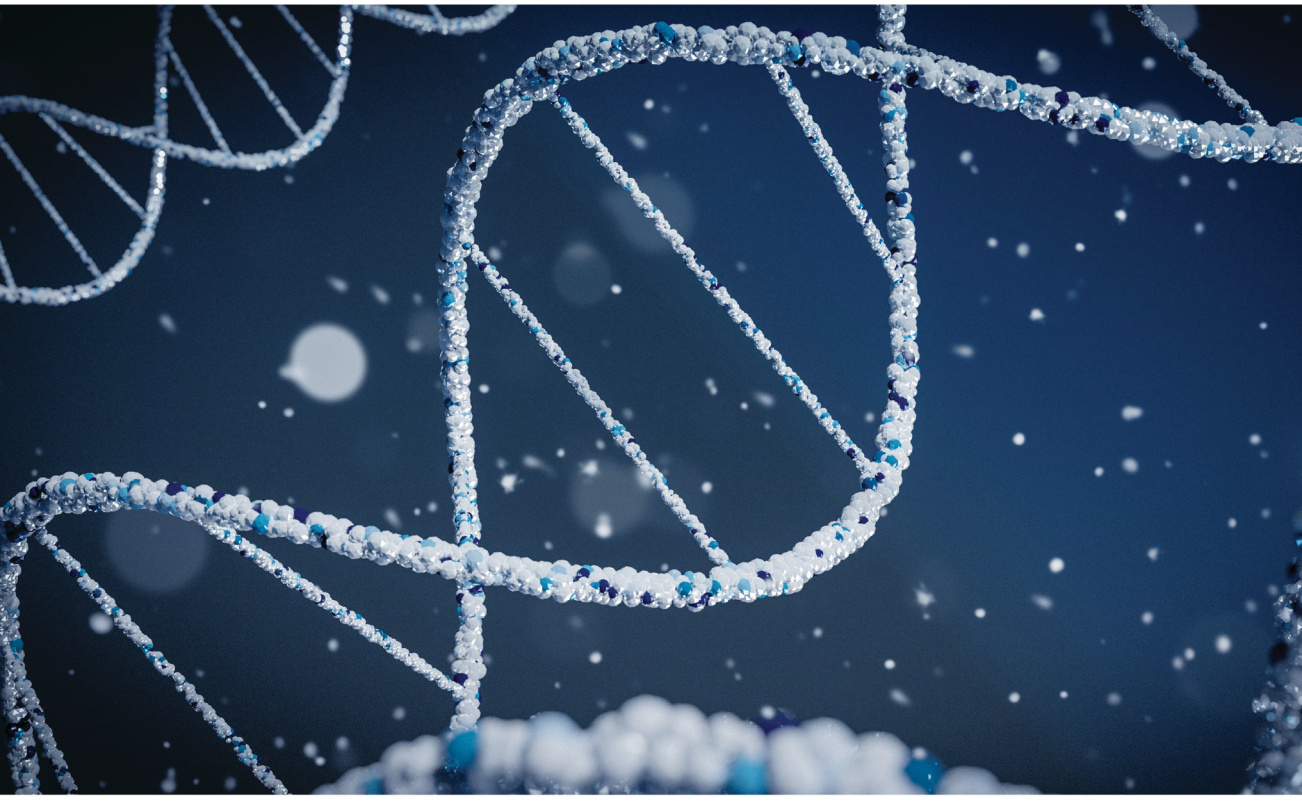
EUROPEAN UNIVERSITY OF TIRANA
Faculty of Medical Technical Sciences

Editor-in-Chief:
Prof. Asoc. Dr. Voltisa Lama
No. 5, issue 2 / 2021
ISSN 2663-7758

MEDICUS

5 ISSUE 2

JOURNAL OF THE FACULTY OF MEDICAL TECHNICAL SCIENCES



VISION 2030: PERSONALIZED MEDICINE

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UETPRESS

MEDICUS No. 5, issue 2/2021
JOURNAL OF THE FACULTY OF MEDICAL TECHNICAL SCIENCES

ISSN 2663-7758

UETPRESS

Published under the series "**ACADEMIC JOURNALS**".

European University of Tirana
University Press "UET Press"
Address: Rr. "Xhanfize Keko", Nd.56, Godina B, Tirana, Albania

Medicus journal has been catalogued at the National Library of Albania and the Library of the European University of Tirana, Albania.

UETPRESS

Published by:
EUROPEAN UNIVERSITY OF TIRANA / ALBANIA
Rr. "Xhanfize Keko", Nd 60, Tirana, Albania
www.uet.edu.al / info@uet.edu.al

Tiranë, 2021.

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EDITORIAL

Personalized medicine in a post-pandemic world

Prof. Asoc. Dr. Voltisa LAMA

Over the past almost two years the health system was focused to respond and resolve the COVID-19 pandemic. It is not yet the end of pandemic, still we need to see from the future and learn how to adapt and how to equip the health system to respond more efficiently to possible other medical challenges in a new era. One of the topics of discussion is how will evolve the medical care post-COVID.

The COVID-19 pandemic is a global experience that tested the ability of national health systems to withstand health shocks while maintaining routine functions. The pandemic exposed long-standing gaps in the health system and further accelerated the crisis. The health care workforce faced with dedication the overload of patients in hospital and outpatient services. On the other hand the people faced the fear, uncertainty, illness and death, social disconnection and economic difficulty.

There have been lessons learnt during the pandemic years and the pandemic had definitely changed the vision of health care's future. There is a need to address several post COVID challenges, firstly how to transition from COVID care to traditional healthcare services. People need care of other pathologies, some of them newly emerged while the pandemic postponed preventative screening and medical appointments, has hindered surgeries and delayed testing on biopsy tissue, as well as other chronic conditions which were placed in the secondary issues, because coronavirus world health emergency took the first place. Despite medical and fatal complications were attributed to coronavirus, clinicians noted that they resulted not only from the virus, but also from the coronavirus deteriorated effect on chronic and/or underlying undetected conditions which were specific to individuals.

Secondly, there were variable effects of the SARS-COV-virus in patient groups with similar characteristics and this polymorphic nature of patients' clinical

course has inspired research about the molecular factors that contribute to disease progression and differentiated response in each individual patient. Humanity's struggle with the coronavirus has fostered a new appreciation of the principles of personalized medicine, especially the value of diagnostic tools that could have helped target prevention strategies to at risk populations. Thus, the vision of the future is personalized medicine approach, which holds promises of prediction, prevention and treatment of illnesses that is targeted to the needs of the individual.

Despite the impact of COVID-19 crisis it does present the health care system with an opportunity to redesign itself. The next decade probably will bring a medical care model transformation. By 2030, the primary focus of healthcare will shift from a "one size fits all" approach towards risk definition, patient stratification and personalized health promotion and disease prevention strategies, which are especially valued for ageing societies. The technological advances in laboratory sciences and the data-rich era will lead to biomarker testing recommendations, disease screening protocols and targeted therapies for patients into standard practices.

COVID-19 and neurologic Complications in Elderly patients

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Abstract

The COVID-19 pandemic continues to prevail as a catastrophic wave infecting over 111 million people globally, claiming 2. 4 million lives to date. Aged individuals are particularly vulnerable to this disease due to their fraility, immune dysfunction, and higher rates of medical comorbidities, among other causes. Apart from the primary respiratory illness, this virus is known to cause multi-organ dysfunction including renal, cardiac, and neurologic injuries, particularly in the critically-ill cohorts. Elderly patients 65 years of age or older are known to have more severe systemic disease and higher rates of neurologic complications. Treatment of neurologic dysfunction of COVID-19 is based on existing practice standards of specific neurologic condition in conjunction with systemic treatment of the viral illness. The physical, emotional, psychologic, and financial implications of COVID-19 pandemic have been severe. Long-term data are still needed to understand the lasting effects of this devastating pandemic.

Introduction

Over the course of one year, the novel SARS-CoV-2 virus has wreaked havoc globally accounting for over 111 million documented infections with a vast toll of death and disability. Although the proportion of severe cases is likely to depend on the study population and epidemiological behavior of the infection in each country or geographic region, current evidence suggests that older individuals and those with compromised immune systems are more likely to develop severe forms of COVID-19 (1,2).

Elderly patients 65 years of age or older are known to have more severe systemic disease and higher rates of neurologic complications. Morbidity and mortality is very high in the elderly population with 6–930 times higher likelihood of death compared to younger cohorts, with the highest risk in elderly patients ≥85 years and especially those with medical comorbidities such as hypertension, diabetes, heart disease, and underlying respiratory illness. Commonly reported neurologic dysfunctions of COVID-19 include headache, fatigue, dizziness, and confusion. Elderly patients may manifest atypical presentations like fall or postural instability (3). Other important neurologic dysfunctions in the elderly include cerebrovascular diseases, cognitive impairment, and neuropsychiatric illnesses (4). Elderly patients with preexisting neurologic diseases are susceptibility to severe COVID-19 infection and higher rates of mortality.

Material and methods

This is a systematic review of the studies regarding the neurologic complications in elderly patients related to Covid-19. The research included four databases (PubMed; medRxiv; COVID-19 Living Evidence database; European PMC)

Results

Many countries that have endured severe effects of the pandemic have also experienced highest morbidity and mortality in the elderly population, particularly those with underlying comorbidities (5). In fact, Italy has one of the world's oldest population, with 23% of people ≥65 years, which is likely the reason for Italy's high case fatality rate (7.2%) compared to other countries (6). In the United States (U.S.), although infection is most prevalent in the 18–29 age group (23%), elderly patients ≥65 years are 5–13 times more likely to be hospitalized and have 9–630 times higher likelihood of death; with the highest

rate of hospitalization and death among patients ≥85 years of age (7). Per the National Vital Statistics System data on the demographic and geographic trends of COVID-19 in the U.S between May 1 and August 31, 78.2% of deaths occurred predominantly in men (53.3%) aged ≥65 years (8). Neurologic dysfunctions of COVID-19 are also more common in the elderly population (9), and the presence of neurologic dysfunction has been identified as an independent predictor of mortality in hospitalized COVID-19 patients (10). As neurologic complications are often associated with disease severity and mortality, characterization of neurologic dysfunction and accurate prognostication is crucial. Here we briefly discuss common neurologic dysfunctions of COVID-19 in the elderly, possible determinants of disease severity in this age group, outcomes, and treatment.

Neurologic Associations and Complications in Aged COVID-19 Patients

The most commonly reported symptoms of COVID-19 are fever, dry cough, fatigue, and dyspnea (11). Elderly patients are likely to present with atypical symptoms such as falls, postural instability, or delirium. The pulmonary manifestations of COVID-19 drive most hospitalizations worldwide, more commonly in patients ≥65 years and those with comorbidities like diabetes and hypertension (12). Critically-ill COVID-19 patients frequently develop multi-organ dysfunction including arrhythmias, myocardial injury, heart failure, arterial and venous thrombosis, disseminated intravascular coagulation (DIC), dysregulated immune response, and neurologic complications (13). Preexisting vascular disease is known to predispose individuals to severe COVID-19 infection, with aged individuals being more susceptible to more severe courses (14).

Acute stroke is another commonly reported neurologic complication of COVID-19, particularly in the elderly population. Li et al. reported a 5% risk of ischemic stroke and a 0.5% risk of cerebral hemorrhage in 221 patients with COVID-19 infection from Wuhan, with the highest prevalence in aged individuals with underlying vascular and thrombotic risk factors such as hypertension, diabetes, and elevated plasma D-dimer levels (15). Recent systematic reviews report stroke incidence of 1–2% in COVID-19 patients, which is significantly higher than historical controls, including a cohort with seasonal influenza. Mortality among hospitalized COVID-19 patients with acute stroke is also extremely high. Reports have noted mortality rates of 31.5–34.4%, with highest impact in older patients. Elderly stroke survivors are also at increased risk of severe infection and suffer from higher mortality, likely related to their

underlying comorbidities and swallowing complications. A recent meta-analysis of 39 studies on COVID-19-associated stroke suggested a mean age of 63.4 ± 13.1 years with male predominance and clinical findings of elevated D-dimer, elevated fibrinogen, and the presence of antiphospholipid antibodies (16). Although many other neurologic and neuropsychiatric symptoms have been reported, focused reports on elderly is generally sparse.

Treatment and Treatment Response of Aged COVID-19 Patients:

As we approach one year since the World Health Organization's (WHO) initial declaration of the novel coronavirus pandemic, limited evidence-based therapies specific to COVID-19 are available with management primarily focused on treatment of associated complications and supportive care. Regarding management of neurologic complications of COVID-19, existing evidence-based therapies are used for specific neurologic conditions, in conjunction with systemic treatment with antivirals, corticosteroids, and immunomodulators, as appropriate.

Delirium management has long been a priority in the care of older adults. Multidisciplinary care focused on prevention of delirium using non-pharmacologic strategies, is the best practice (17). Non-pharmacologic interventions include patient-centered care with frequent re-orientation, regular visits from family and friends, optimization of hearing and vision by ensuring access to hearing aids and glasses, adequate hydration, adequate sleep, early mobilization, and minimization of unnecessary lines, tubes, polypharmacy, and precipitating medications. In centers with pandemic-related visitation restrictions, care teams can help meet the emotional needs by displaying family photos, facilitating the use of technology to connect patients with their families, and assessing patients' desire to access spiritual care. Early mobilization is the single intervention with the strongest evidence of decreasing the incidence and the length of delirium. Pre-COVID literature suggests that delirium can be prevented with appropriate in-hospital multimodal approach in about 30% of cases (Siddiqi et al., 2016). Regular clinical assessments for pain, agitation, and delirium with validated screening tools can help with early recognition and management (18). Patients on immunosuppressants and those with neuroinflammatory diseases like multiple sclerosis should continue treatment of their underlying illness while applying precautions to prevent viral spread and ensuring access to healthcare via teleneurology.

Discussion

Elderly patients with COVID-19 are susceptible to neurologic conditions like acute stroke, acute encephalopathy, neuropsychiatric manifestations, and complications related to underlying CND. Reports from heavily affected countries like China, Italy, and the U.S. have informed that elderly population suffer a high rate of COVID-19-associated mortality (19). As neurologic dysfunctions of COVID-19 lead to increased morbidity and mortality, systematic studies on acute and long-term implications of neurologic complications of COVID-19 are imperative.

One of the biggest concerns of the COVID-19 pandemic is the tendency to periodically overwhelm hospitals and medical centers at the local, regional, and national level. A finite supply of healthcare resources led healthcare leaders to craft directives that address scarce resource allocation. The Italian Society of Anesthesiology, Analgesia, Resuscitation, and Intensive Care published guidelines that informed care during the outbreak in Northern Italy in March-2020 (20). Although this policy was criticized for overreliance on chronologic age and resource prioritization for younger patients, it prompted a search for more equitable criterias. Numerous national and international societies have released policy recommendations to guide resource allocation which involves a few common themes. First, it is inappropriate to use chronological age alone as an exclusion criteria. Second, given the heterogeneity in the baseline health status of aged adults, use of objective measures such as the Clinical Frailty Scale or Sequential Organ Failure Assessment are thought to be valid and equitable alternatives in assessing potential benefit of therapeutic intervention. Third, implementation of protocols to prioritize advanced care planning is not only an integral component of patient-centered care but may also help in allocation of limited resources by promptly identifying patients who opt not to be intubated or resuscitated. In one study, only 2.9% of COVID-19 patients older than 80 years survived to hospital discharge after receiving cardiopulmonary resuscitation (Hayek et al., 2020). Hence early discussions regarding goals of care is important, particularly in patients with neurologic dysfunctions. Depending on the type and severity of the disease, neurologic conditions often hold a grave prognosis, reduce life expectancy, or are associated with difficult to control pain and depression. Additionally, caregivers of patients with neurologic conditions are known to have similar rates of distress and burnout as that of cancer patient caregivers (Kim and Schulz, 2008). In severely ill patients with persistent encephalopathy or coma requiring full time care, burden of disease is tremendous from clinical, social, and economic standpoint. Given the high burden of disease both on patients and caregivers, early goals of care discussions

become extremely important in patients with neurologic dysfunction. Lastly, healthcare systems need to work on facilitating access to in patient and outpatient palliative care and hospice services for COVID-19 patients.

Strained healthcare systems and rising healthcare costs are global problems predating the coronavirus pandemic. With the additional economic burden related to severe COVID-19 illness and the short and long-term disability associated with neurologic complications, the financial hit is likely to be staggering. For perspective, the estimated annual direct and indirect costs for ~795,000 strokes in the U.S. from 2014 to 2015 was $45.5 billion, while healthcare cost related to delirium alone was $164 billion in 2011 (21). Although the actual economic impact of COVID-19 and related neurologic complications is yet to be determined, it is likely to have profound financial implications for an extended period of time.

The scientific community is only beginning to evaluate the long-term effects of the pandemic. Robust long-term data are lacking, especially pertaining to neurologic complications. One of the first studies to focus on outcomes after hospitalization for COVID-19 found that 44% of Italian patients rated their quality of life as worse (≥10 point difference on a scale of 100) since contracting COVID-19. Though patients were assessed at a mean of 60.3 days since symptom onset, 87.4% reported at least one ongoing COVID-19-related symptom, particularly dyspnea and fatigue. Prolonged symptoms are also reported among those with mild COVID-19 infections. In a telephone survey of American adults with mild COVID-19 illness conducted 14–21 days after a positive PCR test, 47% of respondents aged ≥50 years reported ongoing symptoms (22). Data on COVID-19-associated neurologic conditions including inflammatory, vascular, autoimmune, and neurodegenerative diseases are urgently needed (23). Similarly, neuropsychiatric conditions related to social isolation are only just beginning to surface and are likely to have significant long-term implications.

Conclusion

In conclusion, COVID-19 has been a catastrophic pandemic, particularly for the elderly, who tend to suffer from neurologic complications as well as a very high rate of morbidity and mortality. The physical, emotional, psychological, and financial implications of this disease have been severe. Long-term data are still needed to understand the lasting complications of this devastating pandemic.

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Case Report: A patient with extreme hyperkalemia beats all the odds

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Abstract

Hyperkalemia is a common finding in patients in hemodialysis and is typically classified as mild, moderate or severe. Severe hyperkalemia is a complex and life-threatening clinical entity, closely associated with increased mortality rates. It generally presents with ascending muscle weakness and paralysis, cardiac arrhythmias and specific ECG changes.

Herein, we present the case of a 30-year-old patient with end-stage renal disease, on hemodialysis. He presents to his hemodialysis session with complaints of progressive weakness and paralysis of his lower extremities, palpitations and dyspnea. His last session was 5 days prior to his ER presentation, after having missed 2 sessions. Laboratory studies revealed a serum potassium level of 10.9 mg/dL. Intravenous calcium infusion was administered urgently and subsequently underwent urgent hemodialysis. The next day he underwent another session due to the post-hemodialysis rebound effect, but on physical examination the lower limb paralysis had improved and normal, sinus rhythm was present.

Considering its silent development and ambiguous clinical presentation, hyperkalemia should invariably be considered in patients with CKD presenting with cardiac and neurological symptoms. Reported cases of severe hyperkalemia with potassium concentrations higher than 10 mg/dL, as in the case of our patient, are sparse and represent rapidly deteriorating, life-threatening conditions, requiring emergent medical interventions to prevent fatal cardiac arrhythmias.

Keywords: *Hyperkalemia, survival, hemodialysis*

Introduction

Chronic kidney disease (CKD) is a major cause of morbidity and mortality worldwide. [1] The number of patients that progress to end-stage renal disease (ESRD), requiring renal replacement therapy (RRT) has been steadily on the rise, due to the increasing number of patients initiating RRT and the rising survival rates of patients with ESRD.

One of the most common complications in patients with chronic kidney disease (CKD) is hyperkalemia. It may frequently be encountered both in the first stages of CKD up to the end-stage and in patients undergoing renal replacement therapy, when renal potassium excretion is severely impaired.

Hyperkalemia develops due to high potassium intake, decreased renal potassium excretion and an abnormal shift from the intracellular to the extracellular compartment. [2-4] Recognizing these pathological mechanisms is essential in

providing adequate treatment. Significant risk factors include worsening renal function in patients with CKD, presence of comorbidities (Diabetes Mellitus, Heart failure) and predisposing medications (potassium sparing diuretics, RAAS inhibitors, NSAIDs, heparin and myorelaxant agents). [2,4,7] Other conditions to be considered in the differential diagnosis include pseudohyperkalemia, hemolysis and prolonged sample processing. [2,4]

In patients on hemodialysis with little to no residual renal function, additional risk factors include low adherence to dietary recommendations, metabolic acidosis, severe anemia requiring periodic blood transfusions and alterations in normal potassium distribution within the intracellular and extracellular space.

Most patients are asymptomatic, however hyperkalemia generally presents with muscle weakness and cardiac arrhythmias. [2,4,7,8] Ascending muscle weakness is the classic clinical manifestation, initially affecting the distal lower extremities and rapidly ascending to the trunk, sparing the facial and respiratory muscles that are affected last. [2,4,7,8] In later stages, flaccid paralysis and areflexia develop, closely resembling Guillain-Barre Syndrome. [4]

Cardiac arrhythmias are a serious concern in patients with hyperkalemia. [2,4,7,8] ECG changes including peaked T waves, with increasing serum potassium levels, wide PR interval, wide QRS complex, loss of P wave, sine waves are evident. [4] They lead to ventricular fibrillation and asystole.[2,4]

Hyperkalemia is typically classified as mild, moderate and severe, depending on the serum potassium levels and ECG changes.

Treatment of severe hyperkalemia constitutes a medical emergency. The patient is started on intravenous calcium gluconate infusion to stabilize the myocardial membrane by antagonizing the potassium's effects, sodium bicarbonate, insulin and glucose infusion to shift extracellular potassium into the cells, cation exchange resins to bind and remove potassium through the gastrointestinal tract and finally hemodialysis, as the only definitive treatment option of effectively removing potassium and lowering serum levels. [2,5,7]

Case presentation

A 30-year-old male patient with a 7 year history of chronic kidney disease (CKD) and currently on renal replacement therapy (RRT) – hemodialysis, presents to the Emergency Room with complaints of progressive weakness and paralysis of his lower extremities, palpitations and dyspnea. His hemodialysis regimen included three weekly sessions, every two days. His last session was 5 prior to his ER presentation, after having missed his last two sessions. Initial arterial blood gas analysis revealed elevated levels of potassium and urgent laboratory

studies, including complete blood count (CBC), renal function tests (RFT) and an electrolyte panel were ordered. They revealed anemia *RBC - 2.95x10^6/µL, Hgb - 8.41 g/dL* (normal range RBC - 4.5-5.5x10^6, Hgb - 13.5-16.5 g/dL), elevated blood urea nitrogen *(BUN) - 403.39 mg/dL* (normal range <50 mg/dL) and *creatinine - 18.87 mg/dL* (normal range <1.2 mg/dL) levels. The electrolyte panel showed a *serum potassium level of 10.9 mg/dL*, *low serum calcium levels* (normal range K - 3.7-5.5 mmol/l, Ca - 8.4-10.2 mg/dL) and *elevated phosphate levels - 8.27 mg/dL* (normal range - 2.7 - 4.5) He was placed on cardiac monitoring. Intravenous calcium infusion was administered urgently and subsequently underwent urgent hemodialysis. The next day he underwent another session due to the post-hemodialysis rebound effect, but on physical examination the lower limb paralysis had improved and normal, sinus rhythm was present.

Complete blood count	Results	Reference range
WBC	8.65 x 10^3/µL	4.5 - 11 x 10^3/µL
RBC	**2.95 x 10^6/µL**	**4.5 - 5.5 x 10^6/µL**
HGB	**8.41 g/dL**	**13.5 - 16.5 g/dL**
HCT	**25.69%**	**41 - 50%**
MCV	87.09 fL	80 - 100 fL
MCH	28.50 pg	26 - 34 pg
MCHC	32.73 g/dL	31 - 37 g/dL
PLT	169.60 x 10^3/µL	150 - 450 x 10^3/µL
LYM%	**11.13%**	**24 - 44%**
MONO%	3.09%	3 - 10%
EO%	0.12%	0 - 3%
BASO%	0.36%	0 - 1%
NEUT%	**85.30%**	**40 - 77%**
Lym	**0.96 x 103/µL**	**1.08 - 4.84 x 10^3/µL**
RDW-CV	11.61%	0 - 14.5%
RDW-SD	40.00 fL	35.5 - 47 fL
PDW	18.00 fL	9.5 - 18.5 fL
MPV	9.10 fL	8.5 - 13.5 fL
P-LCR	25.00%	14 - 45%

TABLE 1 - Complete blood count

Metabolic panel	Results	Reference range
Creatinemia	**18.87 mg/dL**	**< 1.2 mg/dL**
BUN	**403.39 mg/dL**	**< 50 mg/dL**
Albumin	4.73 g/dL	3.5 - 5.2 g/dL
Total protein	7.63 g/dL	6.4 - 8.3 g/dL
Fasting glucose	93.09 mg/dl	74 - 110 mg/dL
ALT (SGPT)	12.59 U/L	10 - 50 U/L
Phosphate	**8.27 mg/dL**	**2.7 - 4.5 mg/dL**

TABLE 2 - Metabolic tests

Electrolyte panel	Results	Reference range
Sodium	137.00 mmol/l	136 - 148 mmol/l
Potassium	**10.90 mmol/l**	**3.7 - 5.5 mmol/l**
Calcemia	**7.64 mg/dL**	**8.4 - 10.2 mg/dL**

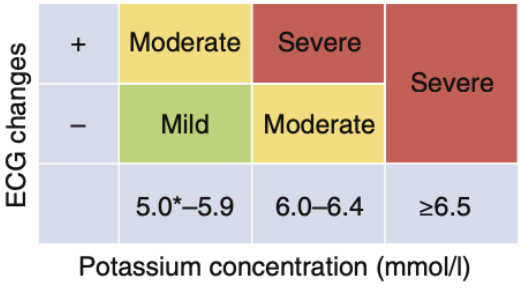
TABLE 3 - Electrolyte panel

Discussion

Potassium homeostasis is tightly regulated by a series of renal and extrarenal mechanisms that respond rapidly and effectively to changes affecting potassium balance. Renal excretion of potassium occurs in the distal nephron, mainly in the cortical collecting duct by the ROMK and BK channels. [2,3,6] Important modulators of renal potassium excretion are *serum aldosterone levels* that are highly influenced by extracellular potassium concentration and *low distal concentration of sodium and water or tubular flow in the nephron*. [2,3,6,7] Elevated levels of both, are associated with increased renal excretion of potassium from the distal nephron. Important extra-renal determinants of extracellular potassium concentration include acid-base balance, circulating catecholamine activity, insulin, plasma osmolality, tumor cell lysis, hemolysis or rhabdomyolysis and potentially hypothermia. [2,4,7,8] Metabolic alkalosis, insulin and stimulation of β2-adrenergic receptor induce a transcellular shift of potassium into the cells. [2,8] Conversely, acute increases in plasma osmolality, massive tumor lysis, hemolysis or rhabdomyolysis promote a shift from the intracellular to the extracellular space. [2] The distribution of potassium between the intracellular and extracellular compartments is strictly modulated by cell membrane Na+–K+-ATPase activity, ensuring a stable resting cell membrane potential. [3]

Hyperkalemia is defined as a critical and potentially fatal condition characterized by serum potassium levels exceeding 5.5 mEq/L. [2] Three primary pathways are implicated in its pathogenesis: increased potassium intake, decreased renal excretion and alterations in the transcellular distribution of potassium. [2-4,6,7] Excessive potassium intake is a matter of concern in patients with CKD, whereas in healthy subjects with intact regulatory mechanisms it is not a significant contributing factor. Acute or chronic kidney failure, disturbances in aldosterone synthesis due to medications (potassium-sparing diuretics, NSAIDs, ACE-I, heparin) or pathological disorders (primary and secondary hypoaldosteronism, pseudohypoaldosteronism, congenital adrenal hyperplasia) and congestive heart failure are the main drivers of reduced renal excretion of potassium. [2, 4,7] Finally, abnormal shifts from the intracellular compartment to the extracellular space, in the context of metabolic acidosis, diabetes mellitus associated with reduced insulin secretion, hyperosmolality, hemolysis, rhabdomyolysis, chemotherapy and tumor lysis, certain medication namely digoxin, succinylcholine and beta-blockers, as well as episodes of hyperkalemic periodic paralysis play an important role in the development of hyperkalemia. [2,4,7]

Based on serum potassium levels, hyperkalemia is classified as mild (5.5-5.9 mmol/l), moderate (6-6.4 mmol/l) and severe (>6.5 mmol/l). [9,10]



Clinical manifestations arise due to a reduction in the resting cell membrane potential, following inactivation of sodium channels and sustained depolarization owing to the decrease in the ratio of intracellular to extracellular potassium and reduced sodium influx, leading to progressive weakness and flaccid paralysis. [7,8] Cardiac manifestation develop on account of delayed depolarization and are associated with specific ECG changes including symmetrically hyper-acute T waves, shortened QT interval, wide QRS complex and prolonged PR interval, loss of P wave and sine waves that progress to ventricular fibrillation or asystole. [4,6]

In our case, the patient was susceptible to hyperkalemia on account of his end-stage renal failure and presented with a pattern of symptoms highly evocative of hyperkalemia. His medical history and the onset of symptoms assisted the differential diagnosis with Guillain-Barre syndrome or other neurological conditions. The patient promptly recovered after a hemodialysis session, thus confirming the diagnosis.

Conclusion

Severe hyperkalemia is a life-threatening condition, demanding a timely diagnosis, urgent and adequate management. Patients with CKD and ESRD on dialysis are particularly vulnerable to electrolyte disorders. Hyperkalemia is a common finding in patients in renal replacement therapy, nevertheless severe hyperkalemia with serum potassium levels higher than 10 mg/dL, as in this case report 10.9 mg/dl, is rare and potentially fatal, due to the high risk of progressing into ventricular fibrillation or asystole.

Patient education on the importance of adhering to the dietary recommendations, as well as their hemodialysis schedule coupled with routine laboratory monitoring of electrolyte levels is essential in preventing and readily diagnosing this critical complication.

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A developmental model of gender identity course based on Hamburg sample of children with gender dysphoria

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Abstract

Aims: *There are few data concerning first signs and developmental trajectories of people with gender variant behaviours and this paper aims to describe them in a clinical sample.* ***Method:*** *This paper presents a chart review of 44 children and adolescents assessed for gender dysphoria in Child and Adolescent Psychiatry and Psychotherapy, at the University Hospital Hamburg, Germany. I used information from these charts to reconstruct the course of cross-gender behaviour and identity in these patients from birth up to the time of assessment and organised it in a model. I looked into the pattern of development being representative of this sample and examined continuity/variability within individuals over time.* ***Results:*** *First signs at behavioural level appeared in most cases since the beginning and were consistently reported during preschool years (84%). A prior period of gender typical behaviour before onset of cross-gender behaviour was rare.* ***Conclusion:*** *A particular finding in this clinic based sample is that gender identity expressed around the age of 3-5 years was not reversed later in life. There was a common pattern of development in majority of cases: first signs in kindergarten age and*

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strongly re-emergence around puberty, which might have implications in referral times of this group in the clinic.

Keywords: *gender identity, gender dysphoric children/adolescents, onset age, first signs, developmental models*

Gender Identity is a sense of oneself in relation to males and females, how one fits with gender. *Gender dysphoria* in DSM-V (DSM-V, 2013), known *as Gender Identity Disorder* (GID) in ICD-10 (WHO, 2010) is a relatively rare condition of atypical gender development in which there is a psychological perception of self as masculine or feminine which is incongruent with sex assigned at birth (De Gascun et al., 2006). Or occasionally the individual might identificate to some category other than male or female (DSM-V, 2013). The essential diagnostic feature is the child's pervasive and persistent desire to be (or insistence that he/she is of) the other-sex to that assigned, together with an intense rejection of the behaviour, attributes, and/or attire of the assigned sex (WHO, 2010).

Compared with other child psychiatric disorders, gender dysphoria has a relatively low prevalence (Cohen-Kettenis et al., 2003). There are no data of exact figures of gender identity in childhood. There are estimates of this prevalence being around 1% (cited by Korte et al., 2008). In one behavioural genetics study, the prevalence is estimated to be 2.3% in 314 non-referred twins of ages 4-17 years old (Coolidge et al., 2002). In Germany would be affected about 280 children every year as cited by Vetter 2007. Although the exact prevalence of GID is unknown, the prevalence of cross-gender behaviour in general is considerable. Depending on the study, the numbers range anywhere from 2.6% to 6% for young boys and 5% to 12% for young girls (Möller et al., 2009). Di Ceglie (2014) reports increase in referrals from 1989 to 2012 of this population in Gender Identity Development Service of London.

Theories of gender development include psychoanalytic theories, gender essentialism, environmental theories and cognitive theories. For a review of gender development theories see Schechner, 2010. Reports on first signs of nonconforming gender identity are almost missing. Parents, the first observers, facing the experience of having a child with gender dysphoria hope is just a phase. Clinicians usually met them after the establishment of cross-gender signs. In general children/adolescents with GD have a long history of cross-gender behaviour before being referred and assessed at the clinic. Fausto-Sterling (2012) argues that the existing clinical theories are underdeveloped and urge that clinicians take a dynamic developmental view of gender identity formation into account. Children are usually referred to the clinic when they are able to

verbalise their desires. A stated desire to be the other sex is usually much later than the expression of cross/nonconforming-gender signs in behavioural level. This expression is not correlated with a certain age, but in a case by case basis. Some of these individuals report having had a desire to be of the other gender in childhood that was not expressed verbally to others (DSM-V, 2013). Only 11% of the children/adolescents referred in the service for gender dysphoric children and adolescents at University Clinic Hamburg Eppendorf voiced to their parents, siblings and/or teachers the wish to be the other sex at a very young age 3-5 years old (Lama-Gjergji V., 2011). Cohen-Kettenis and Pfäfflin (2010) recommends that it should be investigated for potentially relevant specifiers as onset age. There are two broad trajectories for development of gender dysphoria: early onset and late onset. *Early-onset gender dysphoria* starts in childhood and continues into adolescence and adulthood; or, there is an intermittent period in which the gender dysphoria desists and these individuals self-identify as homosexual, followed by recurrence of gender dysphoria. *Late-onset gender dysphoria* occurs around puberty or much later in life (DSM-V, 2013).

While extensive theoretical and empirical work has been invested in understanding the mechanisms underlying the trajectories of normative gender development (Schechner, 2010), most of this work has primarily focused on stages of gender development (i.e Kohlberg is focused on the cognitive ability of child to acquire gender concepts and sex roles), developing of gender stereotypes, interests, activities and preferences, prejudice. Understanding the changes that correspond with the passage of time is a hallmark of developmental studies, including the study of gender development. The few longitudinal studies of gender typing that exist have paid relatively little attention to the issue of stability (Martin and Ruble, 2010). Regarding clinical studies very few elucidate aspects of developmental processes, i. e. gender identity variability/stability across age. Martin and Ruble (2010) in their review of patterns of gender development stress that it would be of great interest in future research to examine the stability and trajectory of gender typing among children at the extremes, such as tomboys or girly girls. They conclude that the study of individual differences in gender typing may be more productive than has recently been thought. Two studies are to be mentioned in this respect: Drummond et al. (2008) and Steensma et al. (2010). This research can provide additional insight in this topic. This paper feature the assessment of children and adolescents consulted in the Clinic for gender identity problems of Child and Adolescent Psychiatry and Psychotherapy, at the University Hospital Hamburg-Eppendorf with attention to onset of cross-gender behaviour and following gender identity developmental trajectories. We argue that these qualitative data provide insight into gender identity development in this population, which is often difficult to ascertain

through empirical study and the stability of subject's gender identity over time. Research questions were aimed in depicting a possible pattern of development for gender dysphoric children and adolescents: 1. How became noticeable first signs of gender dysphoria, at which age did they appear for the first time? Onset age describes the very first time when gender dysphoria appears in behavioural level and/or is experienced by the child. 2. Which was the course of symptoms? How did evolve signs from birth up to the time of referral at the clinic? 3. Is it a prior period of conformity with sex assigned at birth for a cross-gender child? 4. Is it an in-between period of conformity with sex assigned at birth for a cross-gender child? The research design was by using information from these charts to reconstruct the course of cross-gender behaviour and identity in these patients. Our approach to answer the research questions being asked was by self-designing a graphic describing the course of each case.

Method

Subjects

At the University Medical Center Hamburg-Eppendorf, Department of Child and Adolescent Psychiatry and Psychotherapy, a "Clinic for Children and Adolescents with Gender Identity Disorder" is provided in cooperation with the Institute for Sex Research and Forensic Psychiatry and the Clinic of Endocrinology Hamburg. The sample of the study consisted of all patients' charts consulted and assessed in the Clinic for gender identity problems of Child and Adolescent Psychiatry and Psychotherapy, at the University Clinic of Hamburg between 2006 and 2010. The participating group in the study consisted of 44 gender dysphoric cases, with age range 4 and half up to 18 year old, 18 males and 26 females (Mean=13.3; SD=3.7).

Research design

Information from medical files was taken out of each case from birth up to the time of assessment at the clinic, with aim of a comprehensive self-designed checklist. A child and adolescent psychiatrist rated the materials from charts in the Hamburg clinic searching information related to the research questions: onset age, reported signs of gender dysphoria and respective age, course of identity during development span, signs of conformity/non-conformity with sex assigned at birth and respective age. The information regarding child development was mostly reported by parents. Because in most cases clinicians had been careful in writing reports in a sort of systematic anamnestic fashion

(actual concerns, developmental history, etc.) and many cases had a large file (25% of the sample were hospitalised) we were able to identify information we were interested. Parents who had more than one child were sensitive to report the gendered patterns of behaviour of their child in terms of gender typical vs. –atypical behaviour. As parents reported in terms of behaviour (for example onset was described by parents as cross-dressing), information from children/ adolescents was useful in eliciting the cognitive component of gender dysphoria. Inconsistencies were discussed with a member of the team, who was also the clinician who knew the cases.

Data were analysed using qualitative content analysis methods. To capture the long-life developmental trajectories (course) of gender identity four categories (see Table 1) were constructed by deduction-induction reasoning. Data on gender/cross-gender behaviour fit in the following categories: a. unspecific signs; b. presumed cross-gender; c. cross-gender; d. behaviour typical to the assigned sex. Categories were defined according threshold level for ICD-10 symptoms. The first three categories include cross-gender behaviour in three different levels of intensity, from the subtle observations of parents (unspecific signs) to the meeting of criteria for gender identity disorder in ICD-10 (cross-gender). "*Presumed cross-gender"* category differs from the "*cross-gender"* category based on the intensity of reported symptoms. When symptoms reported in a certain period of time did not meet all ICD-10 criteria, the behaviour fell in the presumed category. This category is included for coding a time period reported as latent. There was a strong presumption that the full criteria will ultimately be met for GID, but not enough information is available or signs were at low intensity. The researcher determines that gender development in this period of time is compatible with prior cross gender history; nevertheless the symptoms might be experienced from children or their parents as less intense. On files there is not enough information reported to include the behaviour of the child/adolescent in full blown "cross-gender" category, however certainly there is no gender typical behaviour and there is not inconsistent or contradicting information.

A self-designed model (Fig. 1) provided a convenient format for organising and communicating the reconstructed developmental trajectories (from birth up to time of assessment) of Gender Identity of single cases, and for capturing the shared pattern of the sample we worked with. The model is illustrated in Graphic 1 and the definitions of categories are explained at Table 1.

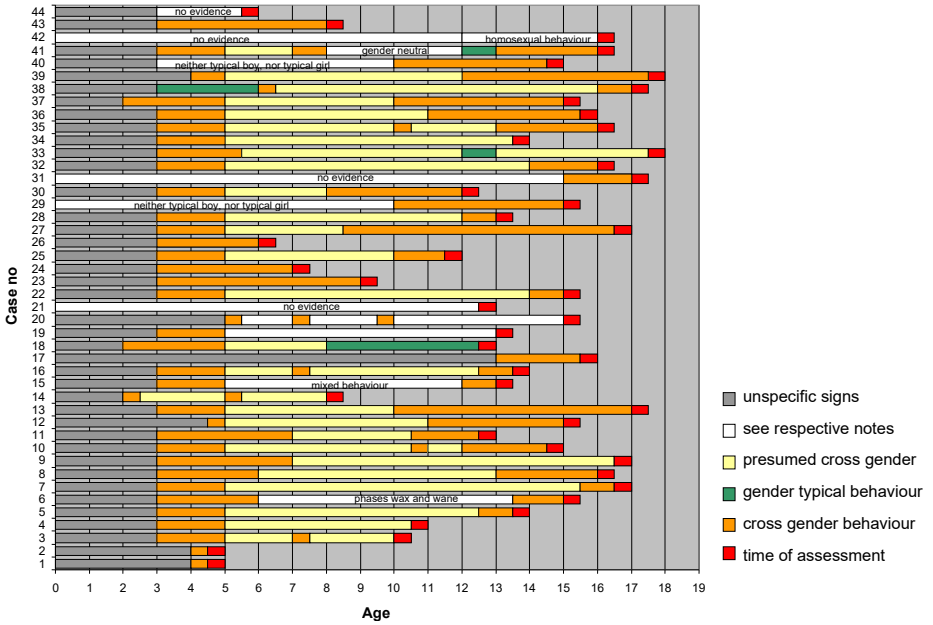
TABLE 1: Description of Categories

DEFINITION OF CATEGORIES	EXAMPLES: DESCRIPTIVE INFORMATION OF CHARTS
Unspecific signs: As unspecific signs are defined parental feelings of the child being since early on different from siblings, the child was perceived by parents as a particular child or has shown a mild aversion of typical gender behaviour i.e. a boy who is easy crying, etc.	Notes of an assigned male child (by mother report): A. has always been different from his siblings. His brothers were genuine boys, rough-and-tumble played, played football. A. showed at the opposite a soft attitude. He was quite as a baby, had a big grin. Even at the ages of 2-2 ½ years old he never liked to sit in dirt. At a very young age of the child mother had a feeling that he was in the wrong body, despite he didn't show direct signs at that time. He was rather "a girl"; he was never, even as baby a boy.
Cross-gender: Cross-gender definition includes report of symptoms, which meet the full ICD-10 criteria for the disorder.	Notes of an assigned male child (by mother report): As a child D. preferred to play with Barbie dolls, liked to have his room painted in pink, and liked girl dresses. D. has always been different as a child and since the age of 7-8 years old played around mostly with girls. Notes of an assigned female child (by mother report): Mother reported an impressive situation when the kid was 3 years old. She came home from a travel abroad with beautiful clothes. D. has reacted with disgust and dislike when she unpacked the presents and immediately left. In kindergarten D. didn't like that children played boys versus girls. She showed at that time confusing reactions, because she didn't know which group to join. At the age of about three to four years, mother has realised that D. was different from other children. She even thought at that time, if she had probably "autistic features". Notes of an assigned female (adolescent report): D. herself confesses to be in the wrong body since long time, but it has been intensified in the recent years. D. recalls kindergarten time when she saw that boys have a penis. She had assumed till that point that she will also get one as she grows older. It was told by kindergarten teacher, that this would not happen. With about five or six years D., who was called at that time with her birth name, renamed herself with a boy name. Since about 13 year olds she insisted not to be called anymore with her birth name. Since 14 years old she understood she was transsexual and that it would not change.

Presumed cross-gender: This category is included for coding a time period reported as latent. There is a strong presumption that the full criteria will ultimately be met for GID, but not enough information is available or signs are at subthreshold level. The researcher determines that gender development in this period of time is compatible with prior cross gender history; nevertheless the symptoms might be experienced from children or their parents as less intense. There is not enough information on medical files to include the behaviour of the child/adolescent in full blown "cross-gender" category, however certainly there is no gender typical behaviour and there is not inconsistent or contradicting information.	Notes of an assigned male (adolescent report): A. remembers himself that this matter has been developing gradually, maybe since he was 5-6 years old. When he was young he was rather shy and it made a "click" in his head at about the age of 7 years old: he has been thought he was not a boy. It was funny to make it clear with himself, at the same time it made him happy. As a boy he feels unhappy. However, when he enrolled school he had other things in mind for a long time and he repressed those thoughts until the fourth-fifth grade. At the age of about 10 years old he preferred again to be different. Girls had been started to make up and A. liked it. At the age of 10-11 years old he confessed it for the first time to his older sister and at the age of 13 years old he confessed it to his mother.
Behaviour typical of the assigned sex: The parent or child evidences a time period when he/she has shown behaviour which is typical of the assigned sex.	Notes of a biological female report: In the sixth grade she had a "feminine" phase, she tied her hair and had worn appropriate female clothes. Notes of a biological female report: Since many years dominated the inner feeling to be a boy. She had never thought something different. Despite that she undertook adaptive efforts. For example she didn't want to be noticed from her schoolmates and even had a phase around sixth-seventh grade, in which she looked as a girl, and even was dressed in pink at that time.

We checked signs at an interval of half a year. When behaviour was in the same coding times were merged. Colours were used as indicators of categories continuing during a time frame: grey area represents the very early unspecific signs reported by parents on behavioural level, yellow and orange are both cross gender phases accordingly latent and full-blown picture. Signs at the time of assessment represented by the red colour are intensely cross gender. The green colour in the graphic represents those cases, which experienced in a certain period of time behaviour typical of the sex assigned at birth.

Fig 1: Onset and developmental pattern of cross gendered behaviour



Results

Most of children/adolescents asked since when did they feel to belong to other gender were reported to answer in a same fashion "Since I ever thought". Before the age of 2-3 years old parents noted and reported unspecific signs, which couldn't be classified as cross-gender ones. We describe them in Table 1. First signs of Gender Identity became noticeable from parents by behavioural expressions during preschool years. Most of children displayed at that time typical behaviour of the other sex (cross-dressing, preferred cross-sex roles in make-believe play, participated in the stereotypical games and pastimes of the other sex), rejected gender stereotypical toys and clothes, showed marked aversion toward their body (i.e. boys wanted to cut penis). From 5-6 years old to entering the adolescence (11-12 years old) a latent phase was reported by children and their parents, their voiced being in continuum with their other-gender identity, but they experienced being less overwhelmed compared to their toddlerhood and adolescence and also showed more adaptive efforts to conform to assigned sex roles. Signs in time of assessment at the clinic (roughly half a year follow up for each subject) were intensely cross gender. Looking at Fig 1, the most common pattern is early cross-gender, followed by presumed cross-gender, followed by a re-emergence of cross-gender in adolescence.

In general children/adolescents with GD had a long history of cross-gender behaviour before being assessed at the clinic. Onset of cross-gender behaviour for most cases with GD (84%) was the toddler/preschool years. Gender Identity Disorder had an early onset in 84% of cases (37 out of 44), that is children showed cross-gender behaviour during preschool years. Only three cases (roughly 7%) had a late onset (cross-gender behaviour in ages 10-13 years old). These children showed a neither typical boy nor typical girl behaviour (outside the gender binary) or unspecific signs during preschool years and childhood. A prior period of gender typical behaviour before onset of cross-gender behaviour was rare. When it happened after the onset of cross gender behaviour had a tendency to be a transitory phase. Only one child showed assigned-gender typical behaviour (in ages 3-6 years old) before cross-gender period (starting at 6 years old). Three other children had an in-between phase of assigned-gender typical behaviour; they had shown cross-gender signs before and after this phase. The course of Gender Identity in cases studied was irreversible and there was a common pattern of development in majority of cases: first signs in kindergarten age and strongly re-emergence around puberty.

Discussion

Concerning age when first signs appear there are very few or not at all research data in literature. In normative samples early studies suggested that labelling and understanding of gender may not emergence until about 30 months of age, but more recent studies have moved the age of understanding gender identity and labelling downward (Martin and Ruble, 2010). In our sample onset of cross-gender behaviour in majority of cases corresponded to the developmental time period in which most typically developing children begin expressing gendered behaviours and interests. The trajectory of gender identity development in this gender variant sample is the same as normative gender trajectory. Gooren, 2002 cites that gender identity/role becomes largely fixed around the age of three years, thus showing a parallel with other steps in the sexual differentiation process in that once their critical period has passed, the nature of gender identity/role can not be reversed. Hamburg data are accordable with the above concept. They indicated that first signs of Gender Identity Disorder appeared in most of the cases (84%) during preschool years and the course of Gender Identity in cases studied was irreversible beyond this age.

Before the age of 2-3 years old parents noted and reported unspecific signs (see table 1) which became strongly marked in behavioural level during preschool years. These findings are consistent with one by Fausto Sterling (2012), who suggests

that by 18 months a transition to symbolic representation and the beginning of an internalisation of a sense of gender can be detected and consolidation is quite evident by 3 years of age.

Our findings of no reversibility in most of cases are not totally consistent with the prospective study of Drummond et al (2008), who provided information on the natural histories of 25 girls with gender identity disorder. At the assessment in childhood (mean age, 8.88 years; range, 3-12 years), 60% of the girls met the Diagnostic and Statistical Manual of Mental Disorders criteria for GID, and 40% were subthreshold for the diagnosis. At follow-up (mean age, 23.24 years; range, 15-36 years), 12% were judged to have GID or gender dysphoria. Regarding sexual orientation, 8 participants (32%) were classified as bisexual/homosexual in fantasy, and 6 (24%) were classified as bisexual/homosexual in behaviour. The remaining participants were classified as either heterosexual or asexual. Drummond et al note that girls who were more cross-sex typed in their childhood behaviour more likely to be gender dysphoric at follow-up. Steensma et al. (2013) found a link between the intensity of gender dysphoria in childhood and persistence of gender dysphoria, as well as higher probability of persistence among natal girls. They concluded that intensity of early GD appears to be an important predictor of persistence of gender dysphoria. In this respect, should be keeped in mind that children and adolescents in our study belonged to a clinical group and the studied cases might be more persistent and severe than nonreferred children with GID. It can be that there are children and adolescents with cross Gender Identity, who desist and therefore are not presented in the clinic. Gender dysphoria remits from childhood to homosexuality in adolescence and adulthood. Cross-gender fantasies and behaviors in childhood appear to be largely predictive of a homosexual sexual orientation in adulthood (Wallien and Cohen-Kettenis, 2008). Even in normative samples (Golombok et al., 2008) results indicated that children who were most gender typed at age 3 and half continued to be so at age 8 years old.

There was noticed a pattern of development in majority of cases: first signs in kindergarten age and rebound around puberty. The intensity lessened over a period of time from about 6 to11 years. The shifts among states (from being cross-gender to presumed cross-gender) make us think about influencing factors. This latent form of gender typing in our opinion may be explained firstly by social ostracism, who applied to all cases. Children are trying to confirm to the social pressure. Many of them at this time are teased, bullied in schools and their parents have conveyed to them the idea that it is just a phase and they will overcome it in puberty. Social ostracism tends to arise during the early years of schooling and is often at a peak in middle childhood, with humiliating teasing by other boys (WHO, 2010). Secondly, there are no major developments of sexual characteristics until puberty. Body image dysphoria becomes more common as children with gender dysphoria approach puberty.

The results of this paper indicate that cross-gender behaviour is appearing early in life, thus showing a parallel with normative gender behaviour development. Gender variant children develop milestones of their gender identity at the same time as developing children who feel comfortable with sex assigned at birth. The form of gender typing that is paramount may vary at different phases of life (Martin and Ruble, 2010). The most common pattern noticed early cross-gender and strongly re-emergence around puberty might imply to peak times of referrals at the clinic.

A limitation of this work is that findings are couched in terms of the gender binary, because most of this sample was intensely cross-identified. There were few cases (see figure 1) who were not clearly positioned. The study was retrospective and time frames were not preselected, we fitted the information reconstructed from charts. Prospective studies with structured measurements and short time frames would be encouraged for more accurate results.

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Legal, social and ethical analysis on compulsory DNA collection in the forensic sciences of Albania

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Abstract

"DNA fingerprinting" through the taking of blood and other secretions of the human body is considered as one of the most revolutionary advances in forensic identification and is of particular interest to forensic medicine. Although DNA identification has to do with personal identity, it is possible to test the material for this examination, from respective laboratories, together with the DNA on the whole. In contrast to fingerprinting (the science of fingerprints, used in forensic practice to identify a person, since the early 1900s), the forensic use of DNA samples for identification requires more care because it risks compromising the privacy and individual freedoms. It is therefore necessary that these examinations strictly respect the ethical rules of consent and confidentiality. In our country, where DNA examinations for resolving criminal and civil cases have started to be performed by the scientific police institute, only after the 2000s, this type of examination was not provided in the 1995 Code of Criminal Procedure. Article 199 of this code only stated that in relation to blood sampling, it can be performed even without the will of the person, if there is no risk to health. Then in 2017, in an amendment of this code, in article 201 / a, is presented the detailed procedure that must be observed for taking samples of blood and other tissues of the human body for performing DNA analysis, where first of all, the consent of the person to be examined must be respected, without excluding the possibility of taking them compulsorily. In this study, the authors, after the presentation of some features of DNA uses in forensic sciences, analyze in detail the important issue of consent and confidentiality, which reflect the principle of independence of the person

in the fields of medical sciences, compared to that of consent and confidentiality in criminal matters, including that of DNA analysis. In conclusion, it is emphasized that the application in Albania of DNA analysis in criminal and civil cases requires great care in implementing the procedures set out in the relevant legislation, including the principles of consent and confidentiality in obtaining and storing their datafor respecting human rights and preserving human dignity.

Key words: *compulsory DNA identification, forensic sciences, consent, confidentiality, Albania.*

1. Introduction

The legal, social and ethical issues of DNA analysis are becoming more and more important today, compared to previous years.

In fact, in contrast to fingerprinting, the forensic use of DNA samples for identification requires more care because it risks compromising the privacy and individual freedoms (Çipi,2003, Michael, 2010).

It is therefore necessary that these examinations strictly respect the ethical rules of consent and confidentiality.

In this study, the authors, after the presentation of some features of DNA uses in forensic sciences, analyze in detail the important issue of consent and confidentiality, which reflect the principle of independence and secret of the person in the fields of medical sciences, compared to that of consent and confidentiality in criminal matters, including that of DNA analysis.

2. DNA genetic profile

Genetic traces of DNA, today they are providing a great help in service of forensic sciences for the correct and impartial solution of various forensic and criminal issues (Çipi et al, 2015,2017,2020):

-identification of unknown fresh or rotten and skeletal corpses, comparing their DNA with the DNA of these victims who may have been preserved before death, or with that of parents or children and other relatives of them.

-determining whether the biological material evidence (blood, semen, hair, etc.) found at the scene, belongs or not to the victim, the defendant, etc.

- issues of determining paternity and maternity.

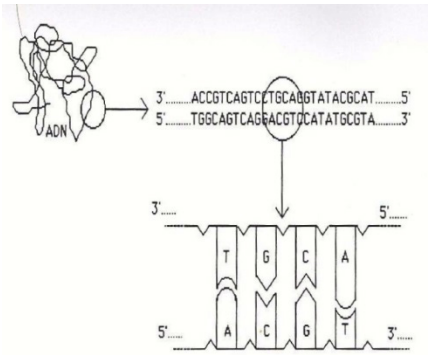
Theoretical basis (Çipi et al, 2015,2017,2020)

Features on theoretical grounds, techniques used for DNA detection are

generally complex. In fact, their application requires the use of highly specialized reagents and apparatus.

The DNA, or deoxyribonucleic acid found in each of the chromosomes of every cell in the human body, is made up of 2 molecules in the form of a double helix. In each band of this helix, (so in each of these two molecules) are located in a variable order, the following 4 nucleotides: adenine (A), thymine (T), cytosine (C) and guanine (G), joined together by connexion of sugar and phosphate molecules.

On the other hand, the nucleotides of each band are coupled with those of the other band of the helix through their hydrogen connections that are realized between guanine and cytosine (with three valences) and adenine and thymine (with two valences). In this way the construction of one band of this double helix will define that of the other, but in the opposite direction, thus giving this helix an antiparallel structure. Schematically, the double helix of DNA can be compared to a twisted scale, in which coupled nucleotides form its scales (10 such for each of the twists of this helix), while the sugar-phosphate groups, the side parts of scale (handrails).



PART OF THE DNA HELIX

THE DOUBLE HELIX OF DNA

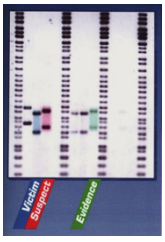
An extended DNA molecule will reach a length of 1.8 m and contain about 3 billion nucleotide pairs. Of these, only 10-20% of them contain the genetic code related to heredity. In connection with this genetic code, in the DNA segments belonging to it, are found encoded messages, represented by many triplets of nucleotides (A, T, G, C), which command the synthesis of proteins, through the respective amino acids of them. They thus make possible the detection of genetic diseases, the prediction of later diseases (predictive medicine), the possibility of DNA manipulation (genetic engineering), so in a nutshell they make possible the so-called decipherment of the human book "dechifrer le livre de l'homme". While the rest of the DNA molecule that is not related to genes, that is, its uncoded part, can contain a number from 200 to 14000 identical, repeated sequences. They are permanent and immutable in each individual and are transmitted regularly from parents to children. They will therefore be considered as completely identifiable individual features for each person, except for uniovular twins, where they will be identical to each other, as they originate from the DNA molecule of the same egg fertilized.

In human cells, in addition to the ordinary DNA found in their nuclei, there is also mitochondrial DNA (mtDNA), present in mitochondria, energy-producing organelles located in the cytoplasm of cells. The sensitivity of mtDNA analysis is higher, which makes it possible to determine genetic traces even from very small samples, such as a single cell, or hair without roots. On the other hand, mtDNA is inherited from the mother, so it will be similar to that of the mother and all other relatives from the mother.

Principles of methods used and circumstances of their application(Çipi et al, 2015,2017,2020)

Identification of repetitive non-coded DNA sequences is usually achieved by following a definite methodology.

At the end of this examination, genetic traces will be taken, or the so-called autoradiogram, or genetic profile containing a series of parallel strips, placed in certain positions. By comparing them with those of the genetic material of the victim, the suspect, etc., based on the position of the audiogram strips (genetic profiles) that are being compared, it will be possible to determine or not accurately determine the identity of the genetic samples analyzed.



DIFFERENT GENETIC PROFILES

Two types of results are possible:

-if one profile turns out to be identical to another, it is a matter of genetic compatibility, - otherwise, when one or more systems present a genetic profile different from the reference sample, this will be considered genetic incompatibility.

So in the absence of comparative material, this type of examination will be worthless.

As a comparative material, e.g. with the sperm found in the vagina of a victim of a sexual crime, there is no need to compare the sperm of the suspect (so sperm with sperm), but also blood, or other tissues, because DNA, that is individual for each person, is found in all cells of an organism.

Another important area of forensic use of genetic DNA traces concerns paternity determination issues with a more or less accurate determination of the identity of the biological father.

Each audiogram of the child being examined must belong to the father or mother; so half of them will be descended from the mother and the other half from the father. Initially, these examinations determine the compatibility of the child's autoradiogram strips with those of his mother; the remaining strips should all match those of the presumed father. If a discrepancy is found between them, in this case this examined person is excluded to be the biological father of this child.

Taking, storing and transporting samples in DNA examinations(Çipi et al, 2015,2017,2020)

The essence of the method of forensic examination of genetic traces through DNA is the comparison between the two samples.

One of them is the sample object-examination, taken from the living or dead individual (or various objects, such as clothes, etc. with which he has been in contact); while the other sample is the comparative, or control, sample taken from a single person or group of suspects, or from DNA bank records belonging to hundreds, or thousands, of individuals.

* * *

From this presentation, although DNA identification has to do with personal identity, it is possible to test the material for this examination, from respective laboratories, together with the DNA on the whole.

For this reason, the laboratories that performs DNA analysis, it must be very careful respecting the principles of consent and confidentiality, protecting privacy and individual freedoms.

In the legal discussions of foreign countries as well as of our country, regarding DNA analysis, the issue of the need to respect the principles of confidentiality and

integrity or independence of the person, expressed by the the concept of consent, which are in fact two of the most important ethical principles during the practice of medicine (Christian Selinger, 2009; Michael, 2010).

According to these views, DNA analysis will be considered a medical procedure and as such, it requires the doctor to apply in these cases these two principles of medical ethics.

Therefore, the compulsory performance of this analysis, as provided in Article 201/1 of the Code of Criminal Procedure (2017), according to this position, would be in opposition to these principles of Medical Ethics.

Is this true?

To answer this question let us analyze the concepts of consent and confidentiality according to Medical Ethics.

3. Consent and confidentiality in the practice of medical professions

Consent

Consent will be considered as a right of the patient which authorizes the physician to carry out the demanded treatment, even if it affects the integrity of the patient, but it is provided in the patient's interest and explained it beforehand to the patient.

In other words, for the patient the given consent for a medical treatment, it means that he has made the choice of treatment (the principle of patient independence) and on the other hand has authorized the physician to apply this medication to his body (principle of respect for bodily integrity) (Parizeau,1993; Post,2003).

The common consent during treatment is several types (Çipi, 2005; Çipi, Meksi, 1996)

- Understood consent, oral consent (verbal), writing consent: eg. for an surgery.

For the application of consent, as an expression of the principle of patient independence, it should have these qualities (Çipi, 2005).

- Conscious consent means giving the patient consent without any obligation, or external constraint, or any manipulation that may have been made to this patient. Thus, in cases where force is used to the patient, or false information has been provided in order to ensure consent, such consent will be considered null .

- Informed Consent is considered when the patient has given the consent after having fully understood the information provided to him from the doctor. For this purpose, the explanations that the doctor gives to the patient in a direct way should be as complete and expressed as clear and understandable as possible.

Today, in the literature of these domains, the term "informed consent" has been widely used, meaning consent in general (Çipi, 2005).

- Substitute consent is a term that is used in cases where consent is sought from legally incompetent persons, for example, from children, mentally handicapped persons, sick in a comatose condition.

The main ethical dilemma, that may arise during the implementation of the consent, concerns the conflict that may arise between the principle of independence of the patient and that of the non-maleficence (beneficence) of the physician.

This conflict is related to the problem of refusal of treatment (Çipi,2005), which occurs in cases that the patient does not accept the medication proposed by the doctor (the patient does not give the consent). Such refusal, which can have severe, even lethal consequences for the patient, tends to strain his relationship with the doctor. In this case, the doctor must respect the decision of the patient, a decision that for the doctor is not in the best of the patient.

Thus, refusal of treatment in medical practice creates a conflict between the patient or his or her third representative and physician who harms the relationship between them.

In Albania, the consent is treated in Article 28 of Code of Ethics and Medical Deontology (2011).

Confidentiality

According to this principle the information that physicians learn about their patients in the course of their professional practice should not be disclosed to others. Good medical practice depends upon patients being able to discuss openly with the physician aspects of their health on the understanding that such details will be kept secret. It follows that any disclosure contrary to the individual's interest is also potentially detrimental to the public interest since it may discourage frank exchanges in future.

In the absence of guarantees that their secrets will be protected patients may withhold important information about their health care and also about the wellbeing of others etc.

In the absence of guarantees that their secrets will be protected, patients may withhold important information about their health care and also about the wellbeing of others etc.

Some other characteristics of this principles are as follow:

- The inclusion of this principle in legislation shows that it has a general interest in the sense that it promotes the normal functioning of health institutions and social services. For this reason this principle is considered to have a public character (social).
- Additionally,medical confidentiality has deeply humane value based on the natural right of privacy, which is known to be part of the normal psyche of a person. In this regard,medical confidentiality will be one of the conditions necessary for the realization of relationships between people, while protecting the privacy and independence of the person as well as promote the developmentof qualities such as respect, love, friendship, trust, etc. (Çipi, 2005).
- *Cases where the principle of medical confidentiality does not apply* are specific situations encountered in dealing with infectious diseases as cholera, typhus, dysentery etc.; psychiatric illness such as schizophrenia, epilepsy that usually make people who suffer from them potentiallydangerous to commit crimes; in violent deaths, unexpected deaths, deaths of pregnant women during abortion, in alcoholics etc. (Çipi, 2005).
- *The issue of collective application of the confidentiality principle* has been due to technical and scientific development of medicine, which has offset somewhat the classic doctor-patient relationship.
- *The conflict between the confidentiality principle and measures to be taken to prevent the disease* has arisen because to achieve a preventive function for various diseases is necessary to collect and transmit information about the health status of individuals by health organizations.

However, the discrepancy between the objectives of the state and the objectives of the individual, poses an ethical dilemma, a conflict between the right to maintain the privacy of the individual and the state's duty to protect public health and welfare.

Certainly, the foremost requirement of every individual is to be treated for the disease from which the individual suffers, possibly in the most confidential manner, thus respecting the principle of upholding medical confidentiality. Yet, even the patient can accept the violation of this principle, if information on this disease will not only serve to prevent this pathology in general, but also to protect the patient's own health (Çipi,2005).

Truth the telling

In terms of the physician medically informing the patient, "telling the patient the truth" (truth telling), constitutes a particular form of medical confidentiality. From the ethical standpoint, the main issue has to do with the attitude of the physician, if he mus tinform the patient about the diagnosis of disease and especially the progress (prognosis) of a serious or fatal illness.

In medical practice, the resolution of this issue is very sensitive and can be accomplished under these three models(Çipi, 1996; (Çipi, 2005).

- *The paternalist model, th*e patient is not informed about thediagnosisandprognosisof the serious illness in order to protect the patient from suffering and death.
- *The libertarian model*(the patient hasacomplete freedom of choice for any medicalaction), according to which the physician informs the patient openly, immediately,and without hesitation about the diagnosis and prognosis of disease.
- *The participatory model*(open dialogue between doctor and patient that is intended to benefit the patient), according to which the physician works with the patient carefully and with tact, preparing the patient spiritually early, informing littlebylittle about the realsituation/seriousillnessor by initially notifyingtherelativesofthepatient.

In our opinion, participatorymodelismostappropriatemanner to handle the way informing the patient is conducted, whichin fact, is implementedinAlbania.

Juridical aspects of medical confidentiality in Albania

Different problems of medical confidentiality were studied in our country, especially after 1990, and were also reflected in their respective legislation. Thus, in the Medical deontology code of 1994, the physician and support staff have the obligation to ensure the preservation of confidentiality (explicitly stated in Articles 11, 12, 13).

In the Code of Ethics and Medical Deontology of 2002, Article 21 included provisions to keep patient confidentiality and in Article 22 – the disclosure of the secret[8].

Similarly, Article 17 of this code writes that: "The patient has the right to know the truth on their disease and to be informed with all results of analysis and other medical documents. However, if the physician judges that the information damages the health of the patient, then the physician is not obligated to inform the patient on the truth or to show them the medical documentation". Thus, under this section, the third model (participatory) is applied, which deals with the issue telling the truth to the patient.

Articles 16 and 18 include provisions that deal with the physician's obligation to inform the patient and the patient's family.

Fom the presentation and discussion of the above data, it should be noted that medical confidentiality is still affirmed as one of the most fundamental principles of medical ethics.

* * *

From what is mentioned above, both of these medical principles in preserving the dignity and independence, or integrity of the patient, have no absolute character (Compulsory and mandatory medical examination, 2018).

This is explained from the ethical and philosophical point of view, with the fact that e.g. one man's freedom cannot have an absolute character, because this would be significantly followed by the violation of another person's freedom. Likewise, the absolute right of consent of an individual will have a negative impact on the autonomy of other persons etc.(Christian, 2009).

Their absence of absolute character is reflected in the concepts of refusal of treatment and compulsory treatment, failure to maintain medical confidentiality in various circumstances, question of the conflict between the confidentiality principle and measures to be taken to prevent the disease, etc.

4. Consent and secrecy in inquiry questions and identifying DNA examinations

Consent and confidentiality in their general sense, in addition to genuine medical applications, are also encountered in criminal or civil cases, or in medical cases intertwined with legal ones (Compulsory anf mandatory medical examination, 2018).

Even in these situations, again they have no absolute character.

For example, the consent of a minor girl, that she has agreed to have sexual intercourse with her, will not be taken into account in the qualification of the criminal offense against her, for the perpetrator of this crime.

Or the consent for conducting medical experiments with prisoners will be considered worthless. In other cases, for experiments performed on prisoners without consent, the doctors who performed them were prosecuted.

The most important problem of informed consent that has begun to emerge in our country is to use it in questions of medical malpractice (Çipi,2005).

Thus, when a physician accused of medical negligence, if he has applied the ethical rule of informed consent, this will protect him from the accusation raised

against him. On the contrary, he will be responsible for this accusation, which may be criminal or deontological.

Even in terms of secrecy, which does not have an absolute character, this is given in the Code of Criminal Procedure of 1995, where in Article 282: the obligation to report infectious diseases, according to the law of infectious diseases in 1993.

However, in this first code of medical deontology, confidentiality has an absolute character because exclusions to medical secrets did not apply. It appears that the application of medical confidentiality was under the influence of the French code of medical deontology.

It is in this period, in 1995, that the code of criminal procedure was enacted and in article 282 indicated that "the medical staff is required to inform the judiciary about third-party individuals that help, or intervene in medical problems associated with a crime."

Under this section of the law of parliament, which overrules the deontology code (in Albania is only approved by the Order of Physicians), the absolute character of medical confidentiality was amended.

Some years later in the new code of medical ethics and deontology (2002), it was included the concept of no absolute character of confidentiality

According to DNA, the need of respecting of these principles is much bigger especially in the case of determining the paternity. The examination of these cases by DNA fingerprinting has a 100 % precision, for determining that the social and legal father is at the same time the biological one of the child (Çipi et al, 2015,2017,2020).

Diffusion of DNA fingerprinting data of this character may have dangerous psychosocial consequences, in reference to the destabilization of individuals, families.

This principle is expressed obviously also in the Universal Declaration On Human Genome and Human Rights of Unesco (1997).

This declaration has the ambition to secure the development of human genetics but respecting the dignity and the human rights for all the humanity. So, in the first article of this declaration it is underlined that:"in a symbolic sense the human genome is the heritage of humanity" (Çipi, 2003).

As for the need for respecting the principle of confidentiality (article 7 of this Declaration) is supported on the right of private life, in fact this is expressed in all the international important and legal documents after the second world war, starting with the Universal Declaration of Human Rights etc.

But on the other hand, according to this article, the confidentiality of these data have to be respected only when they belong to an identified person (Çipi, 2003).

So, if these data would be anonymous that they don't belong to a concrete person this principle wouldn't be applied.

A limitation like this of the confidentiality principle is necessary for justifying some uses of genetic data, for example in the field of epidemiological studies.

Also, there are some circumstances in which this principle may not be respected for the genetic data. For example, those prescribed by the article 9 of this Declaration according to it: "in order to protect human rights and fundamental freedoms, limitations to the principles of consent and confidentiality may only be prescribed by law, for compelling reasons within the bounds of public international law and the international law for human rights" (Çipi, 2003).

As you can see in this article, limitation are not only for the secret but also for the consent.

So, for example, all the genetic data will not be kept secret in the cases when they have to do with penal cases, or civil one, which in fact they correspond to the medico-legal genetic fingerprinting. This because is affected or threatened the life of a person etc. (Çipi, 2003).

In Albania a particular attention has been showed to the issue of consent for DNA analysis

These analysis for resolving criminal and civil cases have started to be performed by the scientific police institute, only after the 2000. So this type of examination was not provided in the 1995 Code of Criminal Procedure. Article 199 of this code only stated that in relation to blood sampling, it can be performed even without the will of the person, if there is no risk to health.

Then in 2017, in an amendment of this code, in article 201 / a, is presented the detailed procedure that must be observed for taking samples of blood and other tissues of the human body for performing DNA analysis, where first of all, the consent of the person to be examined must be respected, without excluding the possibility of taking them compulsorily.

Article 201/a

Compulsory collection of biological samples or performance of other compulsory medical procedures.

1. Compulsory collection of biological samples from a defendant or other persons, or performance of a compulsory medical procedure can only be conducted in accordance with the provisions of this article.
2. The prosecutor, with the consent of the defendant or other persons, can request the collection of biological samples, for the purpose of establishing the DNA profile. Same provisions are applied on the performance of medical procedures.

3. Consent is given in writing. The person whose sample will be taken or will be subject to a medical procedure, signs in the presence of the prosecutor a declaration consenting and confirming on being notified on the reason for the collection of the biological sample or performance of the medical procedure.
4. Such consent for minors is given by the parent or the legal guardian.
5. Upon request of the prosecutor, the court can decide for biological samples or medical procedures to be taken or conducted without the consent of the person and, if necessary limiting his freedom, if no danger comes to his health and if necessary to prove the evidence. Medical procedures that threaten the life of the person, his physical integrity or health, that may harm the unborn child or which, according to medical protocols, may cause illegitimate pain. ….

12. When the biological sample or medical procedure is collected or performed on the suspect or the defendant, his/her defense lawyer's presence is obligatory.
13. In case of collection of biological evidence or performance of a medical procedure on a minor, the presence of his/her parent, legal guardian or trusted person is obligatory.
14. Results of analysis of biological samples or medical procedures collected contrary to the provisions of this article cannot be used." Article 201/b of ACCP provides for the destruction of the biological samples collected.

In fact, in the DNA analysis, which is performed in the scientific police institute of our country, the procedure of obtaining the consent is strictly applied, by the person from whom material is taken from his body for its performance, except in cases when it is taken compulsorily.

So, according to this law, giving consent by the person to whom this analysis is being performed, has no absolute character.

In fact, this attitude is in concordance with that of consent and confidentiality in Medicla Ethics and the respective international legislation (Doutremepuich, 1998; Henning, 2010; Budowle & Simon, 2002).

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In conclusion must be stressed that the application in Albania of DNA analysis (obtaining and storing their data) in criminal and civil cases requires great care in implementing the procedures set out in the relevant legislation, including the principles of consent and confidentiality for respecting human rights and preserving human dignity.

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Refractory Shock. Casuistics

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Abstract

Introduction
Shock Syndrome is an acute progressive circulatory insufficiency where the Heart is unable to circulate the blood in time unit, for supplying with O2 to the cells and to take out from them CO2 and other final and intermediate toxic metabolites. Shock is acute inadequate organ perfusion to meet the tissue's oxygenation demand. Shock means: an Acute suffering of cells and organ`s tissues of organism. The term refractory shock is applied when, in spite of apparently adequate therapy, the shock state continues. There are three types of refractory shock: Refractory (or Irreversible) shock, Refractory (Septic) shock, Refractory (Cardiogenic) shock (RCS).

Diagnosis
Evaluation should focus on the identification of the primary cause and reversible secondary contributors, such as hypovolemia, pump failure, or obstruction that is causing shock. Differential diagnosis must be done with: septic shock, vasodilatory shock and cardiogenic shock.

Treatment
Coronary PP > 50 mm Hg, Improve myocardial function, C.I. < 3.5 is a risk factor, 2.5 may be sufficient. Fluids first, then cautious pressors. Remember aortic DIASTOLIC pressures drives coronary perfusion (DBP-PAOP = Coronary Perfusion Pressure) .If inotropes and vasopressors fail, intra-aortic balloon pump Temporary circulatory support with extracorporeal membrane oxygenation (ECMO). Sol. natrium bicarbonat 8.4% (PH ≤7.2).

Recomandation
Refractory shock which is mainly caused by cardiogenic shock and Septic shock are severe conditions which cause increased mortality in patients with such conditions. Advances in the treatment of these serious conditions have enabled the healing of these patients and the relative reduction of Mortality.

Key Words. *IS-Inflammatory Shock; HS – Hemorrhagic Shock; CS-Cardiogenic Shock, CVP-Central Venous Pressure; UO – Urine Output; BP – Blood Pressure; HR – Heart Rhythm; MAP-Mean Arterial Pressure; CO/CI-Cardiac Output/Cardiac Index; SVR-Systemic Vascular Resistance; PAP-Pulmonary artery Pressure; SvO2- Mixed Venous Saturation ; (a-v)DO2- arterial-venous difference of Oxygen Deliv*ery; OE/R-Oxygen Extraction Ratio.

Definition and Terminology of Shock Syndrome

Is an acute progressive circulatory insufficiency where the Heart is unable to circulate the blood in time unit, for supplying with O2 to the cells and to take out from them CO2 and other final and intermediate toxic metabolites. Shock is acute inadequate organ perfusion to meet the tissue's oxygenation demand. Shock means: an Acute suffering of cells and organ`s tissues of organism.

Pathologic Physiology. There are four important factor that influence in Shock Syndrome:

-Acute Hypoxia; -Hypotension -Metabolic Acidosis -Paralytic Capillary Vasodilatation (during Septic and/or refractory Shock).

Classification of Shock Syndrome.

Shock Syndrome have four main categories:

1- Hypovolemic –non-hemorrhagic Shock and Combustion Shock, and Hemorrhagic Shock
2- Cardiogenic –acute cardiac pathologic problems and cardiac trauma prob lems
3- Distributive- including: Septic, Anaphylactic, Toxic, Pharmacological, Neurogenic, Endocrine,
4- Obstructive Extra-cardiac Shock – Thoracic Trauma, Cardiac Tamponade, Tension Pneumothorax, Massive Pulmonary Embolus

Definition of Refractory Shock

The terms refractory shock and irreversible shock are widely used by physicians and other medical workers to refer to types of shock that present particularly difficult problems. The term refractory shock is applied when, in spite of apparently adequate therapy, the shock state continues. Commonly, the treatment later proves to have been inadequate, in which case the shock was not true refractory shock. This often occurs following a major injury in which there is internal bleeding, leading to underestimation of true blood loss and therefore to inadequate transfusion. In certain cases, however, even if the therapy actually is appropriate, the shock state persists; if patients in such cases respond to further special treatment, then this is true physiological refractory shock.

Shock is a syndrome characterized by signs and symptoms, which are the result of the different organs response to a situation of low perfusion for their basic metabolic needs. The temporal sequence of the manifestations follows a pattern of inverse priority in the economy of human body physiology. Cryptic shock and two-hit clinical model of physiological deterioration are nowadays established concepts that need to be kept in focus if we want to prevent shock from reaching a NRP ('no-return point').

The term "cryptic shock" is often used for patients with deceptively normal hemodynamic parameters, yet presenting high risk for morbidity and mortality because of global ischemia with increased lactate blood level. If blood pressure is normal, but lactate blood level is high secondary to global tissue ischemia, some call this condition Normotensive shock instead of "cryptic shock".

The term "Cryptic Shock" is often used for patients with deceptively normal hemodynamic parameters, yet presenting high risk for morbidity and mortality because of global ischemia with increased lactate blood level.

If blood pressure is normal, but lactate blood level is high secondary to global tissue ischemia, some call this condition Normotensive shock instead of "cryptic shock" (Sylvain Beurtheret et al., 2013).

Cryptic shock and two-hit clinical model of physiological deterioration are nowadays established concepts that need to be kept in focus if we want to prevent shock from reaching a NRP ('no-return point').

In fact, Cryptic Shock is an unifying concept – Circulation from normal physiology to cessation of life.

Actually, some patients can even be in Hypertensive shock! ....For example:

(a) in cardiogenic or hypovolemic shock with marked sympathetic system activation,
(b) during a hypertensive crisis due to pheochromocytoma, or
(c) during eclampsia

In those cases, shock is easily diagnosed by finding out that organs are dysfunctional or failing while lactate blood level is high! And this, despite normotension or even hypertension!

Refractory (or Irreversible) Shock ensues as consequence of direct hit or as result of inadequate or delayed treatment and is characterized by drug-resistant hypotension.

Refractory (Septic) shock is a persistently low mean arterial blood pressure despite vasopressor therapy and adequate fluid resuscitation.

Refractory (Cardiogenic) shock (RCS) is defined as cardiac and circulatory failure resulting in organ hypoperfusion unresponsive to conventional medical therapies (W.G. Prout)

It is important to note that many physicians do not believe that patients with normal blood pressure can be in shock

For those non-believers, they should at least admit that a previously chronically hypertensive patient with blood pressures running chronically in the 180/100 mmHg range, and presenting to the emergency room department with a blood pressure of 100/70 ("normal BP"), can be in full blown shock!

In these cases, compensatory mechanisms are at play (vasoconstrictive autonomic system) and maintain blood pressure through severe increase in systemic vascular resistance. This severe vasoconstriction induces tissue ischemia/hypoxia and, as a consequence, lactic acidosis.

Note that, without betablockade, these patients tell you that they are sick: they are tachycardic! and in severe cases, sweating profusely!

In severe or prolonged shock states, the myocardial blood supply is sufficiently diminished to damage the heart's pumping action temporarily or permanently. Also, noxious products of inadequately perfused tissues may circulate and affect the heart muscle.

While the flow of blood through major vessels is under the control of the nerves, circulation through the capillary beds is of a more primitive type and is under the influence of local metabolic products. In shock, arteriolar constriction causes inadequate flow through the tissues, and local waste products increase. These cause dilation of the capillary sphincters and opening of the whole capillary bed, which thus contains an increased proportion of the blood volume. The capillaries become further engorged with slowly flowing blood, and fluid leaks through the vessel walls into the tissues. Thus, the body is further deprived of circulating blood volume.

Widespread clotting of the blood can occur during capillary stagnation. This leads to severe damage to the cells unsupplied by flowing blood. Later, when enzymes dissolve the fibrin of the clots, the flow through these areas carries toxic metabolic products to vital organs—such as the heart, kidneys, or liver—and the ensuing damage leads to irreversibility of shock.

Some characteristics of Refractory Septic Shock

Refractory septic shock is a persistently low mean arterial blood pressure despite vasopressor therapy and adequate fluid resuscitation.

Refractory septic shock is due to a dysregulated immune response that is caused by a bacterial or a fungal infection in the blood. Endotoxins like lipopolysaccharide (LPS) from bacteria stimulate the release of pro-inflammatory mediators including tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1). These cytokines activate leukocytes resulting in the release of additional inflammatory mediators promoting widespread inflammation. This leads to refractory septic shock, which adversely affects the cardiovascular, respiratory and renal systems. In this review, current therapies to manage septic shock are examined and novel treatments are proposed to make sepsis more manageable in the clinical setting. ICU patients diagnosed at an early stage have the highest rate of survival as they can be effectively treated to prevent the onset of septic shock. However, patients that have progressed into later stages of sepsis have complications due to septic shock. We suggest treating these patients with cytokine inhibitors and anti-LPS molecules (cationic lipids and poly-L-histidines) in addition to therapeutics for organ-localized complications. This two-pronged approach treats the adverse effect due to inflammation that has already occurred and prevents further inflammation, resulting in an improved clinical outcome.

Some characteristics of Refractory Cardiac Shock

Refractory cardiogenic shock (RCS) is defined as cardiac and circulatory failure resulting in organ hypoperfusion unresponsive to conventional medical therapies. Despite recent advances, therapeutic options are limited, and RCS is almost uniformly fatal when emergency circulatory support cannot be initiated in a timely manner. If such patients can be stabilized by extracorporeal membrane oxygenation (ECMO), possible outcomes include ECMO weaning to recovery (bridge to recovery), heart transplantation (bridge to transplantation), or implantation of a long-term assist device (bridge to bridge). When this strategy based on temporary circulatory support is available in specialized and experienced centers, up to 40% of the patients with RCS can survive to hospital discharge in various pathophysiological situations, including acute myocarditis and acute myocardial infarction (Combes et al., 2008).

Nonetheless, this strategy is currently restricted to a very limited number of tertiary-care centers with specialist capabilities for instituting and supporting ECMO. In remote hospitals, however, without ECMO capability, management

of RCS patients is considerably more difficult, as transfer to tertiary centers is often essential to save the patient but is often not feasible in such medically unstable patients. We hypothesized that instituting ECMO in remote institutions followed by stabilization and transfer might be logistically feasible, allowing an improved rate of survival.

To test the feasibility of offering ECMO (Extra-corporeal membrane oxygenation) support to RCS patients in remote hospitals, we set up a specific program based on coordinating staff and a Mobile Unit of Cardiac Assistance (MUCA), able to initiate and manage circulatory support in institutions that do not host local circulatory support teams.

Causes of Refractory Shock

Refractory shock with vasodilatation is caused by sepsis, hemorrhagic shock, after cardiopulmonary bypass, milrinone intoxication, organ donors receptors, burned patients and after placement of ventricular assistance dispositive. Inappropriately low levels of vasopressin (VP) which plays an important role in the maintenance of systemic vascular resistance index (SVRI) and mean arterial pressure (MAP) are present (Asaumi 2005; Bonanno 2011).

- Infectious Disorders (Specific Agent)
- Meningococcemia/meningococcus
- Infected organ, Abscesses
- Peritonitis, acute
- Granulomatous, Inflammatory Disorders
- Pancreatitis, acute
- Hemorrhagic pancreatitis, necrotizing
- Allergic, Collagen, Auto-Immune Disorders
- Anaphylaxis, generalized
- Idiopathic Anaphylactoid Reactions/Recurrent
- Anatomic, Foreign Body, Structural Disorders
- Internal bleeding/trauma
- Arteriosclerotic, Vascular, Venous Disorders
- Mesenteric artery embolism
- Reference to Organ System
- Disseminated intravascular coagulopathy
- Pathophysiologic
- Capillary leak syndrome
- Drugs

- Iron intoxication, acute
- Poisoning (Specific Agent)
- Mercury salts/bichloride acute toxicity

Pathology-physiology of refractory shock

Irreversible shock ensues as consequence of direct hit or as result of inadequate or delayed treatment and is characterized by drug-resistant hypotension.

The clinical aspects of shock syndromes are described from their inception as compensated physiology to a stage of decompensation. The clinical significance of hypotension, fluid-responsive and non fluid-responsive hypotension, is discussed. Untimely or inadequate treatment leads to persistent subclinical shock despite adjustments of the macrohemodynamic variables, which evolves in a second hit of physiological deterioration if not aggressively managed. Effects of inadequate perfusion on cell function.

There are four stages of shock. As it is a complex and continuous condition there is no sudden transition from one stage to the next. At a cellular level shock is the process of oxygen demand becoming greater than oxygen supply.

Initial

During this stage, the state of hypoperfusion causes hypoxia. Due to the lack of oxygen, the cells perform lactic acid fermentation. Since oxygen, the terminal electron acceptor in the electron transport chain is not abundant, this slows down entry of pyruvate into the Krebs cycle, resulting in its accumulation. Accumulating pyruvate is converted to lactate by lactate dehydrogenase and hence lactate accumulates (causing lactic acidosis).

Compensatory

This stage is characterised by the body employing physiological mechanisms, including neural, hormonal and bio-chemical mechanisms in an attempt to reverse the condition.

As a result of the acidosis, the person will begin to hyperventilate in order to rid the body of carbon dioxide (CO2). CO2 indirectly acts to acidify the blood and by removing it the body is attempting to raise the pH of the blood. The baroreceptors in the arteries detect the resulting hypotension, and cause the release of epinephrine and norepinephrine. Norepinephrine causes predominately vasoconstriction with a mild increase in heart rate, whereas

epinephrine predominately causes an increase in heart rate with a small effect on the vascular tone; the combined effect results in an increase in blood pressure. Renin-angiotensin axis is activated and arginine vasopressin (Anti-diuretic hormone; ADH) is released to conserve fluid via the kidneys. These hormones cause the vasoconstriction of the kidneys, gastrointestinal tract, and other organs to divert blood to the heart, lungs and brain. The lack of blood to the renal system causes the characteristic low urine production. However the effects of the Renin-angiotensin axis take time and are of little importance to the immediate homeostatic mediation of shock.

Compensatory Shock have three main elements of Path-Physiology:
-Hypoxia - (low PaO2, low SvO2,)
-Metabolic Acidosis -(low Ph, high PaCO2 and high lactates in blood),
-Hypotension (low BP, low MAP, low PAP, high/low SVR).

Compensatory significances:

1. Maintain normal arterial pressure
(a) returned blood volume↑
Auto blood transfusion
Auto fluid Transfusion
Aldosterone and Antidiuretic Hormone (ADH) y ↑
(b) cardiac output ↑
(c) peripheral resistances↑

2. Maintain blood supplying to heart and brain
(a) blood vessel of brain
(b) coronary artery
(c) normal arterial pressure

Progressive

Should the cause of the crisis not be successfully treated, the shock will proceed to the progressive stage and the compensatory mechanisms begin to fail. Due to the decreased perfusion of the cells, sodium ions build up within while potassium ions leak out. As anaerobic metabolism continues, increasing the body's metabolic acidosis, the arteriolar smooth muscle and precapillary sphincters relax such that blood remains in the capillaries. Due to this, the hydrostatic pressure will increase and, combined with histamine release, this will lead to leakage of fluid and protein into the surrounding tissues. As this

fluid is lost, the blood concentration and viscosity increase, causing sludging of the micro-circulation. The prolonged vasoconstriction will also cause the vital organs to be compromised due to reduced perfusion. If the bowel becomes sufficiently ischemic, bacteria may enter the blood stream, resulting in the increased complication of endotoxic shock (Fine et al., 1959).

Cellular and tissue suffering of Organs and Systems that result to the inadequate perfusion on cell functions.

First: Kidneys, Skin (to save main Systems SNC, Heart &CVS, and Respiratory System);

Second: all other organs: Gastro-intestinal System, Endocrine System, and finally: SNC damage, with C-V and Respiratory Failure.

Refractory

At this stage, the vital organs have failed and the shock can no longer be reversed. Brain damage and cell death are occurring, and death will occur imminently. One of the primary reasons that shock is irreversible at this point is that much cellular ATP has been degraded into adenosine in the absence of oxygen as an electron receptor in the mitochondrial matrix. Adenosine easily perfuses out of cellular membranes into extracellular fluid, furthering capillary vasodilation, and then is transformed into uric acid. Because cells can only produce adenosine at a rate of about 2% of the cell's total need per hour, even restoring oxygen is futile at this point because there is no adenosine to phosphorylate into ATP.

Changes in Micro circulation

The microcirculation undergoes massive alterations during sepsis/septic shock (Ravin and Fine, 1962). There are numerous changes, including slowing of capillary blood flow due to depressed perfusion pressure as a result of systemic pressure reduction and local arteriolar constriction. Observations suggest that the microcirculation is shut off early capabilities in severe sepsis, allowing the effects of hypoperfusion and attacks by microorganisms to prevail in their destructive widespread capillary dilation may ultimately occur.

However, with blood flow diverted through some arteriovenous channels, important areas of capillary exchange are bypassed. Decreased capillary blood flow during shock results from failure to allow normal passage of cellular elements, including erythrocytes and neutrophils. This defect occurs, in part, because of decreased perfusion pressure, decreased deformability of red and white cells, constricted arterioles, circulating obstructive fragments (including

hemoglobin), and plugging of microvessels with "sludge." Other factors are adherence of cells to capillary and venular epithelial membranes creating increased resistance to flow, loss of fluid through abnormal transcapillary exchange, differential vascular resistance changes between various beds (e.g., intestinal vs. muscle), and the relative absence of regulatory neurohumoral control of small vessel segments of the circulation. During sepsis/septic shock, endothelial cells are reported to modulate vascular tone, control local blood flow, influence the rate of leakage of fluids and plasma proteins into tissues, modulate the accumulation and extravasation of white cells into tissues, and influence white cell activation. As a result of the predominance of many destructive factors, a subsequent round of tissue damage may occur. Because of prolonged capillary vascular stasis, deficient flow, and factors released from injured cells, the microcirculation becomes a trap for uncontrolled bacterial growth enhanced by sustained hypoxemia, acidosis and toxemia. These events may combine to contribute to the loss of normal cell integrity and death of the host.

Microcirculatory alterations improve rapidly in septic shock survivors but not in patients dying with multiple organ failure, regardless of whether shock has resolved.

The initial responses to endotoxemia are detectable in the microcirculation as a microvascular inflammatory response characterized by activation of the endothelium stimulating these cells from their normal anticoagulant state to a procoagulant state with increased adhesiveness for leukocytes and platelets. Concomitantly, arteriolar tone is lost and reactivity to a variety of agonists is modified. Tissue damage subsequently results not only from reduced perfusion of the exchange vessels, but also from injurious substances released from activated, sequestered leukocytes as well as activated endothelial cells, macrophages, and platelets. This is the result of endotoxins inducing activation and interaction of a number of effector cells, cascades, and acute-phase responses, such as the complement, coagulation, bradykinin/kinin, and hematopoietic systems accompanied by the release of a myriad of mediators. These include eicosanoids, cytokines, chemokines, adhesion molecules, reactive free radicals, platelet-activating factor, and nitric oxide. This paper briefly reviews the microvascular responses to endotoxemia and discusses some of the mechanisms involved.

Refractory Shock with Irreversible conditions of all organs functions cause:

- irreversible vasodilatation and diminishing of systemic vascular resistance,
- pooling of blood (sludge) to the system (capillary sphincter relax)
- Release of Microbial and Fungal toxins (Baumgarten et al., 2006).
- Primary and Secondary Inflammatory Mediators
- Metabolic Acidosis

-Vasodilatation -is fourth element at Path-Physiology during the Refractory (Irreversible) Shock.

a. In Case of Hemodynamic Refractory Shock (HS, CS)

Vasodilatation is caused by:

- Hypoxia (in lack of O2), and because of much cellular

ATP- adenosine cause – an capillary vasodilation,

- Metabolic Acidosis -from stagnant waste products of cells, especially Lactic Acidosis

-production of NO (nitric oxide)

- pooling of blood (sludge) to the system (pre and post capillary sphincter relax)

$ATP + H2O \Rightarrow ADP + Pi + H+ + Energy$

Acidosis results from the accumulation of acid when during anaerobic metabolism the creation of ATP from ADP is slowed.

H+ shift extracellularly and a metabolic acidosis develops.

ATP production fails, the Na+/K+ pump fails resulting in the inability to correct the cell electronic potential.

Cell swelling occurs leading to rupture and death.

Oxidative Phosphorylation stops & anaerobic metabolism begins leading to lactic acid production. (Ramana et al ., 2006).

b. In Case of Refractory Septic Shock (IS)

Vasodilatation is produced by:

- Microbial toxins: Endotoxins like lipopolysaccharide (LPS)

-Primary and secondary Inflammatory mediators as: Histamine, Kinine/ Bradikinine (TNF-α), (IL- pooling of blood (sludge) to the system (pre and post capillary sphincter relax) 1 , IL-6, Lysosome,, Prostaglandine, eicosanoids, cytokines, adhesion molecules, reactive free radicals, platelet-activating factor,

- NO (nitric oxide)

-Hypoxia

-Metabolic Acidosis Metabolic Acidosis -from stagnant waste products of cells, especially Lactic Acidosis

- Pooling of blood (sludge) to the system (pre and post- capillary sphincter relax).

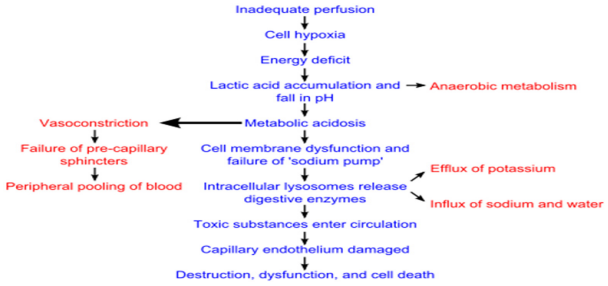

TABLE 1

Microcirculatory mechanisms are:

- Ischemic hypoxia stage
- Stagnant hypoxia stage
- Refractory stage has these Cellular and molecular mechanisms:

In the Microcirculation System the following phases are observed in Refractory Shock the following features are observed to:

-Relaxation of post-capillary sphincters

-Loss of Peripheral Vascular Resistance.

-Acidosis is a local accumulation of metabolic products because of, Alteration of hemorheology,

Endotoxins, Effects of humoral factors (Looney et al., 2006; Coimbra et al., 2006). In these cases have:

Effective circulating blood volume is diminished↓ ↓, temporarily has an increased of Blood flow resistance ↑ ↑, is diminished blood pressure ↓ ↓, is diminished Blood supply for vitals and dysfunctional.

1. In case of Ischemic hypoxia stage (compensatory stage) has: Microcirculatory changes, Small blood vessel constriction, Precapillary resistance↑↑ > postcapillary resistance↑, Closed capillary↑, Blood inflows vein by straightforward pathway and A-V shunt.

Characteristics of inflow and outflow: inflow and outflow↓↓; inflow < outflow.

2. In case of Stagnant hypoxia stage (reversible decompensated stage) has: Acidosis derived from Local accumulation of metabolic products, Endotoxins, Effective circulating blood volume is diminished ↓ ↓:

(See the tables: 2,3, 4 and 5):

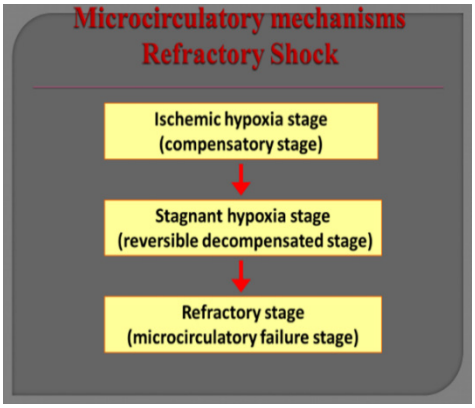

TABLE 2

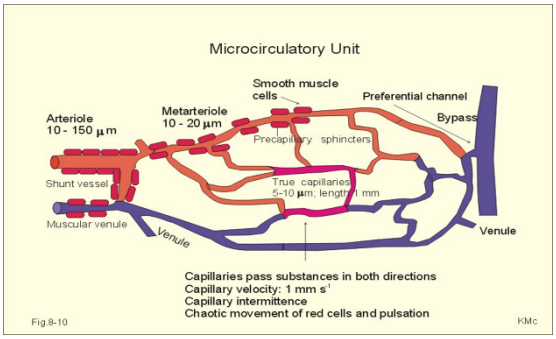

TABLE 3

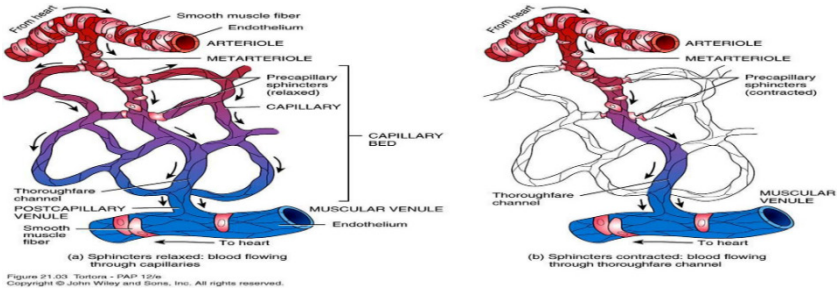

TABLE 4

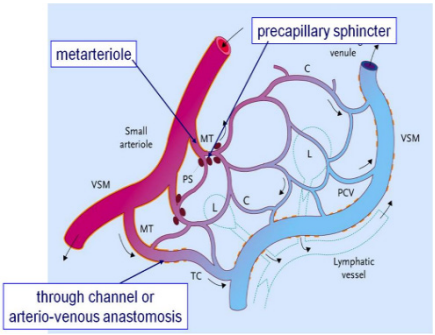

TABLE 5

Clinical manifestations

Is essential to monitor Vital signs During Refractory Shock patient is in very grave condition:

- Cardio-vascular system: Tachycardia and dysrhytmias, hypotension,
- Pulmonary System: Tachypnea, Superficial respirations, dyspnea,
- Mental Status: Changes, is frightened, anxiety, confusional condition, and coma.
- Skin e mycoses: Patient is pale, with cold extremities, and cyanosis
- Diuresis: Oliguria
- Thermoregulation: Hypothermia, but during hyperkinetic phases of Septic Shock can be high temperature,
- Lactic Acidosis.
- Cardiac Output - diminished
- PAOP - increased
- SVR - increased
- Left ventricular stroke work (LVSW) – DIMINUISHED
- Coronary Perfusion Pressure
- Coronary PP = DBP - PAOP
- Coronary perfusion = Δ P across coronary a.

So is necessary t is essential to monitor symptoms to understanding their disease, to describe the patient's physiologic status, to facilitates diagnosis and treatment of shock, and continuing monitoring of Vital Signs. See the Tables 6, 7, and 8:

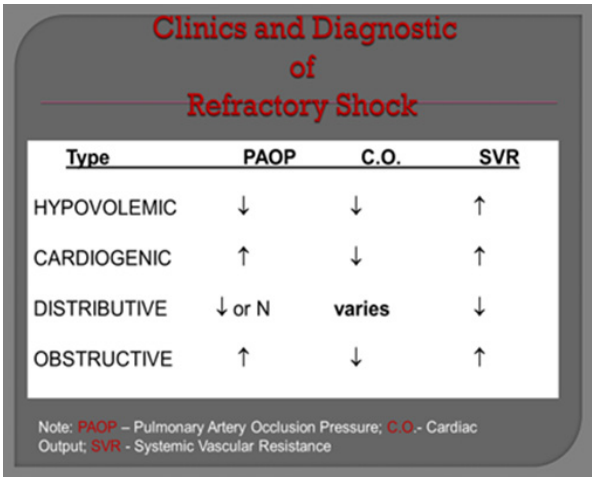

TABLE 6

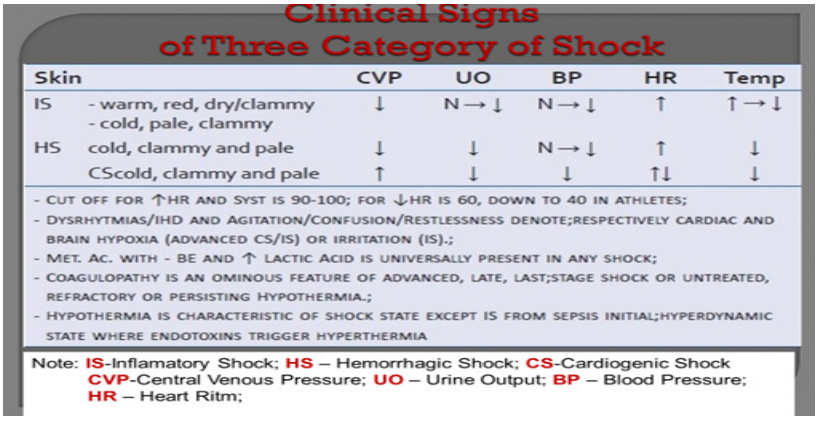

TABLE 7

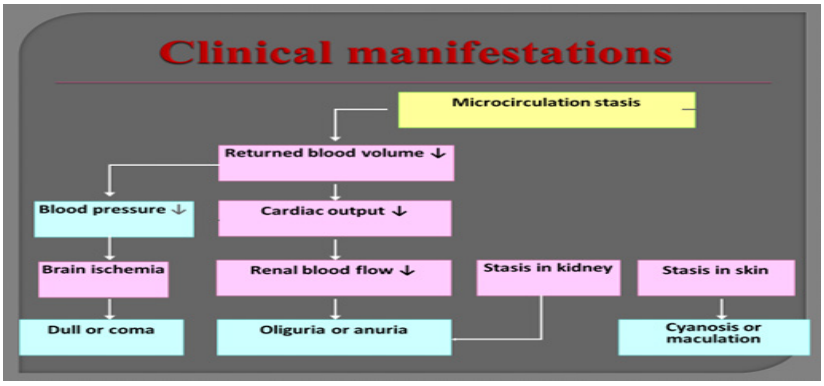

TABLE 8

Signs of Refractory Septic Shock are:
± cardiac output
±PAOP
SVR - diminished
Signs of Refractory Cardiac Shock are:
Cardiac Output - diminished
PAOP - increased
SVR - increased
Left ventricular stroke work (LVSW) – Diminished
Coronary Perfusion Pressure
Coronary PP = DBP - PAOP
coronary perfusion = BP across coronary (Trzeciak et al., 2007)

Diagnosis of Refractory Shock

Evaluation should focus on the identification of the primary cause and reversible secondary contributors, such as hypovolemia, pump failure, or obstruction that is causing shock. Patients must be placed on continuous cardiopulmonary monitoring (Bernard et al., 2001) The following labs should be monitored: Complete blood count with differential (CBC-d), basic metabolic profile with liver function test, disseminated intravascular coagulation (DIC) panel, arterial blood gas, urinalysis, and pan cultures (blood, urine, wound, tracheal if intubated). Inflammatory markers, including C-reactive protein or procalcitonin and lactate levels, should be monitored. A chest x-ray should be obtained to monitor the degree of ARDS.

Differential Diagnosis

Differential Diagnosis must be done with: Septic shock, Vasodilatory shock and cardiogenic shock. Is necessary to evaluate these parameters (Krejci et al., 2016):

Measured	*Calculated*
Blood pressure	Mean BP
Pulmonary A. pressure	Mean PAP (Pulmonary Artery Pressure)
Heart rate	Cardiac Index
Cardiac Output	Stroke volume index
Stroke volume	Mean BP
Wedge pressure	SVRI (systemic vascular resistance index)
CVP (Central venous pressure)	LVSWI (Ventricular Stroke Work Index, Left) BSA (body surface area)

It is necessary to evaluate during diagnostic and therapy oxygen delivery and hemodynamic calculations of the patient in ICU as well (see the tables 9, 10, 11, and 12).

PITT COUNTY MEMORIAL HOSPITAL

Hemodynamic Calculations

	units			units			units
C.O.	5.70 l/min					C.I.	2.50 l/min/m2
HR	89 bpm		SV	64.0 ml		SI	28.1 ml/m2
ABP S	100 mmHg		SVR	800 DS/cm5		SVRI	1823 DSm2/cm5
ABP D	49 mmHg		PVR	253 DS/cm5		PVRI	576 DSm2/cm5
ABP M	68 mmHg		LCW	5.3 kg-m		LCWI	2.3 kg-m/m2
PAP S	49 mmHg		LVSW	59.2 g-m		LVSWI	26.0 g-m/m2
PAP D	24 mmHg		RCW	2.64 kg-m		RCWI	1.16 kg-m/m2
PAP M	34 mmHg		RVSW	29.61 g-m		RVSWI	12.99 g-m/m2
PAWP	16 mmHg						
CVP M	11 mmHg						
Height	64 in					Calculation Time:	
Weight	130.0 kg		BSA(D)	2.28 m2		29 JAN 02 3:57	

TABLE 9

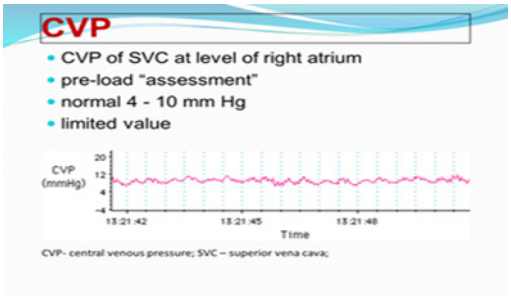

TABLE 10

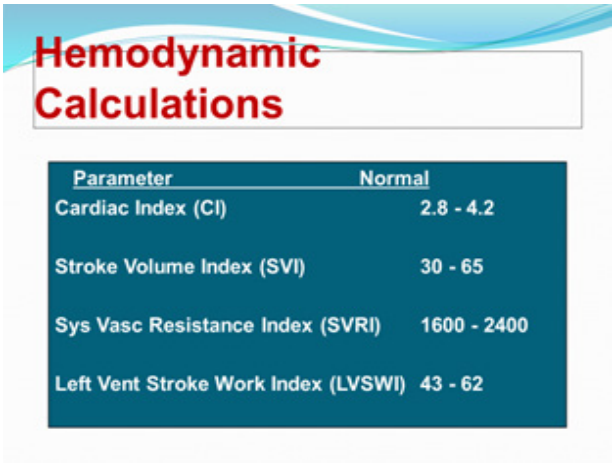

TABLE 11

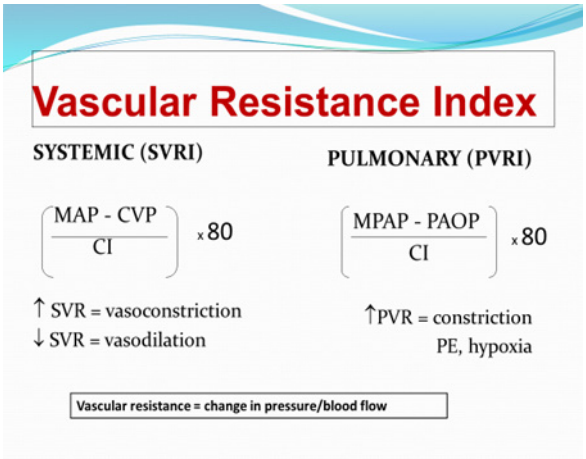

TABLE 12

Monitoring and Stroke work as well:

LVSWI = (MAP-PAOP) x SVI x 0.0136
normal = 43 - 62
VSWI describe how well the ventricles are contracting and can be used to identify patients who have poor cardiac function.
ventricular stroke work = Δ pressure x vol. ejected

Important is monitoring, Pulmonary Artery Catheter as: Indications, volume status, cardiac status. Is important to evaluate and to prevent the complication of pulmonary artery catheterization: technical, anatomic, physiologic.

Special Problems during Diagnostic and Therapy

Oxygen Delivery (DO2I)

O2AVI = CI x CaO2 x 10

Normal values suggests that the heart & lungs are working efficiently to provide oxygen to the tissues. < 400 is bad sign. Is necessary to evaluate:

Oxygen Consumption

VO2I = CI x (CaO2 - CvO2)

If VO2I < 100 suggest tissues are not getting enough oxygen (Bagshaw et al.,2006), (Slade et al., 2003)

Diagnostic Mistakes

- JVP is low CS and HS
- Central Cyanosis is not eligible in HS
- Elderly patients with ATS and HPT can be in shock with a Systolic pressure of 120-130 mHg

- Pts β-blockers or antidysrhythmic drugs do not manifest reflex tachycardia and can be in shock with normal HR.
- Steroids mask septic Shock signs
- Hypoglycemia, drunkness, not lethal carbon monoxide poisonings, syncope and vaso-vagal attacks can mimick shock initial skin changes
- Cocaine abusers are bradycardic or do not exhibit reflex tachycardia
- Caffeine intake before shock onset and phosphodiesterase inhibitors can deceive its recognition and assessment by causing tachycardia.

Treatment in General:

Goals of Shock Resuscitation are:

Restore blood pressure

Normalize systemic perfusion

Preserve organ function

CI = 4.5 L/min/m2

DO2I = 600 mL/min/m2

VO2I = 170 mL/min/m2

Critically ill patients who can respond

Oxygen Therapy (mecanical ventilation)

Improve microcirculation, Volume replacement, Acidosis correction, vasoactive drugs application, Treatment of DIC, Blockage of humoral factors, Cell protection, Organ protection.

Treatment of Refractory Cardiac Shock:

Coronary PP > 50 mm Hg

Improve myocardial function, C.I. < 3.5 is a risk factor, 2.5 may be sufficient.

Fluids first, then cautious pressors

Remember aortic DIASTOLIC pressures drives coronary perfusion (DBP-PAOP = Coronary Perfusion Pressure)

If inotropes and vasopressors fail, intra-aortic balloon pump

Temporary circulatory support with extracorporeal membrane oxygenation (ECMO)

Sol. Natri Bicarbonici 8.4% (PH ≤7.2)

Despite recent advances, therapeutic options are limited, and RCS is almost uniformly fatal when emergency circulatory support cannot be initiated in a timely manner.

This strategy based on temporary circulatory support in specialized and experienced centers; up to 40% of the patients with RCS can survive to hospital discharge in various pathophysiological situations.

Patients requiring CPR for cardiac output and the elderly, most probably cannot benefit from circulatory support, in this context. (Carlson et al., 2006), (Gary et al., 1998).

Nonetheless, this strategy is currently restricted to a very limited number of tertiary-care centers with specialist capabilities for instituting and supporting ECMO.

In remote hospitals, however, without ECMO capability, management of RCS patients is considerably more difficult, as transfer to tertiary centers is often essential to save the patient but is often not feasible in such medically unstable patients (Jaski et al ., 2010).

If such patients can be stabilized by extracorporeal membrane oxygenation (ECMO), possible outcomes include (Combes et al., 2008) ***:***

(i) ECMO weaning to recovery (bridge to recovery),
(ii) heart transplantation (bridge to transplantation),
(iii) implantation of a long-term assist device (bridge to bridge).

- Vasopressors & Inotropic Agents
- Dopamine: δ-agonist-8-20 mcg/kg/min
- Norepinephrine: α-agonist -adrenergic- 1 – 100 mcg/min
- Epinephrine: α-adrenergic - 1 - 10 mcg/min
- Amrinone: 0.75 -1.5 mg/kg - 5 - 10 mcg/kg/min drip, esterase inhibitor, positive inotropic and vasodilatory effects.
- Dobutamine: α –β- agonist-5 - 20 mcg/kg/min.
- ACS CoT ATLS - restoration of vital signs and evidence of end-organ perfusion
- Swan-guided resuscitation

C.I. ≥ 4.5, DO2I ≥ 670, VO2I ≥166

- Lactic Acid clearance
- Gastric Ph

Current treatments used to manage septic shock

This therapy can be used to the Sepsis, Anaphylactic, Acute adrenal insufficiency, Neurogenic.

Therapy is:

Oxygen Therapy (mecanical ventilation)
Prompt volume replacement - fill the tank
Early antibiotic administration - treat the cause
Inotropes - first try Dopamine
If MAP < 60 mmHg:

Dopamine = 2 - 3 mcg/kg/min

Norepinephrine = titrate (1-100 μg/min

Sol.Natri Bicarbonici 8.4% (PH ≤7.0)

Steroids –Fludrocortisone 50 μg po q day; Hydrocortisone 200-300 mg/day in divided doses for 7 days

Treating septic shock is a complex clinical task that requires an accurate assessment of the patient's clinical stage on the bacteremia–refractory septic shock continuum. Current therapies are tailored to the distinct stages involved in refractory septic shock development. In the first stage–bacteremia, antibiotics are used as a first line of defense to control the infection [. Although this is administered early, it has a very limited efficacy in controlling immune dysregulation that occurs due to the bacterial infection.

The majority of current therapeutics target the late phase of refractory septic shock development. In the late stages, vasopressor therapy is routinely used however recent literature has shown that although this method can restore systemic blood flow it also results in decreased microcirculatory and mesenteric perfusion. This causes blood flow to divert away from the jejunum and pancreas, which leads to an adverse effect as decreased blood supply to the gastrointestinal system results in cell death. In addition, other therapeutics used to treat severe sepsis include the use of antioxidants, which have proven to be more effective due to their limited side effects. Investigations of antioxidant vitamin therapy by Carlson et al. showed that administration of Vitamins A, C, and E resulted in a significant decrease in the activation of the innate immune system (mediated by the proinflammatory transcription factor family, NF-κB). This in turn, decreased cytokine release, thereby minimizing inflammatory damage and resulting in improved myocardial contractile function. Other adjuvant therapies are also used, such as recombinant human activated protein C (rhAPC). A study by Looney et al. showed that administering rhAPC had an anti-coagulant, anti-inflammatory, anti-apoptotic and profibrinolytic effect, but the exact mechanism through which rhAPC exerts its benefit in severe sepsis is unclear.

Therapies used during the septic shock stage are targeted at restoring systemic circulation and treating failing components of individual organ systems. Fluid resuscitation is first used to maintain blood flow to organ systems and prevent further damage. In addition, mechanical ventilators are used to assist the patient in breathing if the respiratory system fails resulting in acute respiratory distress syndrome (ARDS). Furthermore, complications associated with the hematological system (such as disseminated intravascular coagulation) are treated with anti-thrombotic medications to prevent blood clotting.

If the symptoms of sepsis are prolonged, the patient's condition continues to deteriorate and the patient ultimately develops refractory septic shock. During

refractory septic shock localized therapies are administered to increase tissue perfusion however prognosis at this stage is bleak and most patients undergo multiple organ failure.

Possible treatments to manage refractory septic shock

Early management in the bacteremia—refractory septic shock pathway is crucial in order to effectively prevent the development of refractory septic shock. Upon identification of a positive blood culture, anti-LPS molecules can play a key role in preventing the progression into the next stage. Bosshart et al. used cationic lipids and poly-L-histidines to successfully prevent the formation of the LPS-LBP complex. As cationic lipids or histidine coils surround and sequester LPS, the LPS molecule is unable to bind LBP, and is therefore inactive and unable to stimulate the release of TNF-α. This prevents the activation of additional pro-inflammatory mediators which can cause further injury through the release of tissue factors (namely leukotrienes and platelet activating factors).

During the septic stage therapeutic interventions might also improve the clinical outcome. A study by Ranmana et al. recently noted that inflammatory signaling and cytokine generation during sepsis is dependent on the enzyme aldose reductase. They concluded that down-regulation of this enzyme using interfering ribonucleic acid (RNA) or a pharmacological inhibitor (sorbinil) decreases the activation of the NF-κB nuclear factor and prevents TNF-α release.

Other Intensive Treatment in ICU

In addition to the above treatments in the ICU these medications can also be used:

1. Methylene blue- loading-dose of 1.5 mg/kg and continuous infusion (1.5 mg/kg/h for 12 h, then 0.75 mg/kg/h for 12 h)-(decreasing vasodilation and increasing responsiveness to vasopressors);
2. Vasopressin Arginine- continuous infusions of 0.04 units/min (with Cardiac Index ≤ 2.5-3);
3. Xigris (drotrecogin alfa (activated) is a recombinant form of human activated protein C: i/v infusion rate of 24; mcg/kg/hr (5 mg vials must be reconstituted with 2.5 mL).
4. Lenitral (Trinitrine) trinitrin the initial optimal dose of 0.39 +/- 0.22 mcg/kg/min;
5. Fentolamine- 5 +/- 3 mcg/kg/min;

6. Pentoxifylline (PTX). phosphodiesterase inhibitor,
7. TP (terlipressin) is an effective vasopressor agent (pediatrics) Doses (1–4) μg/kg/min.
8. Using Cationic Lipids and Poly-L-Histidines to successfully prevent the formation of the LPS-LBP (lipopolysaccharide -LPS binding protein) complex
9. Antioxidant vitamin therapy by Carlson et al. showed that administration of Vitamins A, C, and E resulted in a significant decrease in the activation of the innate immune system (mediated by the pro-inflammatory transcription factor family, NF-κB);
10. Recombinant Human activated Protein C (rhAPC)- had an anti-coagulant, anti-inflammatory, anti-apoptotic and profibrinolytic effect;
12. Sorbinil -using interfering ribonucleic acid (RNA) decreases the activation of the NF-κB nuclear factor and prevents TNF-α release.

Complications

End organ dysfunction
Multi-organ failure
Death

Prognosis

Depend from:
Poor prognostic features in Sepsis syndrome
Age more than 60
Multiorganic failure
Renal failure
Respiratory Failure
Hepatic failure
Hypothermia or Leucopenia
HAI - hospital-acquired infection
DIC – Dissemination Intravascular Coagulation
Underlying Disease (Malignancy, Immunocompromised)

Mortality

Mortality in Sepsis: Mortality Bacteremia 15-20%; Bacteremia plus Shock = 30-40%; Shock plus ARDS=40-60% (Journal of Critical Care, Volume 38, April 2017, Pages 284-288).

Mortality in Refractory Cardiogenic Shock is 45.5% within first 30 days after treatment (American Heart Journal, Volume 158, Issue 4, October 2009, Pages 680-687).

Recomandation

Refractory shock which is mainly caused by cardiogenic shock and Septic shock are severe conditions which cause increased mortality in patients with such conditions.

Advances in the treatment of these serious conditions have enabled the healing of these patients and the relative reduction of Mortality.

It is important that the diagnosis of Shock conditions is made as soon as possible so that treatment is started immediately in order to avoid serious conditions such as Refractory Shock.

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Colorectal Cancer, Patient's profile and Clinical Presentation in Albania

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Abstract

Introduction

Colorectal cancer (CRC) is a multi-factorial disease with high malignancy, and the fourth leading cause of cancer death worldwide. This study was performed to assess the epidemiological, patients' profile and clinic-pathological characteristics of CRC in Regional Hospital, Durres.

Methods

This is a retrospective study where being included all patients diagnosed with CRC at Surgery ward in Durrës hospital from January 2016 to December 2020. A statistical software SPSS version 21.0 was used for data analyze.

Results

During five years of CRC cases investigation, a total of 136 patients were treated in regional hospital of Durrës city. Of these, 97 (71.3%) patients had cancer of colon and others patients 39 (28.7%) had rectal cancer. Most of the patients (47%) resulted with left-side tumors and (24.3%) with right-sided tumors. Male with CRC resulted 62.5% and female 37.5% with ratio man versus female 1.66. The commonest symptoms were abdominal pain or discomfort 39.7%, diarrhea or

constipation 27.9%, changing in bowel habits 16.9%, rectal bleeding and anemia 15.4%. About the stage of CRC, in stage I resulted 24.3% in stage II 42.6%, stage III 14% and stage IV 19.1%. CRC in descending colon and rectum were commonest in females (22.05%) while in males the ascending colon is the commonest (26%).

Conclusion

During this retrospective study, the cancer of colon cancer resulted more frequent versus or than rectum cancer. Males were the most predominant gender in this study and left side-tumors more frequently occurred on patients over 60 years old. We have found varied clinical presentation among our patients, but abdominal pain or discomfort and diarrhea or constipation were the commonest symptoms. Patients with CRC on the sate II has a predominance in number compared to patients diagnosed with other stage of tumors.

Keywords: *CRC malignancy, clinical presentations, side of tumors*

Introduction

Colorectal cancer is one of the leading causes of cancer-related morbidity and mortality in the world [1] and affects males and females despite their socioeconomic status [2-4]. There are estimated 1.93 million new CRC cases diagnosed, and 0.94 million CRC caused deaths in 2020 worldwide. The global new CRC cases is predicted to reach 3.2 million in 2040 [5]. Main risk factors include advanced age, family history, male sex, and lifestyle factors.

Most colorectal cancers are diagnosed after symptoms have developed [6]. One of the commonest modes of presentation of advanced disease are symptoms of large bowel obstruction necessitating emergency treatment, which often leads to an increased morbidity and mortality [7]. Other warning signs and symptoms of CRC are bloody stool, unexplained weight loss, anemia, lower abdominal lump, rectal bleeding, and chronic abdominal pain [8-10].

Presentation of patients suspected with symptoms of CRC is usually to primary care. Most papers on the symptoms of colorectal cancer [6] give an emphasis the need of a specialized assessment and interpretation of symptoms. This is the main reason that most of cases with CRC worldwide are diagnosed only at very advanced stages. Surgery in patients with colorectal cancer who are admitted as an emergency is associated with a perioperative mortality of 20% and morbidity of 50% [11-13]. These patients tend to have late-stage cancer and are often physically frail. Various procedures, including preoperative colonic stenting, have been tried in order to improve outcomes but with varying degrees of success [12, 14].

An alternative way of improving overall outcomes in this patient group is to identify and treat the cancer before it causes symptoms so severe that an emergency admission to hospital is necessary. This study was performed to assess the epidemiological, patients' profile and clinic-pathological characteristics of CRC in Regional Hospital, Durres.

Methods

Setting and Design

This paper presents a retrospective hospital records-based study which included review of patients' records diagnosed with CRC at Surgery ward in Durrës hospital from January 2016 to December 2020. This hospital is the second largest and a referral hospital center in Albania.

Data collection

We have designed a questioner to collect all the necessary information regarding the patients hospitalized in the Surgery ward for CRC with following items: Firstly, we write the socio-demographics data in which are included: patient's name, gender, age, residence. Secondly. We write the histopathological reports in which are included cytopathologic features, site of affection, prominent cytological characteristics the lesions, disease stage, and the presence of any predisposing pathology.

Data analysis

A total of 136 patients were treated for CRC in regional hospital of Durrës city during five years of investigation. Data were analyzed by using SPSS (Statistical Package for the Social Sciences) version 21.0. For categorical data, frequency and percentage were used for expression and continuous data were expressed by using mean and standard deviation. Test such as Fisher Exact, and Chi square were used for comparison. P value < 0.05 was considered significant.

Results

Overall, 136 patients treated in regional hospital of Durrës, the mean age resulted 74±8.2 and minimum and maximum age were 41 years old and 89 years old

respectively. Male with CRC resulted 62.5% (85/136) and female 37.5% (51/136) with ratio man vs female 1.66. We found a strong association between the sex and CRC. Table 1 shows the sociodemographic variables within colon rectal cancer's patients.

Regarding the age among patients with CRC for the period of five years, 6.6% (9 patients) resulted in the age groups 40-49 years old. With the aging, we see an increase in the number of patients with CRC. For the age 50-59 years old the number of cases were 8.1% (11 patients), for age 60-69 years old were 19.8% (27 patients), for age 70-79 years old were 28.7% (39 patients) and for them ≥ 80 years old were 36.8% (50 years old).

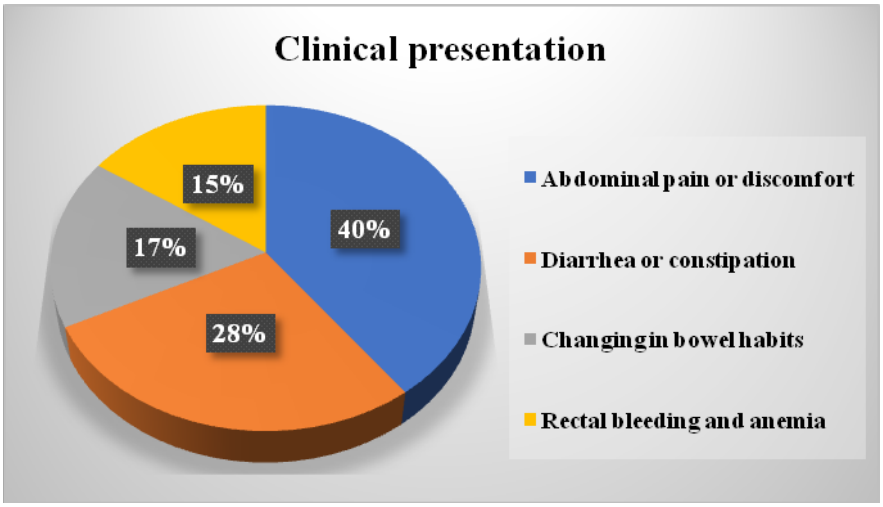
Related to the residence, most patients were from urban area 58.1% (79/136) and them in rural area were 41.9% (57/136). In this case we did not find and association with CRC.

TABLE 1. Sociodemographic characteristic of patients with CRC

Sociodemographic variables	Total number	Percentage	P value
Sex			0.003
Male	85	62.5%	
Female	51	37.5%	
Age groups (year)			0.001
40-49	9	6.6%	
50-59	11	8.1%	
60-69	27	19.8%	
70-79	39	28.7%	
≥80	50	36.8%	
Residence			>0.05
Urban	79	58.1%	
Rural	57	41.9%	

The commonest symptoms were abdominal pain or discomfort 39.7%, diarrhea or constipation 27.9%, changing in bowel habits 16.9%, rectal bleeding and anemia 15.4% (figure 1).

FIGURE 1. Clinical presentation of patients with CRC



The clinical presentations of CRC in relation to gender are presented in table 2. Almost half of them 50.7% are coming in Surgery l ward as an emergency for CRC, 32.4% case are referred by the Primary health care and others 16.9% are coming from outpatients' hospital clinics.

For the site affection of cancer, 97 (71.3%) patients had cancer of colon and others 39 (28.7%) patients had rectal cancer. Most of the patients 47% (64 patients) after clinical diagnostic procedures were presented in Surgery ward determined to have a left-side tumors and 24.3% (33 patients) were presented with right-sided tumors and most of them belonged to younger age group of patients under 60 years old. Sub-site distribution displayed no significant difference in relation to gender. In our study Stage II and I were the main stage of CRC among our patients in percentage 42.6% and 24.3%. Instant cases with stage III stage and IV represented 14% and 19.1% respectively.

Regarding the metastasis at diagnosis 38.2% of them presented distant metastasis, 33.8% local metastasis and 27.9% did not present metastasis. For all clinical presentation male present a predominance versus female and none of them displayed significant difference in relation to gender.

TABLE 2. Clinical presentations CRC relation to gender

Variables	Patients		Sex	
	No	%	Female	Male
Referral site				
Emergency	69	50.7%	25	44
Primary health care	44	32.4%	17	27
Outpatient hospital clinics	23	16.9%	9	14
Site affection				
Right colon	33	24.3%	13	18
Left colon	64	47.0%	23	41
Rectal cancer	39	28.7%	15	24
Stage of CRC (TNM classifications)				
Stage I	33	24.3%	16	17
Stage II	58	42.6%,	19	39
Stage III	19	14%	7	12
Stage IV	26	19.1%.	9	17
Metastasis at diagnosis				
Local	46	33.8%	18	28
Distant	52	38.2%	21	31
None	38	27.9%	12	26

Discussion

The advancements made in understanding colorectal cancer path physiology have led to the increased treatment options. These treatments have effectively inhibited cancer progression and prolonged overall survival. [15, 16]. Even though of so much progress has been made in the field of CRC treatment, this tumor still remains a major problem for public health and humanity itself. CRC has a tendency to increase with advancing age along with fairly rare incidence below 40 years of age, especially in western world [17]. This increasing trend with age is seen as well in our study, most of patients 85.3% were over 60 years old, only 14.7% were under 60 years old.

In 2020, the global CRC incidence rate in men (23.4 cases per 100,000 persons) is 44% higher than in women (16.2 cases per 100,000 persons). In our study we

have also a predominance in men versus female with a strong significance p =0.003.

Geographic factors, including travel time and spatial accessibility to CRC screening providers, may influence adherence to risk-appropriate screening. Rural populations are particularly vulnerable to access barriers, resulting in possible geographic disparities in health services utilization. Available evidence indicates that rural residents are less likely than urban residents to receive CRC screening and to be up-to-date with CRC screening guidelines. Geographic proximity to cancer screening providers may explain differences in screening utilization between rural and urban groups [19]. In this study we have analyzed the residence area with patients with CRC. 58.1% of the living in urban area and 41.9% in rural area. No significant association were found between the residence and presence of CRC to our patients.

The risk of men developing advanced adenoma or cancer is roughly double versus women [20,21]. Furthermore, men develop advanced adenoma and colorectal cancer earlier in their lives than women [21, 22]. A recent study demonstrated that male sex increases the risk to a similar extent as a positive family history of colorectal cancer [23]. The finding in this paper shows that left side of colon is the predominant site of CRC in both sexes. Proximal left and right colon is more common site in males. The main predominance is seen as well for the rectal cancer in male. There are some but non-significant gender differences in presentation and cancer staging in this study. Stage II and I are the most predominant stage and more advanced cancer regarding metastasis, among both genders, are reported in this study. This emphasizes the need to enhance early detection by proper screening [24]. All these changing trends of increase in incidence, detection at young age, advance stage at the time of presentation and variation in sub site distribution are resulting from myriad of factors [17].

Conclusion

During this retrospective study, the cancer of the colon cancer resulted more frequent versus rectum cancer. Males were most predominant gender in this study and left side-tumors has affected the age more than 60 years old. We have found varied clinical presentation among our patients, but abdominal pain or discomfort and diarrhea or constipation were the commonest symptoms. Also, the stage II of CRC has a predominance compared to other stage of tumors. Screening of the population can reduce incidence and death from colorectal cancer. Therefore, prevention and early detection are crucial in order to detect and remove pre-neoplastic adenomas and to detect cancers at early stages.

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Epidemiological profile of patients with depression in Shkoder, Albania

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Abstract

Introduction

Depression is a prevalent mental healthcare problem and a common cause of disability worldwide. As people age, their physical and mental health conditions begin to deteriorate. Late-life depression affects about 6 million Americans ages 65 and older. The aims study was to evaluate the prevalence of depression and associated risk factors in older people living in Shkodra district.

Methods

This is a cross-sectional study based on a mental health screening among the elderly in Shkodra district. All elderly over 60 years who accepted voluntarily to

coming in community center of mental health screening and to be part of this study were recruited for at least 3 years. A standardized questionnaire which measures depression and associated factors were filled for each of them. The software SPSS version 20.0 was used for data calculation. P-values less than <5% were taken as significant.

Results

Over all 138 patients with depression were conducted in this study, the average was 72±11.02std, with min age 61 years old and max 92 years old. Related to the severity of depression, as mild depression resulted 37.7% of participants, moderate 42.08% and severe 20.3%. Almost 42.7% of participant were male and 57.3% were female statistic significant between them p =0.03. Regarding the living area 65.9% living in rural area and 34.1% in urban area without significant association. A significant association were seen between age, gender and sedentary living and depression in multivariate analysis.

Conclusion

Older adults are more vulnerable and severely affected by the mental health especially the depression. Early recognizing of problem due to depression and motivation to participating for a healthy live after retirement may improve their mental life and of quality of life.

Keywords: *Depression, older people, Shkodra district*

Introduction

A mental disorder is a syndrome characterized by a clinically significant disturbance in cognition, emotional regulation, or behavior of an individual that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning [1]. They are often associated with significant distress or disability that affect social, occupational, or other important activities, according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition) [2] and ICD-10 (International Classification of Diseases - 10th Revision). About 90% of psychiatric manifestations are related to nonpsychotic disorders, mainly depressive disorder, including symptoms such as insomnia, fatigue, irritability, difficulty in memory and concentration, and somatic complaints [3].

Depression is a common illness worldwide, with an estimated 3.8% of the population affected, including 5.0% among adults and 5.7% among adults older than 60 years. Approximately 280 million people in the word have depression [4]. Major depression is a commonly occurring, serious, recurrent disorder

linked to functioning and quality of life, medical morbidity, and mortality [5, 6].

Depression results from a complex interaction of social, psychological, and biological factors. People who have gone through adverse life events (unemployment, bereavement, traumatic events) are more likely to develop depression. Depression can, in turn, lead to more stress and dysfunction and worsen the affected person's life situation and the depression itself [7]. Information on the prevalence and correlates of depression does not exist for most countries, but, in more studies the available data indicate that aspects of descriptive epidemiology (e.g., age-of-onset, persistence) are quite consistent across countries. Also, some of consistent socio-demographic correlates have also been found across studies. There are interrelationships between depression and physical health. For example, cardiovascular disease can lead to depression and vice versa [5].

Method

Study design: This is a cross-sectional study based on a mental health screening among the elderly in Shkodra district. All elderly over 60 years who accepted voluntarily to coming in community center of mental health screening and to be part of this study were recruited for at least 3 years.

Study population: Individuals aged 60+ years old that were presented to community mental health center with problems mental disorders were eligible to be part of this study. For all participants (138) we were used the Revised Clinical Interview Schedule for the detection of common mental disorders and epidemiological data to elderly people for the period January 2017 until to December 2019. Gender, age, residence, marital status and condition of living were some of the demographic data. For the classification of the mental disorders, we are based on diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders DSM-5. 5th ed (DSM_V) [8] and in the International Classification of Diseases and Injuries 10th Revision (ICD_10) [9]. A standardized questionnaire which measures depression and associated factors were filled for each of them. Exclusion criteria: Patients with other mental health problem were excluded.

Statistical analysis: Data were analyzed using the statistical package for social science (SPSS) version 20.0, and summarized using descriptive statistics of frequency, as well as mean and standard deviation. We used the chi-square and Fisher exact tests for categorical variables and Student *t* test and Mann-Whitney *U* test for continuous variables. Multivariable logistic regression was used to estimate odds ratios (OR) adjusted for the potential correlation between the risk factors: gender, age, and other risk factors. Differences between samples were considered significant at $p < 0.05$.

Results

Over all 138 elderlies conducted in this study, the min age resulted 61 years old and max 92 years old with average 72±11.02std. In the age groups 60-69 years old resulted 21% (29/138) of patients, in the age groups 70-79 years old resulted 45.6% (59/138) of patients and in the age groups more than 80 years old resulted 33.3% (59/138) of patients with depression. Regarding age, there was a significant difference among age groups and depression for Wald χ^2=21.6 p value 0.01.

Almost 42.7% (59/138) of participant were male and 57.3% (79/138) were female statistic significant between them p =0.03. Regarding the dwelling 65.9% (91/138) living in rural area and 34.1% (47/138) in urban area, we not found a significant association.

Related to the marital status our depressive patients were as below, 3.6% (5/138) were single, 30.4% were widow, 9.4% were divorced and most of them were married 56.4%. for the marital status among our patients with depression, there was a significant difference with 95% CI p value 0,014. Our patients were asked about the monthly income that have in their family (table 1).

TABLE 1. Demographic characteristics of study population

Demographic variables	Total number	Percentage	*P value*
Gender			
Female	79	57.3%	0.03
Male	59	42.7%	
Age (years)		E	0.01
60-69	29	21%	
70-79	63	45.6%	
≥80	46	33.3%	
Dwelling			>0.05
Urban	47	34.1%	
Rural	91	65.9%	
Marital statue			0,014
Single	5	3.6%	
Married	78	56.5%	
Widow	42	30.4%	

Divorced	13	9.4%	
Monthly income			0.0001
Without	9	6.5%	
Social assistance	11	8%	
100-200 lekë* (monthly income)	39	28.3%	
200-400 lekë* (monthly income)	43	31.1%	
More than 400 lekë* (monthly income)	36	26.1%	
Heredity			0.04
Without	97	70.3%	
With	41	29.7%	
Employment status			>0.05
Employment	35	25.4%	
Unemployment	103	74.6%	
Life style			0,004
Living alone	65	47.1%	
Living with family	73	52.9%	
Physical activity			<0,0001
Yes	42	30.4%	
No	96	69.6%	

About 6.5% (9/138) of them referred that did not have a monthly income, 8% (9/138) living with many of assistance given by the municipality of Shkodra, 28.3% (39/138) living with monthly income 100-200 thousand lekë (lekë is Albanian money), 31.1% (43/138) living with monthly income 200-400 thousand lekë and 26.1% (36/138) of patients living with more than 400 thousand lekë. A strong association were seen between the monthly income and the presence of depression among our patients Wald χ^2=54.8 p value 0.0001.

For the heredity or a family history of depression, most of patients 70.3% (97/138) confirmed that did not have and the others 29.7% (41/138) confirmed a familiar with depression. The p value resulted 0.04.

According the employment status, the most predominant patients were retired, consequently we have included in the category of unemployed. So, only 25.4% of our depressive patients resulted in category of employment and 74.6% in category

of unemployment. And in these cases, we did not find an association with the presence of depression.

Life style and physical activity play a significant role in mental health especially for the depression disorder. Our patients referred that living alone in 47.1% of cases and living with family in 52.9% of them. Regarding the physical activity, 30.4% have a daily activity and 69.6% referred a sedentary life. In two cases we found a strong association with depression. P value resulted < 0.05 (table 1).

Based on severity of depression evaluation by medical staff (physicians) of Community Center of Mental Health of Shkodra district, patients in mild depression were 37.7% (52/138) of participants, moderate 41.8% (58/38) and severe 20.4% (28/138). In table 2 we have presented the distribution of severity of depression according the gender of our patients. As seen, female patients have a predominance in the total number and in the same time have a predominance in the moderate 45.6% and severe depression 21.5% is we compared to male for the same severity of depression. Male resulted in 37.5% of patients resulted in moderate depression and 18.6% in severe depression. For the mild depression we have the same number of patients between female and male, but the percentage for female resulted 32.9% and for male 44.1% (table 2).

TABLE 2. Type of depression according to female-male

Type of depression	Total number	Female		Male	
		No	**%**	**No**	**%**
Mild depression	52 (37.7%)	26	32.9%	26	44.1%
Moderate depression	58 (42.0%)	36	45.6%	22	37.3%
Severe depression	28 (20.3%)	17	21.5%	11	18.6%
Total	**100%**	**79**	**100%**	**59**	**100%**

Discussion

Depression is a common and substantial mental health problem in the community worldwide in the past two decades during the era of emergence of Internet and online health information [10]. According to the WHO, an important barrier to effective care for depression is inaccurate assessment and that people who are

depressed are often not correctly diagnosed [11, 12]. The aims study was to evaluate the epidemiological profile of patients with depression in Shkoder district. We have included 138 elderly patients that were diagnose with depression for at least 3 years. More of epidemiological profile are reported by a wide range of literatures worldwide as risk factors for stimulation or severity of persons with depression. So, it has long been known that marital dissatisfaction and discord are strongly related to depressive symptoms, with a very similar patterns for men and women [13-16]. Kessler and Bromet, in their study document that women typically have a two-fold increased risk of major depression compared to men, individuals who are separated or divorced have significantly higher rates of major depression than the currently married, and prevalence of major depression generally goes down with age [5].

Some literatures mention that personal earnings and household income of people is one of most striking aspects of the impairment associated with depression [17-20]. Causal effects of low income on depression have been documented in quasi-experimental studies of job loss [21]. Also, depression is known to be associated with unemployment, most research on this association has emphasized the impact of job loss on depression rather than depression as a risk factor for job loss [21,22].

Based on a multivariate analysis our study shows that some of those factors such as women in the population, aging, marital status, heredity, monthly income, life style and physical activity aggregate the prevalence of depression in elderly people in Shkodra district. On the other hand, we did not find an association regarding the dwelling and employment status.

As we mention before major depression generally goes down with age [5]. In this study we have presented the type of depression within our patients. Most of patients were in moderate depression (42.0%), a high number were in mild depression (37.7%) and few of them were in severe depression (20.3%).

Conclusion

Older adults are more vulnerable and severely affected by the mental health especially the depression. Early recognizing of problem due to depression and motivation to participating for a healthy live after retirement may improve their mental life and of quality of life. On the other hand, application of the epidemiological studies in different population are very important to determine this problem, being very useful and relevant in the decisions and planning of public mental health policies, in the organization of services and also, in the development of prevention and treatment programs.

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Diabetic patients on hemodialysis

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Abstract

Introduction: *Diabetes Mellitus is one of the leading causes of end-stage renal disease (ESRD) worldwide. Good glycemic control plays a key role in reducing the progression of macro and microvascular damage in patients on hemodialysis.*

Aim of the study: *To investigate the prevalence of Diabetes Mellitus in patients with chronic hemodialysis. Evaluation of the prevalence of comorbidities such as Arterial Hypertension, Chronic Heart Failure and Neuropathy in patients with diabetes mellitus undergoing chronic hemodialysis.*

Methodology: *This is a cross-sectional study involving 70 adult patients (age > 18 years) who underwent hemodialysis for at least three months, three times a week and who consented to participate in the study. The study was conducted for a period of one month, January-February 2021, at the Mother Teresa Hospital Center, Tirana, hemodialysis ward. Demographic data (gender, age), good quality HD, height, weight before and after dialysis, causes of kidney failure, other diseases such as Diabetes Mellitus, cardiovascular disease and neuropathy were obtained using medical records of patient records.*
Results: *The study included 70 patients. Of them 65.7% were male. The mean age of patients treated with chronic HD was 52 ± 15. The prevalence of Diabetic nephropathy in our study was 15.7%. In the group of patients where the primary disease for ESRD was Diabetes, the percentage of concomitant diseases was: Hypertension 10%, Chronic Heart Failure 10% and Neuropathy 5.7%. In the rest of the patients the percentage of concomitant diseases was: Hypertension 55.7%, Chronic Heart Failure 45.7% and Neuropathy 7.1%. Patients with DM had 6 months to 10 years of HD treatment time.*
Conclusions: *We do not have a statistically significant relationship between the*

occurrence of diseases such as Arterial Hypertension, Chronic Heart Failure and Neuropathy and patients with DM treated with chronic hemodialysis.

Keywords: *diabetes mellitus, hemodialysis, hypertension, chronic heart failure, neuropathy.*

Introduction

There are two main types of dialysis:

1 – Hemodialysis
2 – Peritoneal dialysis

Hemodialysis is the purification of blood from metabolic products which are filtered and removed through a semi-permeable artificial membrane which is located outside the body. The word 'hemodialysis' comes from the Greek language and consists of the words 'hemo' which means 'blood' and 'dialysis', which means 'release from something'. The process of hemodialysis replaces some of the functions of the kidneys. This process helps remove the end products of protein metabolism (urea and creatinine, etc.), also regulates the amount of electrolytes and acidity in the body. Through this process can not be replaced kidney function which is responsible for the secretion of the hormone responsible for the normal functioning of the bone marrow (erythropoietin), regulates blood pressure by (renin, bradykinin, kallikrein, prostaglandin) and vitamin D3 activation. Peritoneal dialysis is the exchange of fluids and dissolved substances between the peritoneal capillaries of the blood and the peritoneal cavity through the 'membrane' which consists of a vascular wall, interstitium, mesothelioma. The movements of matter follow the physical laws of diffusion and connective transport, while the movements of fluids are related to osmosis. The transfer of dissolved substances across the peritoneal membrane occurs through two major mechanisms, diffusion and convection. The rate of transport of diffuse dissolved substances is proportional to the difference in concentration between blood in the peritoneal capillaries and fluid in the PD. Substances pass from the blood into the peritoneal capillaries, into the filled cavity of peritoneal dialysis, where they must pass at least three structures that can provide resistance: the capillary wall, interstitial tissue, and cellular mesothelial layers. Diffusion and ultrafiltration occur in two directions throughout this resistance. Diabetes Mellitus is a metabolic syndrome with multiple etiologies. It is characterized by chronic hyperglycemia associated with a disorder of

carbohydrate metabolism that results from a defect in the secretion or action of insulin, or as a combination of both factors together. It is also characterized by specific microvascular complications, macrovascular complications due to accelerated atherosclerosis, and various other complications, including neuropathy, pregnancy with complications, and an increased chance of infections. Regarding the diagnostic criteria of diabetes, it is accepted as diabetes if the sober (venous) glycemia is 126 mg / dl (7.0 mmol / l), or if the occasional plasma glycemia is 200 mg / dl (11.1 mmol / l)) two hours after taking 75 g of glucose by mouth. In asymptomatic persons, performing the test in only one case is not sufficient to establish the diagnosis (e.g. to begin treatment of Diabetes). This should be confirmed after at least one more test is performed the following day.

Epidemiology & etiology

Diabetes (mainly type 2) is an increasingly common cause of end-stage renal disease (ESRD) in all countries, and accounts for almost 40% of dialysis patients in the US and 20% in Europe. Patient survival is much worse compared to patients without diabetes, with a high number of patients dying within the first 3 months of dialysis. The leading cause of death is cardiovascular disease. The prognosis is better for patients who have had a transplant.
Most non-renal complications of diabetes will continue to progress after starting dialysis, including:

- arterio-coronary disease
- retinopathy
- cataracts
- cerebrovascular disease
- peripheral vascular disease
- peripheral neuropathy
- sexual dysfunction
- depression

The increasing prevalence of diabetic neuropathy among patients with end-stage renal disease (ESRD) occurs mainly from the increasing prevalence of type 2 diabetes in the general population. The incidence of end-stage renal disease (ESRD) among patients with type 1 diabetes is decreasing as a result of better management of blood pressure, blood glucose levels, and the use of ACEI / ARBs. Diabetic patients on dialysis have higher vascular comorbidity than non-diabetic patients.

Study

Objective

- Evaluation of the prevalence of Diabetes Mellitus in patients with chronic hemodialysis.
- Evaluation of demographic and laboratory data in diabetic patients with chronic hemodialysis.
- Evaluation of the prevalence of comorbidities and complications in diabetic patients with chronic hemodialysis.
- Nursing care and development of plans for the education and management of diabetic patients with chronic hemodialysis.

Methodology

The cross-sectional study was conducted within the period January-February 2021. Our study included 70 patients who were presented at the Mother Teresa Hospital Center in Tirana.

Demographic data (gender, age), good quality hemodialysis, weight before and after dialysis, causes of kidney failure, concomitant diseases such as Diabetes Mellitus, cardiovascular disease and neuropathy were obtained using medical records of patients.

Routine laboratory data evaluated monthly for each patient using standard automated techniques were also obtained using medical data.

Criteria

Inclusion criteria : adult patients (age > 18 years), who performed hemodialysis for at least 3 months, 3 times a week and who gave consent to participate in the study. Exclusion criteria : patients with acute kidney injury, malignant diseases, major surgery, septic condition.

Results

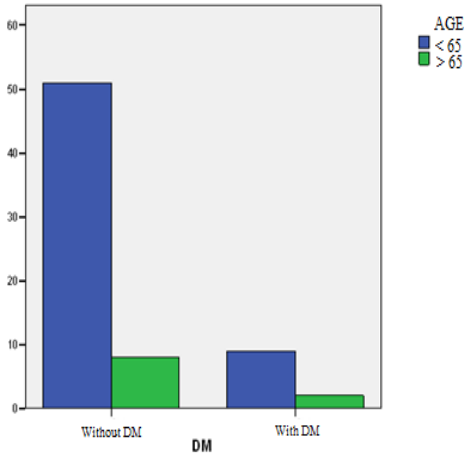
1. Prevalence ratio between diabetes mellitus and age

			AGE		Total
			< 65	≥ 65	
DM	No	Number	51	8	59

		% of total	72.9%	11.4%	84.3%
	Yes	Number	9	2	11
		% of total	12.9%	2.9%	15.7%
Total		Number	60	10	70
		% of total	85.7%	14.3%	100.0%

TABLE 1

The mean age of patients undergoing chronic hemodialysis treatment was 52 ± 15, male/female ratio 46/24 (65.7% / 34.3%). The prevalence of Diabetes Mellitus in the group of patients taken in the study was 11 patients (15.7%). In the whole group 10 (14.3%) patients were ≥ 65 years old and only (2.9%) of them were diabetic.



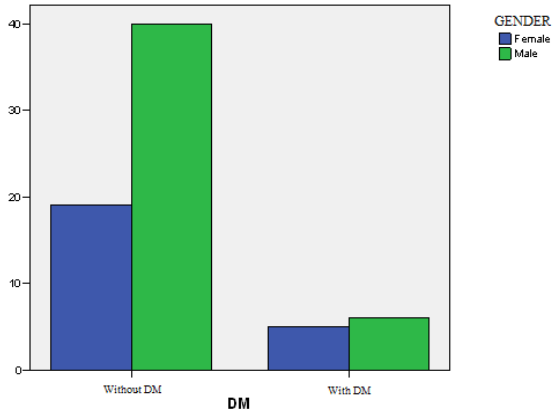
Prevalence ratio between diabetes mellitus and gender

The male/female ratio in the group of diabetic patients with chronic hemodialysis was 6 (8.6%) / 5 (7.1%) but had no statistical significance.

			Gender		Total
		Female	Male		
DM	No	Number	19	40	59
		% of total	27.1%	57.1%	84.3%
	Yes	Number	5	6	11
		% of total	7.1%	8.6%	15.7%

Total	Number	24	46	70
% of total	34.3%	65.7%	100.0%	

TABLE 2

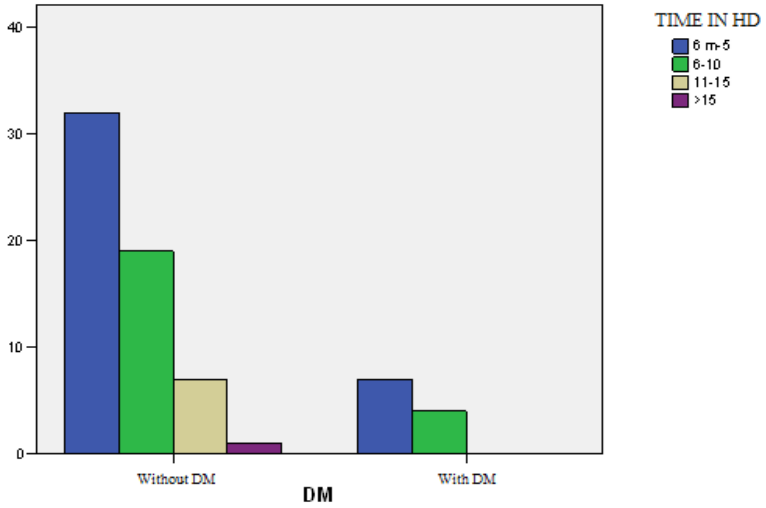


3. Prevalence of diabetes mellitus and time of treatment with hemodialysis

Patients with diabetes mellitus had 6 months to 10 years being treated with hemodialysis.

			TIME IN HEMODIALYSIS TREATMENT				Total
			6 M-5 YEARS	6-10 YEARS	11-15 YEARS	>15 YEARS	
DM	No	Number	32	19	7	1	59
		% of total	45.7%	27.1%	10.0%	1.4%	84.3%
	Yes	Number	7	4	0	0	11
		% of total	10.0%	5.7%	.0%	.0%	15.7%
Total		Number	39	23	7	1	70
		% of total	55.7%	32.9%	10.0%	1.4%	100.0%

TABLE 3



4. Prevalence of diabetes mellitus and hypertension in patients with chronic hemodialysis

Hypertension was present in 65.7% of the group of patients treated with chronic hemodialysis. 10% of patients with diabetes mellitus also had arterial hypertension for which they were treated with medications of several classes.

			HTA		Total
			Without HTA	With HTA	
DM	No	Number	20	39	59
		% of total	28.6%	55.7%	84.3%
	Yes	Number	4	7	11
		% of total	5.7%	10.0%	15.7%
Total		Number	24%	46	70
		% of total	34.3%	65.7%	100.0%

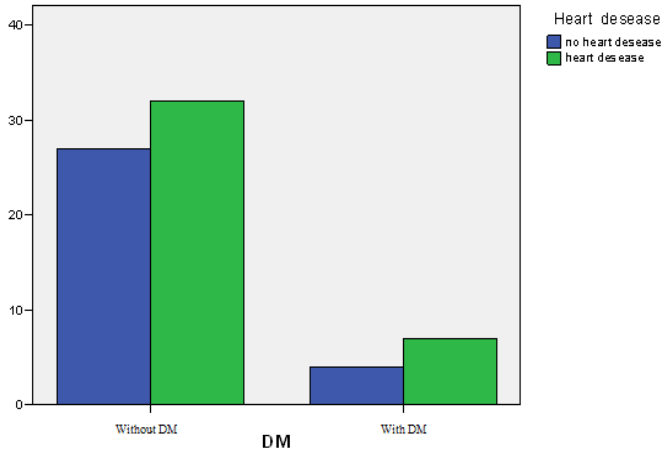
TABLE 4

5. Prevalence of diabetes mellitus and chronic heart failure in patients with chronic hemodialysis

Chronic Heart Failure (CHI) was present in 55.7% of the group of patients on chronic hemodialysis treatment. 10% of patients with diabetes mellitus also had CHI.

			CHI		Total
			Without CHI	With CHI	
DM	No	Number	27	32	59
		% of total	38.6%	45.7%	84.3%
	Yes	Number	4	7	11
		% of total	5.7%	10.0%	15.7%
Total		Number	31	39	70
		% of total	44.3%	55.7%	100.0%

TABLE 5



6. Prevalence of diabetes mellitus and neuropathy in patients with chronic hemodialysis

Neuropathy is a significant complication in diabetic patients and in patients with chronic hemodialysis.

			NEUROPATHY		Total
			Without NEUROPATHY	With NEUROPATHY	
DM	No	Number	54	5	59
		% of total	77.1%	7.1%	84.3%
	Yes	Number	7	4	11
		% of total	10.0%	5.7%	15.7%
Total		Number	61	9	70
		% of total	87.1%	12.9%	100.0%

TABLE 6

7. Differences between patients with DM and without DM in hemodialysis

	DM	N	Mean	Std. Deviation
Age	No	59	53.32	12.331
	Yes	11	53.82	14.247
Weight at the end	No	59	67.6271	14.41162
	Yes	11	69.4545	16.71145
BMI	No	59	23.7758	3.84643
	Yes	11	25.5127	5.35973
Years of hemodialysis	No	59	6.051	3.6338
	Yes	11	4.909	3.0068
HgB	No	59	10.671	1.5063
	Yes	11	10.600	1.5944
AST	No	58	24.95	19.805
	Yes	11	26.45	20.978
ALT	No	58	33.60	37.845

	Yes	11	30.27	28.886
Serum iron	No	59	78.74	53.625
	Yes	11	59.91	42.677
Cholesterolemia	No	59	167.58	38.675
	Yes	11	180.82	37.727
Triglyceridemia	No	59	152.10	70.990
	Yes	11	205.09	142.168
Uremia	No	59	159.88	36.264
	Yes	11	149.18	37.032
Creatinemia	No	59	9.778	1.9012
	Yes	11	8.227	1.5938
Na	No	59	135.08	2.615
	Yes	11	133.18	2.272
K	No	59	5.475	.8130
	Yes	11	5.300	.8379

TABLE 7

Disscusion

This study included 70 patients who were presented at the Mother Teresa Hospital Center in Tirana. Patients were adults (age >18 years), who underwent hemodialysis for at least 3 months, 3 times a week. Patients with acute illness, malignancy, major surgery and septic condition were not included in the study. The mean age of patients undergoing chronic hemodialysis treatment was 52 ± 15. We note that the average age of patients treated with chronic hemodialysis in our country is lower compared to data from studies in America where the average age is 56 ± 15.

The male / female ratio was 46/24 (65.7% / 34.3%). So we have approximately the same percentage with the data of other studies which show that men are more at risk than women to be affected by chronic kidney disease, consequently to be treated with hemodialysis.

The prevalence of diabetes mellitus in the group of patients taken in the study was 11 patients (15.7%). We note that the prevalence of diabetes mellitus in our country is lower compared to the prevalence in America. In the whole group 10 (14.3%) patients were ≥ 65 years old and only 2 (2.9%) of them were diabetic. The male/female ratio in the group of patients with diabetes mellitus and treated with chronic hemodialysis was 6 (8.6%)/5 (7.1%), but there was no statistical significance.

Hypertension was present in 65.7% of the group of patients treated with chronic hemodialysis. 10% of patients with diabetes mellitus also had arterial hypertension for which they were treated with medications of several classes. Chronic Heart Failure (CHI) was present in 55.7% of the group of patients on chronic hemodialysis treatment. 10% of patients with diabetes mellitus also had CHI. It was concluded that only 5.7% of the patients in the study group treated with chronic hemodialysis were positive for both diabetes mellitus and neuropathy. Since the number of patients taken in the study represents a small percentage of the population treated with dialysis in Albania, we can say that the study is relatively limited and as such its results should be taken with reservations.

Conclusion

Based on the collected data, we do not have a statistically significant relationship between the occurrence of diseases such as Arterial Hypertension, Chronic Heart Failure and Neuropathy and patients with DM treated with chronic hemodialysis.

Recommendations

Most units start at higher GFR levels than for non-diabetic patients (10-15 mL / min to 20 mL / min) as uremia symptoms may appear earlier, and renal function tends to deteriorate more rapidly in patients with diabetes. This is also important to avoid malnutrition. When determining when dialysis should begin, the degree of impairment of renal function should be closely reviewed. The use of ACEIs and ARBs, reduction of proteinuria and good control of blood pressure can result in very slow rates of deterioration of renal function. However, dialysis should be started earlier in documented patients with rapidly deteriorating renal function, especially those patients with persistent severe proteinuria and poor blood pressure control.

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Oncology and a time of crisis. Science, complexity, ethic values, and incertitude. An argumentative essay

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Abstract

Who faces a neoplastic disease is more bewildered than in the past, in spite of the improvement of the possibility of cure and priority attributed to this subject by the health institutions and medicine, compared to few decades ago. Nevertheless, disorientation is increasing due to many factors, also beyond those of the scientific and welfare context of cancer and is related to the general background of crisis. The landscape of crisis involves the changes occurring in both epistemic and contextual values, and methodology of science at large, as well as those particular of the medical field, including oncology. The perceived ltoss of reliability of universal laws and the limits of general theories, in favor of the conception that elementary events concurr to outcomes, makes the scientific appraisal more probabilistic than deterministic. This framework of "complexity" is characterized by non-linearity in the causal links, opacity of the investigated subject, and emergence of the phenomena we observe and analyze. In oncological medicine, the present deterministic "gold standard" of the random comparative trials, grounding the so-called evidence-based medicine (EBM), and the guidelines for clinical management - although being the most reliable resource - are critically considered. In fact, new "systems biology" approaches, based

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on big data analysis and advanced statistical methods, may bridge the gaps between the biological/pre-clinical and clinical investi-gations, hopefully allowing "precision" or "personalized medicine". Artificial Intelligence is consi-dered an indispensable tool to this regard. However, also this approach couldn't effectively work without a sound, general theory on cancer, presently not at hand. Moreover, all of the above contexts suffer of the pressure of industry, interested in the economic impacts. On the other hand, the costs of cancer management, increasing at a higher rate compared to care results, motivate the health authorities to take physicians out of the personal professional and trust relationship with the patients. In this situation, oncologists have mainly to cooperate – often in a subordinate position - with bureaucratic professionals for the implement-tation of pre-established guidelines. As a consequence, patients are institutionalized and deprived of the reassuring presence of an entrusted doctor, thus experiencing enhancement of distress and solitude feelings. This connects with crisis in the social domain, defined as a strength that conquers autonomy without a manifest theory of itself, thus without a project, but with an impact capacity producing high perceivable effects. This existential landscape characterizes the present time as "the age of incertitude". Complexity and uncertainty thus exist also in society. The social pact between individual and state (relinquishing of a part of freedoms by the former in exchange for security by the latter) is compromised, and the indeterminate nature of the crisis obscures any solution. The statements on the right to health are perceived as abstract formulations, generating mistrust in institutions and further distress. From the physicians' point of view, this must not imply loss of responsibility, but even more so imposes a great ethic commitment. They must operate as best as they can, despite being aware that the desired effects could be vanished by context. This is a further subject to consider in the relationship between medicine and health institutions: the former must preserve its own statutory purposes of prevention and care of diseases in the best possible way, even if the inherent epistemic complexity and the contextual background makes this task more problematic than in the past. Indeed, medicine should cooperate with health institutions, developing the necessary attitudes given the present social background, but not in a subordinate role, as far as its intellectual and operative domains are concerned. Another factor of crisis must be considered, that is, communication. A diagnosis of cancer, an ominous event, induce to look for any glimmer of hope and entrusts false believes or pseudo-scientific results, because these appear easier to comprehend and promise clear-cut good results, compared to the scientific argumentations, hard to understand and expressed in terms of probability. The present cultural background of society is affected by the lack of humanistic education, that is, what grounds critical thinking. Biomedical researchers and physicians, sometimes suffering of the same deficiency, regrettably have also other faults, that is, defects in intellectual honesty such as egocentrism and self-reference that can generate mistrust in science on the long run. After examining

these items in the light of the available data and authoritative sources of the related literature, we reached the conclusion that a "new alliance" can be promoted between oncological science and society, based on "the humanism of science". Improving intellectual honesty by the biomedical community, as well as critical thinking also in society is mandatory. This can be obtained with suitable educational programs in high school and university. Cultural empowerment, and a realistic approach to the epistemic and ethics issues on cancer may mitigate the related individual and social discomfort and - hypothetically - improve clinical outcomes through the increased patients' compliance to therapy and prevention programs.

Key words: *Oncology, Complexity, Time of Crisis, Crisis in Science, Crisis in Medicine, Crisis and Society, Communication in Science, Communication in Medicine*

Introduction. The present landscape.

Presently, it is a sound data item that oncological medicine has achieved increasingly success-ful results over the last decades, due to the progress of medical research. However, this matter-of-fact should be quantitively regarded in the light of statistics, from a critical point of view. The trend of the improvement of the 5-year overall survival (OS) rates for all cancers is less, in the first 15 years of the present century, compared to the last 25 of the former one.

Five-year OS rates, in fact, increased by 15 % from 1974 to 2001 in USA, for all cancers and in all ethnic groups [1], whereas a more far-reaching study, on a global scale, shows for the period from 2000 to 2014 an improvement of the age-standardized 5-year OS hardly approaching 5 %, with rare exceptions, for the most incident neoplasms, presumably representa-tive of the impact of innovative diagnostic and therapeutic practices. The 5-year OS for breast carcinoma in Northern Europe and USA is unchanged over these 15 years.[2] The two studies cannot be directly com-pared, due to the relevant differences in methodology and sample sizes, but the trend here conside-red clearly emerges, even if in coarse terms. The above remark should be framed taking in consideration the different growth in cost trends of cancer research, its products, and cancer care: the differential, for the two math functions, is less for results than for costs. (Figure 1).

This forethought is fundamental, when addressing the relationships between medical knowledge and society in general and also, ultimately, physicians and patients. In fact, as early as in 2011, a special oncology commission of *The Lancet* journal stated: "... *The cancer profession and industry should take responsibility and*

not accept a sub-standard evidence base and an ethos of very small benefit at whatever cost; rather, we need delivery of fair process and a real value from new technologies", thus formally establishing the necessity of reliable and quantitative evaluations of health outcomes and costs, on the grounds of both equity and affordability. [3] As a deviant and ominous consequence, many health institutions have equivocated these sacrosanct principles, in an interpretation that may be read as: "medicine is a too serious issue to be entrusted to physi-cians", similar to the famous sentence on war by Georges Clemenceau (*La guerre! C'est une chose trop grave pour la confier à des militaires*). This conceptual drift ties also in misinter-pretation of multidisciplinerity, that is, not in the correct sense of a cooperation among specialists in different medical and related scientific disciplines, but including instead bureaucracy and health politics professionals with an equal (or even higher-order status). More, health institutions declare as a statutory paradigma the centrality of patient, thus implicitly assuming the role of an impersonal deuteragonist for themselves.

However, from the point of view of patients, when they need cancer treatment, the perception of this complex and not fully understood situation is that their personal problem is just one - and not necessarily the most important - among other ones. Their incertitude and sense of loneliness is enhanced, as a result, shouldn't they have a main reference point in a trusted doctor inside the institution. This point will be addressed more in depth in a following section on the subject of medical responsibility: here we just underline that a medical doctor must be educated "*to acquire leadership, teamwork, and communication skills*" besides a medical scientific background. [4] In fact, the medical profession is based not only on epistemic grounds: the present substantial evolution of sciences, not only in the biomedical field, requires a reflection on updating education regarding both purely scientific issues, and the contextual values of objectivity and intellectual honesty as well, to the purpose of correct relationships between science scholars and society. [5]

On the other hand, there are many negative aspects of the widespread diffusion of too general, apodictic or uncontrolled information, or even false data concerning cancer that permeate people, and confuse those individuals whose general education is defective, in that lacking the development of critical sense. Firstly, confusion exists regarding the difference between the concepts of "welfare" and "health". WHO and UNICEF, during the forty years since their first Conference in Alma-Ata (1978), to the last one held in Atama (2018), maintained the following statement: primary care and essential public health are the core of integrated health services, to be pursued through multisectoral policy and action, and empowerment of peoples and communities. Pope Francis, in his message on the occasion of the last conference, stated: *"Health is not a consumer*

good, but a universal right: let us unite our efforts so that health services are available to all" (Pope Francis - @ pontifex # Health ForAll). These affirmations, that are indisputable in the domain of ethics of values, nevertheless are relevant mainly insofar as meant directed to political authorities in terms of welfare improvement. Unfortunately, these statements may be manipulated on the grounds of affordability and opportunity, and objectivity may be often underevaluated or sidelined. On the other hand, when improvement of health is considered from a medical point of view, what is pursued is the absence of disease, that should be identified as a commitment to prevent and cure diseases under the epistemic perspectives of science, and the moral allegiance to the principles hinted at before (objectivity and intellectual honesty) besides personal responsibility.

The theme of objectivity deserves further consideration. According to The Stanford Encyclo-pedia of Philosophy: "*Scientific objectivity is a characteristic of scientific claims, methods and results. It expresses the idea that the claims, methods and results of science are not, or should not be influenced by particular perspectives, value commitments, community bias or personal interests, to name a few relevant factors. Objectivity is often considered as an ideal for scientific inquiry, as a good reason for valuing scientific knowledge, and as the basis of the authority of science in society*". [6] However, these authors recognize that presently the distinction between epistemic and non-epistemic values is strongly debated even within the official epistemological sphere. Nevertheless, we have to consider here the extreme "dark side of postmodernity" in the general framework of society, often taking hold against sound scientific disclosures and maintaining alternative and ontological confused point of views regarding genuineness, natural energy, narrative reports of empiric experiences, etc., and even trusting in questionable characters and believes borderline to witchcraft. Among these last misconceptions, is the use of the Cuban blue scorpion venom and shark cartilage against cancer. Sadly, some of other deviant tendencies have been uncritically considered by health institutions, on the grounds of political opportunities and a misunderstood interpretation of democracy. Examples are the Italian "Metodo Di Bella" for cancer therapy [7] and the worldwide ideological movements against infectious diseases vaccinations [8] and GMOs in agriculture. [9]

Thus, the present landscape of the relationships between medicine (and science in general) and society is problematic due to the above factors, that further exacerbate the discomfort and incertitude of the oncological patients. In the present paper, we consider these issues to this regard, in the framework of crisis in sciences, society, and communication, with the aim to promote a cultural operation for basing appropriate strategies to be adopted for countering a tendency towards a decline in a fundamental aspect of our civilization.

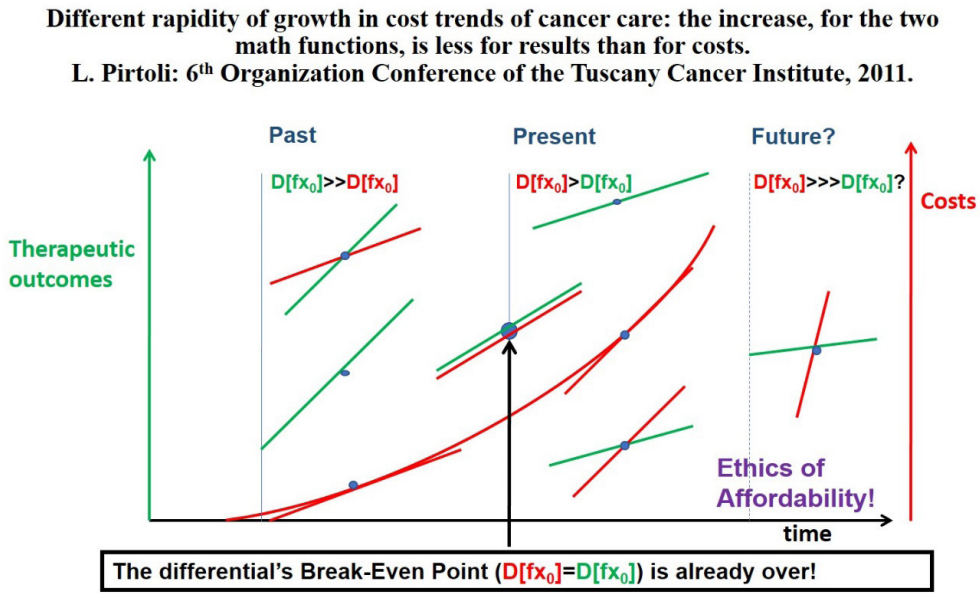

FIGURE 1. Different rapidity of growth in cost trends of cancer care.

The crisis in Science and Medicine

In a recent essay, [10] one of us (SZ) synthetically retraced the crisis of the fundamentals in the hard sciences, remarking that even Euclid has hesitated in applying his fifth postulate (regarding the unique parallelism of one straight lines with respect to another one lying on the same plane, up to infinite). Briefly, the first non-Euclidean geometry arose – in fact - when all the Euclid's postulates were deemed acceptable but the fifth one, thus admitting the possibility of an infinite number of parallel lines passing through a point external to another straight line (hyperbolic geometry). It must be remarked that this statement has anticipated the principle of denial of the insights, that is, their devaluation, even of those that Karl Popper included in "the context of discovery". An insight, in fact, is just the beginning of a hypothetic-deductive process, which needs a factual demonstration through experiments (context of confirmation). Similarly, regarding mathematical sciences, the twentieth century started with a general loss of the reliability of intuitiveness, that had grounded the millennial issue of natural numbers, and the coming of a substantialistic conception of mathematics, that is, the set theory: a purely functional and relational vision of numbers. In physics, the turning point has come from the revision of the Newtonian mechanistic, and is focused on thermodynamics. This last domain,

in fact, doesn't refer to the mechanic energy of bodies (i.e.: kinetic energy) but deals with their inherent energy, due to molecular motion, that is, depending on physical quantities implying statistical values, somehow exiling of pure deterministically approachable relationships. The overall context of complexity in this field has been synthetized by Ilia Prigogine (a Nobel Prize-awarded scientist for studies on these issues) as follows: "*Mais dès le XIX siècle nous avons l'idée d'évolution, en biologie, en sociologie, et cette idée d'évolution domine le XX siècle … mais qui dit évolution dit qu'il faut qu'il y ait une différence entre l'avant et l'après, qu'il ait apparition de nouveauté ou je dirais plutôt d'événement. En somme, je dirais que l'histoire intellectuelle de l'Occident a été dominée par le conflit entre la notion de loi et la notion d'événement*". [11]

Therefore, elementary and irreversible events cooperate for complex phenomena. Accordin-gly, the concept of evolution - since the Darwinian intuition, to the gene mutation-based present interpretation - dominates the realm of biology, entailing the passing of time, that is, before and after an impacting event. The recent, intellectual history of the western countries was ruled by the conflict between the notions of "universal law" and "event". Presently, this last is prevailing in science at large, after the coming of quantum mechanics, which is inherently and uncompro-misingly probabilistic. Science becomes increasingly probabilistic and decreasingly determi-nistic, at the present time.

However, complex biological systems (included those addressed by cancer biology) are characterized by nonlinearity in the causal relationships, opacity regarding interpretation, and "emer-gence" of the functional phenomena we observe. Approaching complexity in biology entails both the context of discovery and that of confirmation (as we will deal with after in more detail) thus requiring in different situations the pure probabilistic and math modelling methodology for the observed and collected data, as well as the deterministic setting of experiments. Somebody maintains that in both cases the *a priori* of a hypothesis lying on a general theory is indispensable, [12] but presently this concept is rarely contemplated as a general state-ment for research in bio-medicine, particularly in oncology.

As a matter of fact, in any case, the present gold standard of the medical community, as a refe-rence for clinical practice, is Evidence Based Medicine. This definition was used by GH Guyatt thirty years ago in an editorial, [13] in which he introduced the concept that medical practice should no longer be based on established authorities (e.g.: textbooks, senior lecturers or physicians) but instead on the critical appraisal of recent publications of relevant studies related to the particular clinical situation. In fact, this new approach was made possible, already at the time, by the availability of web access to medical literature data bases (MEDLINE in this report). This process was subsequently,

formally systematized for medical education purposes in a *JAMA* paper, authored on behalf of the Evidence-Based Medicine Working Group, established in the meanwhile. [14] Only later this approach was applied to clinical research, grounding the procedure of random comparative trials (RCTs) for innovative therapeutic disclosures versus the present standards of care. A less diffused implementation of RCTs was carried out for diagnostic tools, due to difficulty in selection of reliable endpoints and for ethic reason: there is a widely shared belief – perhaps questionable - that the most advanced diagnostic technology should be employed whenever available. Presently, the clinical guidelines of the preeminent medical associations indicate the "level of evidence" of the procedures, ranging from the lowest (case reports) to the highest ones (RCTs), placing in between the expert panels' opinions and the retrospective studies. This pragmatic setting is successful and many outstanding results came from RCTs for therapeutic agents in oncology. However, the above framework for medical science doesn't systematically include as a prerequisite the value of results from the pre-clinical research. At the present time, in fact, there is a huge quantity of drugs and other agents, shown as very promising after experimental studies in cell cultures, animal models and *in silico* elaborations, deserving clinical validations that cannot be accomplished, due to lack of funding in many cases. Thus, translational research from bench to bedside through RCTs is usually implemented when industry decides to support it, often following in-house, preclinical studies, and not necessarily due the perspectives of a high therapeutic effectiveness measured by reliable endpoints (OS or disease-free survival) but, e.g., progression-free survival, i.e.: the disease respond to therapy just as long as the drug is administered. That is, drug-centered, instead of patient-centered trials. Further, market prospects prevail: a small prognostic advantage, just beyond the limit of statistical significance in a very prevalent pathology, may be valuated more than a great prognostic improvement in less frequent diseases, from an economic standpoint.

More, the RCT process is inherently reductionistic: the impact of the supposed "determinant" agent is tested in the clinical experiment, in the context of strict patient selection, methodology and endpoints. It may happen that the results are not coherent with the "real world" of the common clinical practice. Anyway, the process is labor-intensive, time-consuming and costly. The evidence for a better outcome, compared to the standard procedure, is achieved after a long-time lapse since patients' recruitment.

Despite all this, the results of RCTs provide the best evidence on which medical practice can be based. However, by no means their deterministic approach is adequate to the increasing complexity of the bio-medical knowledge. An attempt to cope with the problem of complexity in cancer was proposed

by two eminent biomedical researchers at the transition to the present century. [15] Taking in account that previous research had shown that tumorigenesis is a multi-step process, during which multiple genetic alterations drive the malignant evolution of the cells, and that cancer incidence is age dependent, it was hypothesized that a limited number of rate-limiting stochastic events grounds the whole transformation, according to a previously developed model. [16] This hypothesis is reductionistic too, but Hanahan and Weinberger deemed it as formally coherent to the Darwinian evolutionism "*in which a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells*". On these grounds, and considering in depth the evidences of the available body of scientific results at the time, they highlighted the convergence of known, genetically-driven, molecular mechanism into the famous "six hallmarks of cancer", that is: self-sufficiency in growth signals; insensitivity to anti-growth signals; evading apoptosis; limitless replicative potential; sustained angiogenesis; tissue invasion and metastasis. The authors predicted that the improvement in definition of the genome-wide gene expression profile, during the coming twenty years since the formulation of their hypothesis, will allow a mechanistic knowledge of the cancer process on which mathematical modelling could predict prognosis and success of therapy according to the principles of rational sciences. Fourteen years later, instead, Weinberger admitted that the above theory has side-stepped the domain of signal transduction biochemistry, as well as tumor microenvironment (including immunity and inflammation), and also that the supervening age of "omics" (that is, besides genomics and transcriptomics: proteo-mics, epigenomics, kinomes, methylomes, glycomes, and matrisomes) could introduce engulfing amounts of data. This author pessimistically wondered about the possibility of achieving a mechanistic insight into such a complex system (systems biology) through computational algorithms, given that "*we lack the conceptual paradigm and computational strategies for dealing with this complexity*".[17] That is, a very similar point of view compared to that one expre-ssed from a different domain (computer science) and a more general point of view on "big-data" by other authors, [12] already quoted. Thus, we have yet to acknowledge the absence of a general theory on cancer, that might hamper the success of computational sciences in disentangling the "emergence" of neoplasia from its biologic complexity. In spite of these perplexities, once again, industry keeps an eye on this issue: an economic estimate of 150 billion euros was made in 2019 and reported by press organs, for the implementation of artificial intelligence (AI) in health programs within 2026. Thus, we should see anyhow the related impact in the oncological field, even if probably with the intellectual reserve already expressed for clinical experimentations. However, a pessimistic future vision seems not justified in

practical terms: a decreasing trend is presently shown in cancer-specific, age-adjusted mortality rate by a very recent epidemiologic study, with a substantial, progressive gain in averting cancer deaths since 1991 (more significant after 2000). [18] This is mainly attributable to prevention, even if treatment breakthroughs have contributed, such as new drugs in hematological malignancies, together with the coming of immunotherapy and target therapy also in other tumors. The "traditional" strategy against loco-regionally confined cancers, based on surgery, radiotherapy, adjuvant or neo-adjuvant chemio-therapy, and hormone therapy, presently achieves definitive cure in many cases, that can be further improved by targeting actionable molecular mechanisms by monoclonal antibodies, tyrosine kinase inhibitors and other selective drugs. Moreover, even in advanced presentations traditional and innovative agents can obtain long-lasting survival rates without severe side-effects, making cancer a chronic disease in many of these patients. This is, e.g., the case of immunotherapy. Molecular target therapy still needs more reliable markers for prognostic prediction and selection of suitable patients, but biomedical research has made considerable advances in this field, even if precision (or personalized) medicine presently is not yet a full-accomplished goal. Resistance to inhibitors of the cellular growth ultimately develops, given the well-known ability of cancer cells to respond to chronic drug administration by adapting their signaling pathways, [19] and due to the genomic instability, but also in this case some progress can be observed in recent results.

Ultimately, what the practitioner should keep in mind is that, in the vast majority of cancer patients, there is a reliable strategy for coping with their clinical situations, should it be aimed at a definitive cure or an effective, hopefully long-lasting achievement of a good quality of life, even if the "magic bullet" against cancer is not available. A sound and updated background of medical culture, experience, assertiveness and intellectual honesty, in relating with patients within a trusting relationship, are usually effective in containing anxiety by reducing uncertainty regarding the nature of their disease. A humanistic education is helpful in this context, and by no means a physician should behave and speak like a technocrat.

The crisis for Society, and Communication in Science and Medicine

In 1942, in the midst of the second world war, Albert Camus (a French writer and philosopher) wrote: *"Ce monde en lui-même n'est pas raisonnable, c'est tout ce qu'on en peut dire. Mais ce qui est absurde, c'est la confrontation de cet irrationnel et de ce désire éperdu de clarté"*.[20] This existential landscape continues to dominate

the present time, that we could call "the era of incertitude", a trait on which philosophers and sociologists converge. This characteristic is present at many levels, from the loss of the epistemic certitudes – previously considered – to the fall of metaphysic believes and the decline of any kind of transcendence. The concept of complexity covers the transformations also in the social, economic, and cultural fields, with the already mentioned features of absence of linearity in the causal relationships, opacity in assessing dynamics, and emergence of functional phenomena whose interpretation is very hard to achieve. Significant events may aggregate into "clusters", with effects that can be additive, synergic, or even contrasting each other. Human actions sometimes generate relevant events, in good and evil according our present moral categories of civil solidarity, but are not absolute determinants of these consequences. However, from our point of view this doesn't imply loss of responsibility, but instead – and even more so – imposes an even greater ethic commitment. It is not a trivial statement: any person must operate as best as she can, despite being aware that the desired effects could be vanished. As Max Gismondi wrote in a paper dealing with realism in political sciences: "*The ethics of responsibility requires one to take responsibility for one's actions, ... knowing all the while that circumstances beyond one's own control may alter the outcome and have unintended consequences*". [21] This world vision, like it or not, is the fundamentally tragic one that dominated the contemporary age since the half of the last century and – not paradoxically - enshrines the ethically correct action as aimed at positive purposes. Ideas and actions of more or less recent historical characters (such as some state leaders in the first half of the last century) have had a strong negative impact on their time, or subsequently. They have the responsibility of all the related consequences, even if synchronous or metachronous co-factors must be taken in account, without exempting them.

The present crisis, generally attributed to economic and financial factors traceable back to the interventions and responsibilities of identifiable persons, however, has acquired an imper-sonal historical substance that involves social and individual domains. As Zigmund Bauman (a distinguished sociologist and philosopher) maintained, this crisis is substantially a strength which gains autonomy without an appearing theory of itself, thus without a project, but with an impact that produces strongly perceivable effects.[22] Complexity, uncertainty, and the lack of a general theory, thus exist also in social sciences. As a consequence, the fundamental social pact between individual and state (relinquishing of a part of freedoms by the former in exchange for security by the latter) is compromised, and the indeterminate nature of the crisis obscures any perspective of a solution. In this framework, the statements on the right to health addressed in the introductive paragraph of this paper may be perceived by people as abstract formulations, generating mistrust in institutions.

This is a further reason grounding the necessity to distinguish medicine from health institu-tions: the former must preserve its ontologic fundamentals, that is, its own statutory purposes of pursuing prevention and care of diseases in the best possible way, even if its present epistemic complexity and the contextual background makes this task more problematic than in the past. Indeed, medicine should cooperate with health institutions, developing the updated attitudes that are necessary, given the present social background, but not in a subordinate role, as far as the intellectual and the operative domains are concerned.

The role of communication is fundamental to this regard, including the related skills that should be the subject of particular bio-medical education programs. Atul Gawande, a surgeon and researcher in the field of public health, said: "*Science . . . is a commitment to a systematic way of thinking, and allegiance to a way of building knowledge and explaining the universe through testing and factual observation. The thing is, that isn't a normal way of thinking. It is unnatural and counterintuitive*". [23] In fact, when society keeps down the certitude of values because these are perceived as unreliable, it seems to get into a loss of critical thinking. "*The tragedy may be not in Cassandra's speaking, but in Troy's inability to hear* ", according to the Gawande's speech. A diagnosis of cancer, that is generally understood as an ominous event, may induce to look for any glimmer of hope and entrust false believes or pseudo-scientific results, e.g., spread throughout the Web, because these appear easier to comprehend and promise clear-cut good results, compared to the scientific argumentation that, contrarily, is hard to understand. Moreover, the possible outcome of the disease is expressed in terms of probability, instead of certitude. The scientific community, including biomedical researchers and physicians, regretta-bly has its faults in this scenario, that is, egocentrism and self-reference. Defects in intellectual honesty in reporting results of personal studies, emphasized beyond their real value in the context of public occasions like interviews, generate mistrust in science on the long run. Gundula Bosch, a philosopher involved in scientific education, maintained the importance of implementing "soft skills" when defining the educational curricula of researchers, in an recent editorial in *Nature.* [5] She wrote that is important to "*get students to reflect on the limits of science, and where science's ability to do something competes with what scientists should do from a moral point of view*", and remarked "*that researchers who are educated more broadly will do science more thoughtfully, with the result that other scientists, and society at large, will be able to rely on this work for a better, more rational world*".

Thus, the necessity exists to reevaluate on a realistic background intellectual honesty by science, including the biomedical field, and critical thinking by both scientists and society in general. This may ground a new alliance of medicine and society, intended to that Ilia Prigogine – already quoted – called "*the humanism of science*".

Conclusions

In our argumentation we tried to focus on the main elements of crisis in science - with particular regard to the biomedicine and clinical aspects of oncology - and crisis in society, underlining the uncertainty aspects grounding both of them due to a common factor, that is, the demise of general principles and theories and the prevailing appearance of complexity in a deeply impacting occurrence, such as cancer, in the present individual and social existential landscape. The unfavorable dynamics of the improvement of outcomes versus costs for cancer management contributed to the subordination of medicine to the politic and bureaucratic establishment in health institutions, thus constraining the personal responsibility of physicians, who are deprived of the relationship of trust with patients, who suffer incertitude and sense of loneliness as consequences. This situation fits into a social background of disenchantment, due to the perception of the poor performance of the social pact, the indeterminate nature of the crisis and the lack of a reliable solution in sight for many existential problems, including cancer. Communication is presently inadequate in disentangling confounding elements, relevant for the distressing experience of cancer patients, that is, ambiguity in fields such as: welfare and health; epistemic and contextual values in science; methodology of the biomedical research; conflicts of interest in clinical studies, less-than-expected results in cancer care. All of the above converge into misinterpretation or even mystification of medical science.

After examining these items in the light of the available data and authoritative sources of the related literature, both in the biomedical and epistemological fields, we reached the conclusion that a "new alliance" can be promoted between oncological science and society, based on "the humanism of science". That is, improving intellectual honesty by the biomedical community, as well as critical thinking of both sides, scientists and physicians, and society. This can be obtained on the grounds of suitable educational programs in high school and university, included in these last both science and humanistic departments' teaching programs. An approach to the subject of cancer based on cultural empowerment, faced through a realistic approach to the related epistemic and ethics issues, may be effective in mitigating the related individual and social discomfort and - hypothetically - in improving clinical outcomes through the increased patients' compliance to therapy and prevention programs.

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