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Electrophysiological alterations of the brain during epileptogenesis

T. Szilágyi, Júlia Metz, K. Orbán-Kis

Sindroamele epileptice sunt printre cele mai frecvente boli neurologice. Numeroase fenomene electrice sunt asociate cu epilepsie, dintre care oscilațiile de frecvență înaltă (HFO) și spikurile intericțale. HFO poate fi reprodus în mai multe paradigme experimentale și/sau clinice și pare că este asociat cu sincronizarea normală sau patologică a sistemului nervos central. Spikurile intericțale reprezintă o activare sincronizată, morfologic bine delimitată, tranzientă a unei populații neuronale. Relația dintre HFO, spikurile intericțale și crizele epileptice nu este pe deplin elucidată în ciuda faptului că spikurile intericțale sunt prezente la marea majoritate a pacienților epileptici.
În acest articol prezentăm pe scurt principalele modificări electrofiziologice la nivel celular și de rețea implicate în epileptogeneză.
Cuvinte cheie: epilepsie, electrofiziologie, oscilații de frecvență înaltă, spikuri intericțale

Epileptic syndromes are one of the most frequent neurological diseases. There are several electrical phenomena associated with epilepsy among which high frequency oscillations (HFO) and interictal spikes. HFO can be reproduced in a large number of experimental and/or clinical paradigms and it seems to be related to normal and pathological synchronization of the central nervous system. Interictal spikes are morphologically defined, episodic, transient discharges of a neuronal population. The relationship of HFO, interictal spikes and epileptic seizures has not been elucidated completely yet although interictal spikes are present at the vast majority of epileptic patients.
In this article we present a short overview of the current knowledge regarding the single cell and network level electrophysiological alterations involved in epileptogenesis.
Key words: epilepsy, electrophysiology, high frequency oscillations, interictal spikes

Epilepsy is one of the most frequent neurological illnesses. Although usually the disease is not lethal, the loss of consciousness can lead do dangerous situations. Psychopathological complications (hiposexuality, memory loss, depression, etc.) and psychosocial factors are also extremely important. The diagnosis of epilepsy still carries a social stigma that can affect all aspects of everyday life including driving, employment, and educational opportunities. Thus epilepsy affects the quality of life for both patients and relatives and causes an important socio-economic burden for the society.

Recurrent unprovoked seizures constitute the minimal criteria for the diagnosis of epilepsy, but this illness cannot be considered and treated as a homogenous disease. Often patterns of symptoms can be recognized which point to the factors influencing seizure type and severity. Therefore instead of the simple denomination: epilepsy, it is better to use the term: epileptic syndromes. Even today the classification of epilepsies is based more on clinical observation than a precise cellular, molecular or genetic understanding of the underlying pathophysiological mechanisms. Although new therapeutic opportunities are developed quite frequently it has been a major debate whether these affect or not the primary alterations in the brain. At the present time all therapeutic approaches are considered anticonvulsive and not antiepileptic[44, 19] as none of the currently used medications in the daily practice could prove its efficacy in this regard.[31] Furthermore the effectiveness of surgical interventions is highly debated.[10] Thus, at the moment, the treatment of epileptic patients aims the amelioration of the quality of life by reducing the number and/or the severity of convulsions. These data emphasize that despite the growing number of drugs developed for epileptic patients our understanding regarding the mechanisms of epileptogenesis is still quite limited and hopefully further research will provide new insights of the disease and will create new and effective antiepileptic drug targets.

At the very foundation of all epileptic syndromes lies the hyperexcitability of a population of neurons with transient abnormally synchronized activity. The aim of this article is to give an overview of the new

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results regarding the altered brain electrical activity during epileptogenesis.

Seizures can be classified clinically into two categories: partial and generalized. Partial seizures originate in a small group of neurons that constitute a seizure focus; therefore the clinical symptoms depend on the location of the focus within the brain. If a partial seizure progresses to other brain regions, the patient may lose consciousness and tonic-clonic convulsions may appear. In this case the symptoms are classified as secondarily generalized seizure. Partial seizures may be preceded by auras. Generalized seizures begin without a preceding aura or focal symptoms and involve both hemispheres from the onset. These two seizure types have different pathophysiological substrates. In this article we will focus on the partial seizures.

The defining feature of partial seizures is that abnormal electrical activity originates from a seizure focus, which is a small collection of neurons that trigger enhanced excitability. Increased excitability may result from altered cellular properties or altered synaptic connections or both. The phases in the development of a partial seizure can be arbitrarily divided into the interictal period, followed by neuronal synchronization, seizure spread, and finally secondary generalization.

First, we should have a look on how electrical activity in a single neuron is altered during the generation of a seizure. Usually neurons in a seizure focus have a stereotypic and synchronized electrical behavior called the paroxysmal depolarizing shift (PDS).[50] The PDS consists of a sudden large, long lasting depolarization (20-40mV, 50-200ms), which triggers a train of action potentials. The PDS is followed by an afterhyperpolarization. Both the depolarizing and hyperpolarizing phases are shaped by the intrinsic membrane properties of the neurons together with the excitatory and inhibitory synaptic inputs they receive. The depolarizing phase is generated mainly by the activation of excitatory glutamate receptors and the opening of voltage gated Ca^{2+} channels.[37] The afterhyperpolarization results from the activation of calcium- and voltage-gated K^+ channels and GABA mediated Cl^- and K^+ currents.[50] Disynaptic feed-forward inhibition is a widespread connectivity pattern in the cerebral cortex which generates an excitatory postsynaptic potential (EPSP) followed by an inhibitory postsynaptic potential (IPSP). Therefore PSD can be considered a gross exaggeration of the normal neuronal activity.

Many other factors influence the excitability of neurons within a seizure focus, e.g. neurotransmitter and potassium uptake by glia cells, action of membrane ion pumps to remove ions that accumulate due to the excess electrical activity. An increase in the extracellular potassium concentration depolarizes the cells therefore enhances excitability.[28] Calcium signalling through glia networks may be a contributing factor too.[22]

As long as the abnormal electrical activity is restricted to some thousands of neurons within the seizure focus there are no clinical manifestations. During the interictal period the abnormal activity is restricted to the seizure focus by the afterhyperpolarization. The GABAergic inhibitory interneurons provide a powerful inhibitory surround. During the development of a focal seizure the afterhyperpolarization gradually disappears and the surround inhibition is overcome. As the seizure begins to spread, the repolarization fails even in neurons beyond the original focus and the cells start to generate high frequency action potential trains. Intense activity results in the failure of GABA response even if the interneurons remain viable.[17] Whether this failure is caused by pre- or postsynaptic mechanisms is not yet clear. Excess activity can trigger action potential trains in neurons that project back to the neurons in the seizure focus, therefore can provide a positive feed-back mechanism for self sustained activity. Structural changes may also contribute to the altered excitability. In some cases loss of certain neuron subpopulation is observed,[23, 42] or very often reorganization of the dendritic tree and synaptic connections or modification of the axonal structure is seen.[43, 32] The alteration of receptor and ion channel density is also described in the literature.[35, 32]

During epileptic seizures besides the synchronization of neuronal activity oscillations of variable frequencies were described.[36, 51] It's a well known fact that a number of physiological processes, such as memory formation, are characterized by both the synchronization of neuronal activity and the appearance of network oscillations. These oscillations are grouped according to their frequency band: slow oscillations, δ (0.5-4 Hz), θ (4-7 Hz), α (7-13 Hz), β (13-30 Hz) and γ (30-80 Hz), ripple (80-200 Hz) and fast ripple (200-600 Hz). The origin of oscillations of different frequencies as well as the conditions in which they appear seems to be various and presumably they have distinct functions in the normal operation of the central nervous system.[6]

Short epochs of high-frequency oscillations (HFO) are considered physiological phenomena implicated in hippocampal information processing and synaptic plasticity.[12] HFO does occur spontaneously in the hippocampus *in vivo*[7] and *in vitro*.[16] HFOs were suggested to reflect synchronous neuronal firing and their occurrence was reported both in epileptic human patients and animal models of epilepsy.[48, 21] As HFOs are often found at the seizure onset[3] they are assumed to contribute to its initiation.[15, 46] Furthermore a specific class of HFOs (above 250 Hz, termed fast ripples) was proposed to reflect the formation of pathologically interconnected neuronal networks contributing to epileptogenesis.[5, 45] *In vitro*, nonsynaptic mechanisms, like gap junction coupling and field effects were proposed to be sufficient for the development of HFOs and synchronously firing neuronal aggregates.[3]

Synaptic activity was shown to contribute to ictal activity;[29] however its impact on HFO formation has not been elucidated sufficiently. Recently the temporal relationship of HFO and status epilepticus was described in the dentate gyrus of the rat[4] as well as the fact that HFO may precede a seizure-like event in a *in vitro* epileptic experimental paradigm.[27] In conclusion one can state that HFO can be reproduced in a large number of experimental and/or clinical paradigms and that HFOs seem to be related to normal and pathological synchronization of the central nervous system.

As neuronal aggregates become synchronized the summated currents become larger and can be seen as abrupt changes from the baseline activity (sharp waves or spikes). Interictal spikes (IS) are morphologically defined, episodic, transient discharges of a neuronal population. During an interictal spike, local neurons undergo a synchronous, paroxysmal depolarization of the membrane potential that triggers a series of action potentials.[38] The relationship of interictal spikes to seizures is not as straightforward as one would expect, based on their reliable presence in the EEG of epileptic patients. Spikes are observed in the setting of an increased probability for spontaneous seizures. In local-onset epilepsy, interictal spikes are localized to the epileptic brain region[24] and frequently disappear after resection of the epileptogenic brain tissue or spontaneous resolution of epilepsy.[49] Thus, generally it is believed that interictal spikes are associated with an increased risk for spontaneous seizures, though some contradictory reports exist – post IS inhibition being protective as it maintains a low level of excitability.[14, 33] Interictal spike frequency increases after rather than before a seizure.[39] Furthermore, the mean interictal spike frequency does not correlate with seizure frequency or response to medication[20] although there is a clear relationship between inhibitory and excitatory interactions and epileptic activity.[52]

These findings do not support the "damp kindling" theory of interictal spikes, in which each spike represents the unsuccessful initiation of a seizure, just as multiple sparks might be required to ignite damp kindling. If that were the case, then spike frequency should be more strongly correlated with seizure probability. One could argue that how frequent is the kindling might be a more important determinant of seizure frequency than the number of ignition trials, in which case, the conditions that favor the evolution of a spike into a seizure would be the feature most highly correlated with seizure frequency. Some seizures start with a "sentinel spike",[13] so this idea cannot be discarded, but there is currently not enough data to support this mechanism. Another possible reason for the coexistence of these two types of synchronous activity is causation: seizures could cause spikes, or spikes could cause seizures.

This hypothesis has been studied but not elucidated especially because although IS does appear both in human and experimental animal models of epilepsy almost immediately after traumatic brain injury the first seizure usually occurs several months to several years after the initial injury.[42] When we consider the mechanisms for epileptogenesis, it is important to remember this slow time scale. A possible explanation could be found in the normal plasticity of the brain. During development, many circuits in the brain self-organize with the aid of synchronous bursts of activity that is nearly identical to interictal spikes.[25, 26] New axon branches grow and synaptic connections are formed in the epileptic brain (processes called sprouting and synaptic reorganization) by the growth of axons back into their network of origin (a local synaptic circuit called recurrent excitation).[41] Increasing and unmasking of positive feedback is associated with spontaneous, synchronous activation of the sprouted neural networks *in vitro*[47] and *in vivo*.[8] Suppressing activity in the experimentally injured cortex can reduce the incidence of subsequent epileptiform activity.[32] Furthermore, there is a clear role for spikes in other forms of synaptic plasticity, such as long-term potentiation (LTP) of synaptic strength. Conditions for induction of LTP at synapses between pyramidal cells include synchronous action potential generation in presynaptic and postsynaptic neurons or postsynaptic depolarization and presynaptic glutamate release. These conditions are satisfied during interictal spike activity.[9, 31] Thus, interictal spikes are likely to both guide the growth of sprouting axons and increase and maintain the strength of the newly formed recurrent connections in the epileptic network.

Despite the fact that patients who have had many seizures are most likely to have many more, there is no clear human evidence for the century-old hypothesis that seizures beget seizures.[2] One explanation for this lack of evidence is the possibility that excesses of any synchronous network activity (including interictal spikes) increase positive feedback[18] and thus the probability of seizures. Interictal activity can thus be considered to develop and maintain the epileptic network between seizures. If interictal spikes are epileptogenic, this would dramatically alter the goals of anticonvulsant therapy. More generally, recognition that interictal activity may develop and sustain the epileptic condition suggests a new antiepileptogenic strategy: suppression of interictal spikes.

In order to study these phenomena two major experimental approaches exist: *in vitro* and *in vivo* models of epilepsy. *In vitro* methods, beside their obvious advantages, possess some major disadvantages as well: (1) there is no possibility for direct conclusions on evolutionarily aspects of the seizures and (2) the progression of seizures to different brain areas (in the process of generalization) cannot be followed. These handicaps can be avoided by the use of *in vivo* experimental models of epilepsy. There are innumerable animal models of epilepsy or epileptic seizures, but only few chronic models of epilepsy are currently used

for studies of epilepsy or epileptic seizures. Chronic models include methods, in which epilepsy or epilepsy-like conditions are induced by electrical or chemical stimulation in previously healthy (non-epileptic) animals, mostly rats. In the most widely used models recurrent spontaneous seizures develop after a self-sustained status epilepticus (SSSE, 6-20 hours), which is elicited either by sustained electrical stimulation of the hippocampus, amygdala, etc or by the systemic or local administration of the excitotoxic glutamate analogue kainate[34] or the cholinergic (muscarinic) agonist pilocarpine.[35] These post-status epilepsy models are characterized by the fact that neuropathological changes reminiscent of mesiotemporal sclerosis (encountered in many patients with temporal lobe epilepsy) and recurrent spontaneous seizures develop after the status. Typically, the spontaneous seizures first occur after a latency period following the SSSE of about 3–4 weeks. The duration of the induced status epilepticus is critical in this respect. In order to induce development of epilepsy, most investigators do not interrupt the status, so that the rats exhibit focal or generalized seizures for hours. These models also present major problems: high mortality, controversies regarding the human relevance of an epilepsy developing on a seriously damaged brain, high frequency of seizures (several/day) that means a sever form of epilepsy, rarely encountered in humans and last but not least these methods produce important discomfort to the animals. In order to avoid these disadvantages, more modern approaches has been developed. Kindling is a model in which there is a progressive increase in electrographic and behavioral seizure activity resulting from repeated application of short electrical stimuli to limbic brain regions such as amygdala or hippocampus. Kindling is widely used as a model of temporal lobe epilepsy, because the clinical phenomenology of the complex-partial and secondarily generalized seizures and the pharmacology of these seizures are very similar to the clinical condition. Although kindling is commonly used as a model of elicited (stimulation-induced) seizures, in view of the kindling-associated phenomena, e.g. progressive increase in seizure severity and duration, decrease in focal seizure threshold, development of spontaneous seizures upon further stimulations, and neuronal degeneration in limbic brain regions, kindling is certainly a chronic model of epilepsy which offers the advantage that seizures can be elicited at will.

A better understanding of the fundamental processes that lie at the basis of epileptogenesis is essential for the improvement of the treatment of these patients which in turn leads to the amelioration of the quality of life. Deciphering the mechanisms that lead to the hyperexcitability of neuronal populations during the development of epilepsy is a critical part of this effort which should lead to the development of effective antiepileptic (not anticonvulsive) drugs and changes in the therapeutic strategies for epileptic patients.

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Metastatic Colorectal Carcinoma (mCRC) Specific Therapy, VEGF Inhibition

L. Landherr

Morbiditatea cauzată de cancerul intestinului gros se află pe locul doi după cancerul pulmonar. De-a lungul timpului doar terapia chirurgicală şi chemoterapia bazată pe 5-fluorouracil (5-FU) au însemnat puţină posibilitatea de vindecare, dar în cazul metastazelor rata de supravieţuire abia depăşea 6 luni. În ultimul deceniu pe lângă introducerea unor noi chemoterapeutice cu efect a apărut şi terapia biologică ţintită iar media ratei de supravietuire a bolnavilor cu metastaze s-a ridicat peste 30 de luni.

Colorectal cancer is 2nd only to pulmonary cancer in mortality due to tumor related illness. For many years, only surgical intervention and 5-fluorouracil based chemotherapy offered slim chances of recovery, however with metastatic disease, survival was mostly limited to less than 6 months. In the past few years, in addition to newer generation chemotherapeutic agents, there have been breakthroughs in targeted biological agents that have increased average survival times to over 30 months.

In 2006 in Europe a total of 412,900 colorectal cancer (CRC) illnesses and 207,400 CRC deaths were reported. Unfortunately, Hungary is one of the leaders of CRC morbidity and mortality as can be seen in Table 1.

Table 1. Colorectal cancer (C18-21) frequency and deaths standardized by age per 100,000 people in surrounding countries by sex (approximated values).[6]

Country	frequency/100.000 of population		Deaths/100.000 of population	
	Men	Women	Man	Women
European Union (EU25)	59.0	35.6	6.5	15.6
Austria	57.6	30.9	29.3	15.6
Czech Republic	94.4.	46.0	51.0	24.1
Croatia	57.0	36.9	40.7	18.1
Romania	40.7	25.1	23.5	14.5
Serbia and Montenegro	41.0	30.4	24.9	14.9
Slovakia	87.1	42.6	43.3	24.4
Slovenia	69.0	36.3	39.6	17.3
Ukraine	41.7	27.0	27.6	15.8
Hungary	106.0	50.6	54.4	26.7

CRC is metastatic in more than 50% of cases and with this course of disease, the prognosis is not favorable. The disease, without definitive care, leads to a poor prognosis of about 5-6 months, even with the best supportive care. Chemotherapy with 5-flourocuracil can prolong the prospective outcome to about 11 or 12 months.

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Initially 5FU is given by bolus than later by long term infusion, than in combination with other drugs (levamisol, methotrexate, folin acid) its effects are potentiated by "biomodulation". In recent years irinotecan and oxaliplatin have proven the most effective treatments for 5FU resistant CRC. Various protocols have been developed with these agents plus 5-FU/FA (5-FU/FA + irinotecan / IFL – regimen / FOLFIRI – regimen, 5-FU/FA + oxaliplatin / FOLFOX – regimen /, 5-FU/FA + oxaliplatin + irinotecan / FOLFOXIRI /, stb.). The oral fluoropyrimidines have also appeared on the market (UFT, eniluracil, capecitabin) which are equally as potent as 5-FU/FA. If we combine capecitabin, oxaliplatinin and irinotecan we potentiate their effects (XELOX, XELIRI). FOLFIRI or FOLFOX are standard therapies for advanced colorectal cancers. These agents have close to the same effectiveness however their toxicities differ. With newer disease progression, the 2nd line drug with patients receiving oxaliplatin is irinotecan, with patients receiving irinotecan is oxaliplatin in addition to the 5-FU/FA (or oral fluoropyrimidin). The triplet of fluoropyrimidin, oxaliplatin and irinotecan increases survival times. The most favorable outcomes in treatment have been demonstrated by targeted biological agents. These agents target the proliferating tumor cells and inhibit their signal cascade. The transmembrane tyrosine kinase receptors that dimerize upon ligand binding and induce an intracellular signal cascade play an integral role in cell proliferation, vascularization, dedifferentiation, and apoptosis inhibition. The receptors can be targeted in 2 different ways, by either targeting the ligand or the extracellular portion of the

receptor with a monoclonal antibody, or by targeting the intracellular portion with a "small molecular" tyrosine kinase inhibitor (TKI). *The vascular endothelial growth factor receptor* (VEGFR) and the epidermal growth factor receptor (EGFR) inhibiting agents are equally as effective in mCRC treatment, increasing the survival time to over 28 months.

In this two part review article, we shall explore the VEGF and the EGF signaling pathways and the latest results of mCRC biological agents efficacy, which is detailed in several English and Hungarian language medical papers.[1,4,16,18,22,23]

VEGF (Vascular Endothelial Growth Factor) Signaling Pathway

Solid tumor growth is closely linked to angiogenesis. Malignant tumor linked neo-angiogenesis is determined by the interaction of the pro and anti-angiogen factors. Angiogenesis is measured by microvessel density (MVD), which is inversely related to advanced CRC survival. Initial stages of angiogenesis are governed by VEGF and other proangiogenesis factors that help in the degradation of the intestinal tissue matrix, allowing the endothelial cells to migrate into the area and proliferate. Immature and randomly situated vessels start to develop but do not mature into a differentiated vascular architecture. VEGF is the highest potential angiogenesis promoting factor of the family of six factors. Among these factors the VEGF-A is the most researched therefore it is called simply VEGF. The VEGF family of factors is activated by the dimerization of the receptor by a ligand, initiating an intracellular signal cascade. Of the 3 VEGF receptors, VEGFR-2 is the most important target for VEGF-A. Under physiological conditions, VEGFR can be demonstrated on endothelial cells and angioblasts. In addition, VEGFR can be found on the surfaces of malignant tumor cells and its increased presence on colorectal tumor cells creates a worse prognosis.[21]

VEGFR-1 plays an integral role regulating the embryonic and physiological development and migration and differentiation of angiogenesis. It is found in CRC in its activated form, and the ligands help in tumor spread and proliferation. VEGFR-2 mediates the most "downstream" effects of VEGF-A (vascular permeability, endothelial cell proliferation, invasion, migration, survival, and apoptosis inhibition). VEGFR-3 plays a role in lymphangiogenesis and its expression on tumor cells is correlated to the spread of tumor cells to nearby lymph nodes.[17] In addition, VEGF has an important role in autocrine function of tumor cells. VEGF expression is mediated by hypoxia through the accumulation of hypoxia inducible factor-1 alpha, which is a target of VEGF. Tumor suppressor genes (PTEN, VHL) mutations lead to the overexpression of VEGF that result in the "upregulation" of VEGFR-1 and VEGFR-2.[8]

A plethora of growth factors (eg. EGF) can also induce VEGF expression.

Several drugs have been developed to inhibit the function of VEGF (eg, anti-VEGF antibody like bevacizumab, or soluble VEGFR) and VEGFR (eg, anti-VEGFR antibodies, small molecular tyrosine kinase inhibitors, ribozym), however it has been observed that not all tumors react to anti-angiogen therapy. This resistance to therapy is a current topic of research. Irregardless, success of treatment of metastatic CRC by antiangiogen agents (bevacizumab) is independent of MVD levels and VEGF expression.[12]

Results of treatment of mCRC by bevacizumab

Bevacizumab (Avastin®), an anti-VEGF humanized monoclonal antibody, blocks the natural VEGF ligand from binding the VEGFR and inhibits the initiation of the intracellular signal transduction cascade. By itself, it is barely effective, however in combination with the traditional chemotherapeutic agents, it has significant advantages (Table 2).

Table 2. Chemotherapeutic agents and bevacizumab combinations in the treatment of mCRC.

Drug	treatment line	cases	PFS (month)	OS (month)
5FU/LV + bevacizumab [14]	1.	209	*5.5 vs 9.2 p=0.0002*	*12.9 vs 16.6 p=0.16*
IFL vs IFL + bevacizumab[10]	1.	815	*6.2 vs 10.6 p<0.0001*	*15.6 vs 20.3 p<0.0001*
FL or IFL vs FL + bevacizumab [13]	1.	490	*5.6 vs 8.8 p<0.0001*	*14.6 vs 17.9 p=0.008*
FOLFOX4 or XELOX vs FOLFOX4 or XELOX + bevacizumab [3, 19]	1.	1401	*8.0 vs 9.4 p=0.0023*	*19.9 vs 21.3 p=0.0769*
FOLFOX vs FOLFOX + bevacizumab CAPOX vs CAPOX + bevacizumab „TREE-trial" [9]	1.	360	*8.7 vs 9.9* *8.3 vs 10.3*	
FOLFOX vs FOLFOX + bevacizumab [6]	2. Fluoropyrimidin and Irinotecan refractory	829	*4.7 vs 7.3 p<0.0001*	*10.8 vs 12.9 P=0.0011*
IRI + cetuximab vs IRI + cetuximab + bevacizumab [20]	3. and 4. line Irinotecan refractory	74	*4.0 vs 8.5 P=0.003*	-

When compared to classic 5FU/LV treated patients, patients treated with a combination of 5FU/LV and bevacizumab had a better progression free survival (PFS) and overall survival (OS).

When FU/leukovorin and irinotecan boluses were administered along with bevacizumab, the tumor reaction rose from 34.8% to 44.8% and the PFS and OS was lengthened by 4-5 months[10], and the general condition of the both the patients with a response and without a response was significantly better.

In 2007 the results of the NO16966 research was published: 1401 patients received FOLFOX4 (continuous and bolus administration of 5-FU, leukovorin, oxaliplatin) or XELOX (capecitabin, oxaliplatin) with or without bevacizumab. In the early period of the research, it was evident that the XELOX combination was not any less effective than then the FOLFOX4 combination ("non-inferiority").[3] The addition of bevacizumab increased the average PFS from 8 to 9.4 months, which can seem negligible, but is statistically very significant, and the OS increased marginally as well.[19]

In the previous research, the diminished effectiveness can be explained by the patients discontinuing treatment with bevacizumab for reasons other than progression of disease. If we account for this fact, than the modified results of FOLFOX4 and XELOX treatment are as follows: with bevacizumab 10.4 months, without bevacizumab 8.1 months median PFS can be demonstrated. As a result, research has been initiated to develop a protocol for the optimal time of treatment with bevacizumab (eg, CAIRO3).

As a 2nd line treatment, addition of bevacizumab to FOLFOX resulted in significant increases of PFS and OS.[3]

In restricted therapies (eg, irinotecan-refractory cases), cetuximab and bevacizumab combinations have further increased the survival time without disease recurrence.[3]

It must be taken into account, that patients refractory to treatment with irinotecan and oxaliplatin, treatment of 5FU/LV plus bevacizumab is hardly effective, with reaction to treatment of only 1-4%.

VEGF or anti-receptor treatments are well tolerated by patients in most cases.[3] The most common side effect of bevacizumab treatment is increased blood pressure. However this can be well managed with potassium channel blocking antihypertensive agents. Thromboembolism, gastrointestinal perforations and severe bleedings are rare, but severe complications of treatment. Increased wound healing has also been demonstrated. Side effects of vatalanib treatment were fatigue, headache, nausea and vomiting and thrombosis.

VGFR tyrosine kinase blocking "small molecules"

VGFR tyrosine kinase blocking small molecules are low molecular weight, ATP simulating proteins that attach to the growth factor receptor tyrosine kinase domain's ATP catalyst attachment site and prevent the downstream signal transduction cascade. There are several such agents under clinical trials at this time that localize to various tumor cells[17]: Vatalanib, semazanib, sunitinib, sorafenib, cediranib, ZD6474 (Zactima), SU 6668, AZD2171, AEE788, AG-013736, etc. For GIST and kidney cell tumors, sorafenib and sunitinib, for HCC sorafenib, and for small cell lung cancer Zactima have proven effective. Sunitinib attaches to the VEGFR, PDGFR, c-KIT, RET, and FMS-like tironsine kinase 3. It was successful in prolonging the survival time of mCRC patients who had been previously treated (but not received bevacizumab). Vatalanib that acts on VEGFR, c-KIT, and PDGFR was tested along with a combination of FOLFOX or FOLFOX4 in the CONFIRM 1 and 2 trials. 1168 patients with the former combination, and 885 patients with the later combination were tested, unfortunately, the results were inconclusive, however, it is to be noted that 12% had a decrease in disease progression risks, however it did not reach the significance value ($p = 0.118$).[7,15] The lack of definitive results is still under investigation. It is interesting to note that those patients who had an increased level of Lactate Dehydrogenize (LDH), a hypoxia marker that induces the secretion of VEGF, had better results with the treatment of Vatalanib.

DISCUSSION

The use of angiogenesis inhibiting agents for the treatment of cancer patients is unquestionable. Oncologists have a variety of options to treat patients with various combinations of chemotherapeutic agents and anti-VEGF agents. Still, there are numerous unanswered questions with regard to anti-VEGF treatments.[11] Anti-VEGF treatments are much more complicated that originally believed. Used as monotherapy agents, they have not proven effective in prolonging patient survival. However they were effective as first-line combination treatments of metastatic colorectal and breast tumors. In colorectal cancer and breast cancer patients who were previously treated with chemotherapeutics, it was only proven effective for colorectal cancer patients. "Multitargeted" tyrosine kinase inhibitors that influence cell growth and angiogenesis have proven somewhat effective in certain types of tumors (kidney tumor, GIST, NSCLC, etc) when used as monotherapy, however vatalanib has proven ineffective in mCRC. An advantage of anti-VEGF therapy is the very low incidence of side effects, therefore it is of great urgency to find various biomarkers that can help determine the appropriateness of starting anti-VEGF therapy early and monitoring its effectiveness. An outstanding question remains; what is the optimum therapy for a refractory disease in a patient who has already received anti-VEGF treatment?

From what we know today, the recommended first line treatment of metastatic CRC would be the combination therapy of fluoropyrimidin (plus oxaliplatin / irinotecan) and bevacizumab.

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The prophylaxis and the treatment of endophthalmitis

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Endoftalmita este o inflamație a țesuturilor intraoculare, ce implică mai ales vitrosul și camera anterioară, ca răspuns la infecții endogene, exogene, traumatisme, tumori, reacții imune, vasculite.
Endoftalmitele bacteriene reprezintă o complicație gravă în chirurgia oculară și a traumatismelor penetrante. Tratamentul trebuie să fie rapid, energic, cu asocieri de antibiotice cu spectru larg, în doze maxime și susținut până la completa vindecare. Medicația începe după prelevarea probelor bacteriologice, cele mai concludente fiind din aspiratul vitreean. De o deosebită importanță este vitrectomia. Se asociază corticoterapia pentru regresia reacției inflamatorii grave.
Profilaxia include o serie de măsuri preoperatorii, intra și postoperatorii.
Cuvinte cheie endoftalmita, chirurgia cataractei, povidon-iodin, vitrectomia

The term endophthalmitis refers to intraocular inflammation predominantly involving the vitreous cavity and anterior chamber of the eye due to endogeneous, exogeneous infections, trauma, tumours, immune reactions, vasculites.
Infectious endophthalmitis is a severe complication of the intraocular surgery and of the penetrating trauma. Treatement must be rapid, agressive, with associations of large spectrum antibiotics in high doses untill the complete healing. Medications starts after the prelevation of bacterial samples, the most important are those from the vitreous cavity. Vitrectomy has a crucial importance. Corticotherapy is associated for the regression of severe inflammation.
Prevention of endophthalmitis includes preoperatives, intra and postoperatives measures.
Key words: endophthalmitis, cataract surgery, povidon-iodine, vitrectomy

Endophthalmitis is an inflammatory reaction occurring as a result of intraocular colonization by bacteria, fungi, or rarely parasites.

It can be endogenous (septicemia) or exogenous (post-operative, post-traumatic) due to microbial contamination spreading from the ocular surface or open incision (wound) or contaminated instruments, intraocular lenses (IOLs) or intraocular foreign bodies.[3]

The occurrence, severity and clinical course of endophthalmitis depend on the route of infection, the virulence and the number of inoculated pathogens as well as the patient's immune system and the time of examination. In 29-43% of cataract operations, intraocular contamination occurs with facultative pathogenic bacteria from the ocular surface without the development of endophthalmitis due to the immune systems of the anterior and posterior chamber, ACAID or POCAID (anterior or posterior chamber-associated immune deviation) which act as a protective barrier and can limit the inflammatory reaction. If this system is compromised in complicated interventions like a posterior capsular defect with vitreous loss, the risk of endophthalmitis increases by a factor of 14.

In microbial endophthalmitis three phases of infection can be observed: an incubation phase, an acceleration phase and a destructive phase.[2]

The incubation with no clinical signs depends on the characteristics of the pathogen agent, last hours or days, generally 16-18 hours. Intraocular bacterial inoculation above a critical level then leads to breakdown of the aqueous barrier with fibrin exudation and cellular infiltration by neutrophilic granulocytes. With the commonest pathogens, Sta. epidermis and Sta. aureus, the greatest infiltration is observed only three days after infection. In the case of primary infection of the posterior part of the eye, inflammation of the anterior chamber occurs initially and this is accompanied within 7 days by a specific immune response with macrophages and lymphocytes in the vitreous cavity. Just 3 days after the intraocular infection, pathogen-specific antibodies can be detected, which contribute to pathogen elimination by opsonisation and phagocytosis within about 10 days. This can produce negative laboratory culture but severe intraocular inflammation. The inflammatory mediators of infiltrating cells, especially cytokines, not only recruit further leukocytes but can directly result in destructive effects, retinal injury and vitreoretinal proliferation.

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It has been suggested that the use of phacoemulsification increases the pressure within the eye forcing bacteria backwards into the vitreous, where early multiplication gives rise to the anterior vitritis characteristically seen behind the posterior capsule.

IOLs are a potential vector for bacteria. There are differences in adherence to different lens materials. Sta. epidermis adheres more to polypropylene haptics than to polymethil methacrylate (PMMA). Hydrophilic heparin-coated lenses demonstrate lower adherence for staphylococci. A recent retrospective study has suggested that the use of foldable IOLs inserted with a sterile injector lowers the incidence of post-operative endophthalmitis.

The incidence of endophthalmitis is different in surgical interventions such as: cataract phaco-emulsification, extracapsular cataract extraction (EEC), trabeculectomy, penetrating keratoplasty, pars plana vitrectomy, post-traumatic injuries.[2]

The most important pathogens causing acute post-operative phacoemulsification endophthalmitis are: B.H.S., S. mitis, S. pneumoniae, E. faecalis, S. aureus, CNS (MRSA, MRSE), Haemophilus influenzae, Pseudomonas aeruginosa, and in chronic endophthalmitis: Propionibacterium acnes, diphteroids, CNS, fungi.[3]

In post-traumatic endophthalmitis the implicated pathogens are: 16-44% CNS, 17-32% Bacillus sp., 10-18% G (-), 8-21% Str., fungus 4-14%, 4-8% Corynebacterium, 1-2% Clostridium.

The patient's medical condition influences the post-operative evolution. About 14-21% of all patients who develop post-operative endophthalmitis after cataract operations are diabetics. Endophthalmitis in diabetics is caused more often by G (-) bacteria. Patients on topically or systemically administered immuno-suppressant therapy (corticosteroids, antimetabolites) at the time of intra-operative procedures have a significantly higher risk of endophthalmitis. The patients with keratoconjunctivitis sicca, acute blepharoconjunctivitis, rosacea or atopic dermatitis have altered conjunctival and lid bacterial flora with a preponderance of Sta. aureus and because of this it is prudent to give them anti-staphylococcal prophylaxis prior to and after surgery according to antibiogramm.

The prophylaxis of endophthalmitis includes a number of intra-operative and post-operative measures.[4]

Operating room

1. air flow design

There are no current guidelines or data regarding the relationship between air flow design and incidence of the post-operative endophthalmitis.

2. The equipment and the instruments must be sterile.

Care is required with both washing and autoclaving the instruments. Single-use of tubing and other equipment is always preferable, if cost allows. Tubing is not easy to effectively sterilize unless an ethylene oxide gas sterilizer is available. Bottles of solution containing BSS (balanced salt solution) should never be kept or used for more than one operating session. Wet areas are easily contaminated with Pseudomonas aeruginosa, which can then cause a devastating endophthalmitis.

Antisepsis

The goal of pre-operative antisepsis is to reduce the likelihood of a wound infection by reducing the total bacterial count in the wound area and in immediate wound environment. For peri-orbital skin antisepsis, a 5 to 10% povidone-iodine solution is recommended which should be allowed to act for a minimum of 3 min, as the skin contains many sebaceous glands. If this is contraindicated (allergy, hyperthyroidism) an aqueous solution of chlorhexidine (0, 05 %) should be used instead.

For antisepsis of the conjunctiva and cornea povidone-iodine 5% for 3 minutes is the chemical preparation of choice. A 10% solution of povidone-iodine can be diluted 1:1 with BSS or isotonic saline. Post-operative, a significant reduction in bacterial count in the conjunctival sac can also be achieved by antisepsis with a 1, 25% povidone-iodine solution.

In 1991 Speaker and Menikoff in their study of 8,083 patients with cataract extraction showed a significant difference between the incidence of endophthalmitis with antisepsis using 5% providone-iodine (0,06%) and the control group in which silver-protein solution was used (0,24%).

From the aspect of tolerability, there is evidence that even a 10% povidone-iodine solution is associated with low external corneal toxicity. On the other hand, considerable side effects can be expected if even a 5% povidone-iodine solution gets into the anterior chamber.

Application of 10 ml of 5% povidone-iodine solution on to a sponge pad 1 hour prior to surgery clamped against the closed lids was associated with significantly fewer positive conjunctival cultures immediately prior to surgery (p=0,02) and at the conclusion of the surgery (p=0,05) compared with the application of 2 drops 5% povidone-iodine.

Studies concerning the use of chlorhexidine digluconate on the conjunctiva or cornea give conflicting results. A 4% chlorhexidine solution induces corneal damage and should not be used. On the other hand, pre-operative conjunctival irrigation with 0,05% chlorhexidine diacetate solution, as used by Per Montan and collab. in Sweden, is found satisfactory.

Clinicians should avoid use of large bottles of readily diluted povidone-iodine or chlorhexidine, because both antiseptics can become contaminated with Pseudomonas aeruginosa. Povidone-iodine solution containing a detergent must not be used because it coagulates the cornea irreversibly.

In conclusion, the available clinical studies recommend povidone-iodine in a concentration of 5% in BSS or isotonic saline as the pre-operative antiseptic of choice. A significant effect for a reduction in the conjunctival bacterial count after surgery has been confirmed when 1, 25% povidone-iodine was used.

The antibiotics have a prophylactic role (pre-, intra-, and post-operative) and also a therapeuti.c one (topical, subconjunctival, intraocular through vitrectomy, systemic administration).

1. Pre-operative topical antibiotic prophylaxis reduces the number of bacteria in the conjunctival sac.

Various antibiotics have been used in the past including chloramphenicole, aminoglycosides, fluoroquinolones.[6]

However a recent retrospective analysis has suggested a lower endophthalmitis rate following use of topical ofloxacin compared to topical ciprofloxacin. The effect of a combined antiseptic and antibiotic approach such as povidone-iodine as an antiseptic solution and ciprofloxacin or ofloxacin as antibiotics has been investigated.

The topical levofloxacin (pre- and post-operative) reaches higher concentrations in CA comparing with ciprofloxacin and ofloxacin, preventing the endophthalmitis. It is recommended to use levofloxacin at 1 hour, 30 minutes, before surgery, immediately at 5, 10, 15 minutes after the operation, and in each 2 hours on the intervention day. Gatifloxacin and moxifloxacin decreased the endophthalmitis rate at 0, 06 -0, 1%, being reserved for severe infections (Pseudomonas); they have toxic corneal effect, inhibiting the healing of the corneal wound (moxifloxacin).

Vancomycin and other reserve antibiotics should not be used for pre-operative prophylaxis.

2. The systemic antibiotic prophylaxis is not routinely recommended. The penetration through the intact ocular structures is very low in any intra-venous antibiotic. The highest intra-cameral antibiotic level is reached with oral quinolone in association with topical quinolone. The patients with severe atopic diseases and staphilococcical conjunctival and lids infections (blepharitis) should benefit from oral antibiotic prophylaxis, quinolone being recommended in these situations.

After a penetrating injury, a prophylactic antibiotic is given systemically, as well as by the intra-vitreal route, and the same drug should be used. Antibiotic cover must include various pathogens (Bacillus sp., Sta. aureus, CNS, Clostridium sp.). A lower incidence of the endophthalmities was demonstrated after the intra-vitreal use of vancomycin 1 mg and ceftazidime 2, 25 mg.

3. The irrigation of the lachrymal passages should not be performed immediately before the operation because the bacteria are washed from the lachrymal sac into the conjunctival sac.

4. Concerning the periorbital area cover there has been no randomized controlled study to demonstrate a decrease of the endophthalmitis risk by cutting the eyelashes before the operation. It is recommended to tape away the eyelashes from the operating field with adhesive tape.

5. The intra-operative prophylaxis with an antibiotic (vancomycin or gentamicin) in the irrigation solution is discussed. It has not been possible to reduce the incidence of endophthalmitis in any prospective scientific study. The studies have had nonconcludent results: in vitro the action of the antibiotic begins after 3 hours and full activity only occurs after about 1 day. This contrasts with the half-life of the drug in the anterior chamber of 3 hours.

On the other hand there is the risk of overdose, aminoglycoside retinal toxicity and the danger of developing resistance which is disturbing with the reserve antibiotic vancomycin. Relevant scientific organizations and authors therefore advise against giving prophylactic antibiotics in the irrigating solutions (Center for Disease Control in 1995 regarding vancomycin, American Academy of Ophthalmology in 1999 regarding vancomycin, and May et al. in 2000 regarding aminoglycosides).[1]

6. Intra-cameral antibiotics. In Sweden, all surgeons administrate intra-cameral 1 mg cefuroxime in 0,1ml saline solution. The cefuroxime is very active against staphylococci and streptococci (except MRSA, MRSE and E. faecalis), G (-) bacteria except Ps. aeruginosa and P. acnes.

The TASS-uveitis as a toxic reaction to different substances from the anterior chamber (disinfectants, antibiotics) compared to endophthalmitis reacts rapidly to steroids. For a patient allergic to penicillin it is recommended to use oral antihistaminic drugs 15 minutes before the operation. In the case of a patient allergic to cephalosporin the cefuroxime can be replaced with vancomycin.

7. The prophylaxis with subconjunctival antibiotic injection has been much used over the last 30 years especially in the UK, but probably has little prophylactic effect on the prevention of endophthalmitis. One of the reasons why this might have occurred is that the frequently used gentamicin in the subconjunctival injection has no effect on streptococci and P. acnes. The subconjunctival injection with cefuroxime gives lower level in the anterior chamber compared to the level obtained by intra-cameral injection route. This method can be used as an alternative for those who don't prefer the intra-cameral antibiotic administration.

8.For the post-operative prophylaxis it is recommended the same pre-operative used antibiotic in each hour after the operation (the bandage is changed every hour post-operative), then 4 times daily one week if the incision was sutured, 2 weeks in case of hydro suture. The quinolones are preferred or a combination

product such as polymyxin/bacithracin/neomycin, the topical chloramphenicol has been demonstrated to be safe for use for one week with the best penetrability remaining an alternative without the risk of causing aplastic anemia. The postoperative antibiotherapy is suddenly stopped (after 2 weeks).[2]

The treatment in acute endophthalmitis is recommended after performing aqueous and vitreous tap and/or vitrectomy, collecting samples for microbiology investigation (Gram stain, culture, PCR).

It is suggested to inject a combination of antibiotics (amikacin, ampicillin, cephalosporines, gentamicin, vancomycin) and corticosteroids (dexamethasone) into the vitreous using separate syringe and 30 G needle for each drug.

First choice: vancomycin 1 mg in 0,1 ml and ceftazidime 2 mg in 0,1 ml.

Second choice: amikacin 0, 4 mg in 0,1 ml and vancomycin 2 mg in 0,1 ml.

Systemic therapy with antibiotics and corticosteroids (prednisolone 1-2mg/kg/day) has adjuvant role in order to maintain an efficient intraocular level, with special care at side effects.[2]

The treatment in chronic endophthalmitis

The Propionibacterium acnes from the capsular sac and capsular adherences is the most frequent agent in the etiology of chronic endophthalmitis, a pathogen very difficult to detect.

It is recommended to use clarithromycin 250 mg twice daily for 2 weeks (well absorbed orally, penetrates well into the eye). The clarithromycin is concentrated 200 times into PMN and macrophages, is effective against intra-cellular G (+) bacteria, Haemophilus sp., and also against many atypical bacteria.

If the treatment with clarithromycin fails should consider removing the IOL, to perform a vitrectomy possibly combined with posterior capsulectomy. If IOL is retained, give trial of therapy with intra-vitreal vancomycin and cefazolin or cefuroxime together with intra-venous systemic therapy for one week.[2]

CONCLUSIONS

The antibiotics (without other measures) don't prevent and don't treat the endophthalmitis.

The prophylaxis consists in a number of medical rules, the hygiene of the patient and the sterilization of the operation are the most important.

The treatment of acute endophthalmitis includes first of all the vitrectomy, the antibiotic therapy alone can't resolve the situation.

The ESCRS recommendations probably will make a protocol (pre-operative, operative) which must be respected medically and also legally.

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Helicobacter pylori infection – endoscopic findings and clinical corelations

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Helicobacter pylori e recunoscut ca un patogen important implicat in inflamația gastro-duodenală, ulcerul peptic și carcinogeneza gastrică.
Material, metodă. Am evaluat 625 pacienti la care s-a practicat gastroscopie in perioada ianuarie - decembrie 2007. Scopul studiului a fost determinarea frecvenței infecției cu Helicobacter pylori la populația studiată si corelațiile cu simptomatologia clinică, diagnosticul endoscopic si histologic
Rezultate: Infecția cu Helicobacter pylori a fost asociată leziunilor esofagiene, cancerului gastric, duodenitei erozive, ulcerului duodenal, altor gastrite. Gastrita activă și metaplazia intestinală s-au asociat mai frecvent cu prezența infecției cu Helicobacter pylori. Pacienții cu simptome clinice majore au prezentat modificări endoscopice importante, independent de vârstă.
Concluzii. Simptomatologia gastro-duodenala e un predictor slab al bolii de bază. Pacienții cu simptome de alarmă necesită efectuarea promptă a endoscopiei. Endoscopia conferă un beneficiu minor pentru tratamentul inițial al dispepsiei. Un diagnostic complet necesită evaluare histologică și endoscopică, corelată cu evaluarea clinică și a prezenței infecției cu Helicobacter pylori
Cuvinte cheie: Helicobacter pylori, simptomatologie, modificări endoscopice, diagnostic histologic

Background: Helicobacter Pylori is known to be an important pathogen involved in gastroduodenal inflammation, peptic ulcers and gastric carcinogenesis.
Methods: 625 patients were enrolled and underwent gastroscopy between January-December 2007. The aim of this study is to determine the frequency of HP infection in studied population, and its correlation with clinical symptoms, endoscopic and histological diagnosis. We correlated symptoms with endoscopic findings and the age of the patients.
Results: HP infection was associated with esophageal erosions, gastric cancer, erosive duodenitis, duodenal ulcer and other gastritis. Active gastritis and intestinal metaplasia were strongly associated with the presence of HP infection. Patients with major clinical symptoms have increased risk to present major endoscopic findings, regardless the age.
Conclusion: Symptoms of gastroduodenal disease are poor predictors of the underlying pathologic state. Patients with alarm symptoms require a prompt endoscopy For the initial management of dyspepsia, endoscopy confers a small clinical benefit. A complete diagnosis consist of an endoscopic and histological evaluation, correlated with the clinical evaluation and the HP status of the patients.
Key words: Helicobacter Pylori, symptoms, endoscopic findings, histological diagnosis

Gastric cancer is one of the leading causes of mortality in the world and many risk factors have been implicated. Many studies have found an increased cumulative risk of gastric cancer and precancerous conditions in individuals with HP infection. Based on this epidemiologic evidence, the World Health Organization (WHO) International Agency for Research on Cancer declared HP as a class I carcinogen in 1994.

Glandular-type gastric adenocarcinoma develops after decades of HP infection. Therefore a long period of incubation must be needed to establish the phenotypical and genotypical alterations that result in neoplasia. During this latency period the gastric mucosa undergoes progressive phenotypical changes, from chronic active gastritis to gastric atrophy, intestinal metaplasia and gastric dysplasia, which have been defined collectively as gastric precancerous lesions. Each of these morphological alterations is associated with an increased risk for gastric cancer.[1]

The diagnosis of HP infection is indispensable in many different circumstances. Numerous invasive and non-invasive diagnostic tests have been developed since the original description of HP by Marshall and Warren in 1982. The invasive biopsy-based tests that include rapid urease test, histology and culture are important generally in the assessment of HP status before eradication. Initial endoscopy allows assessment of treatment indications of HP infection such as peptic ulcer disease and mucosa-associated lymphoid tissue lymphoma (MALT-oma). In view of the irregular distribution of HP, all the biopsy-based tests may theoretically cause a false-negative result. The inherent risk of sampling error can, however, be virtually eliminated by obtaining several biopsy samples from not only the gastric antrum, but also the gastric corpus.

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In contrast to biopsy-based methods, non-invasive tests asses the global presence of HP in the stomach, even when the bacteria are irregularly distributed on the gastric mucosa.

Despite uncertainty about the endoscopy in the evaluation of dyspepsia, many patients will ultimately undergo endoscopy to evaluate dyspeptic symptoms. The purpose of this analysis is to characterize patients who have endoscopy and determine their endoscopic findings and their HP status. These data could help inform the decision to perform endoscopy in clinical practice, by identifying those patients most likely to have serious pathology.

MATERIAL AND METHODS

Patients

A total of 625 patients, who came to the hospital, between January-December 2007, for gastroenterological examination, were included in the study. Patients from surgical departments were not included.

We have completed a structural questionnaire. Demographics, medical history and a detailed history of different symptoms were obtained. Patients were asked about the use of medication, specifically acid-suppressant drugs and non-steroidal anti-inflammatory drugs (NSAID).

We identified two separate groups of patients: patients with minor symptoms – upper abdominal pain or discomfort, reflux symptoms or bowel irritable syndrome symptoms and patients with major symptoms – almost permanent abdominal pain, including overnight pain, which didn't react to acid-suppressant drugs, and alarm symptoms – dysphagia, weight loss, inapetence, vomiting and evidence of gastrointestinal bleeding (hematemesis, melena, anemia).

Endoscopic examination was performed to each patient. Indications for examination included presence or absence of alarm symptoms.

Endoscopic findings

Standard esophago-gastro-duodenoscopy (EGD) was performed using a 98 mm diameter endoscope. After completion of the EGD, the endoscopy report was obtained and the relevant findings in the esophagus, stomach and duodenum were recorded and rated as major and minor as follows: major findings in the esophagus were tumor and Barrett esophagus; in the stomach – erosive gastritis, ulcer, tumor; in the duodenum – ulcer. Minor findings in the esophagus were erosions, ring, varices and hiatal hernia; in the stomach – simple erosions, ulcer scar, biliary reflux, gastric resection, other gastritis; in the duodenum – ulcer scar, erosive and non-erosive duodenitis. The major and minor findings for the esophagus, stomach and duodenum were compared with the clinical information obtained before the endoscopy.

In patients who presented major endoscopic changes, gastric biopsy and histopathological examination were performed. Patients were tested for the presence of HP infection using the serological test (anti-HP IgG antibody) or gastric biopsy with Giemsa stain.

Statistical methods

The primary aim of the study was to determine the frequency of the HP infection in the studied population, the correlation between the HP infection and the symptoms, the endoscopic findings and histological changes. The study followed which category of patients are susceptible to have HP infection (if there are differences between genders and urban/rural environment) and if the clinical complaints could raise the suspicion of a particular disease which claims more accurate methods of diagnosis like endoscopy and biopsy.

The primary hypothesis was that young patients without alarm symptoms will not present significant gastrointestinal diseases, while the alarm symptoms will impose the need of endoscopy and biopsy, regardless the age of the patients. The significance of factors associated with gastrointestinal diseases was evaluated by using 2x2 contingency tables and the chi-square test. A two-tailed p value < 0.05 was considered significant. We have constructed logistic regression analyses to identify factors associated with important endoscopic outcomes.

RESULTS

Patient demographics

A total of 625 patients (333 women and 292 men) with ages between 20 and 87 years were included in the study (Table I). Symptoms described by the patients enrolled in the study are summarized in Table II. The status of the HP infection was established using gastric biopsy or serological test. The gastric biopsy revealed the presence of HP-gastritis in 166 patients, while a number of 279 patients presented anti HP-IgG antibodies. (Figure 1 and Figure 2)

Endoscopic findings

Endoscopic findings are summarized in Table III. Major findings in esophagus were the following: Barrett esophagus (n=7) and tumors (n=5). In 168 patients major gastric findings were detected. These included erosive gastritis (n=85), gastric polyps (n=42), gastric ulcer (n=21) and gastric cancer (n=20). A number of 51 patients had duodenal ulcer. Minor endoscopic findings are listed in Table III.

Gastric samples were obtained from the antrum, gastric body or incisura angularis – Table IV.The histological changes are summarized in Table V.The association between the HP infection and the clinical symptoms was performed (Table VI). Inapetence, weight loss, evidence of GI bleeding were strongly associated with the presence of HP ($p<0.05$). HP infection was associated with the following endoscopic findings: esophageal erosions ($p<0.01$), gastric cancer, erosive duodenitis, duodenal ulcer and other gastritis (Table VII). The testing for HP infection plays an important role in the management of these lesions.

Table I. Characteristics of study population (n = 625)

SEX		
Female	333	53,3%
Male	292	46,7%
ENVIRONMENT		
Urban	326	52,2%
Rural	299	47,8%
HABITS		
Smoking	138	22,1%
Alcohol	72	11,5%
MEDICATION		
NSAID	53	8,5%
Acid-suppressants	44	7%
PAST MEDICAL HISTORY		
PMH* ulcer	103	16,5%
PMH gastric neoplasia	10	1,6%
FPMH** gastric neoplasia	9	1,4%

*PMH – past medical history
**FPMH – family past medical history

Table II. Distribution of symptoms in all study patients (n = 625)

SYMPTOM	NUMBER	PERCENTAGE	SYMPTOM	NUMBER	PERCENTAGE
Major pain	266	42,6%	Irritable bowel syndrome	138	22,1%
Dysphagia	24	3,8%			
Nausea / Vomiting	199	31,8%		219	35%
GI bleeding	30	4,8%	Minor pain		
Inapetence	163	26,1%		94	15%
Weight loss	202	32,3%	Reflux symptoms		

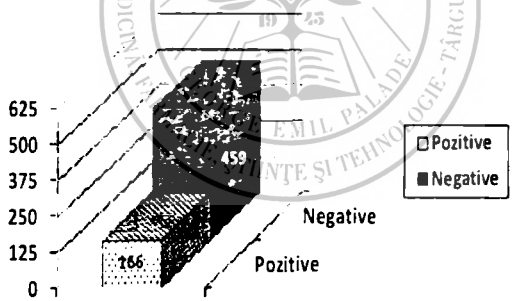

Figure 1. Histological diagnosis of HP infection

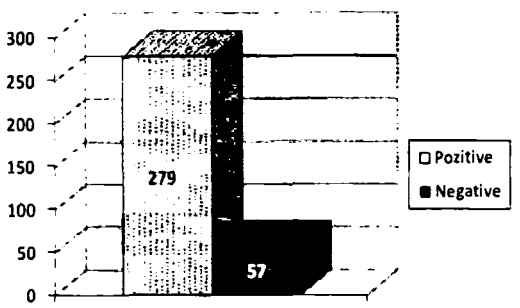

Figure 2. Serological diagnosis of HP infection

Table III. Distribution of endoscopic findings in all study patients (n = 625)

SITE	NUMBER	PERCENTAGE	SITE	NUMBER	PERCENTAGE
	Esophagus		Esophagus		
Esophageal tumors	5	0,8%	Hiatal hernia	34	5,4%
Barrett esophagus	7	1,1%	Ring	3	0,5%
			Varices	19	3%
			Erosive esophagitis	37	5,9%
	Stomach		Stomach		
Erosive gastritis	85	13,6%	Other gastritis	272	43,5%
Gastric polyps	42	6,7%	Ulcer scar	3	0,5%
Gastric ulcer	21	3,4%	Remnant stomach	41	6,6%
Gastric cancer	20	3,2%	Biliary reflux	69	11%
			One gastric erosion	5	0,8%
	Duodenum		Duodenum		
Duodenal ulcer	51	8,2%	Erosive duodenitis	42	6,7%
			Nonerosive duodenitis	8	1,3%

Table IV. Biopsy sites

Antrum	336	53,8%
Gastric body	98	15,7%
Incisura angularis	3	0,5%

Table V. Histological diagnosis

HP gastritis	166	26,6%
Active gastritis	176	28,2%
Atrophic gastritis	55	8,8%
Intestinal metaplasia	80	12,8%
Dysplasia	7	1,1%
Gastric adenocarcinoma	10	1,6%
Signet-ring cell carcinoma	10	1,6%
Hyperplastic polyps	19	3%
Barrett esophagus	7	1,1%
Other biopsies	39	6,2%

Table VI. Association between symptoms and hp infection

SYMPTOMS	HP INFECTION (p value)
GI bleeding	0,05
Major pain	0,07
Dysphagia	0,31
Nausea/Vomiting	0,06
Inapetence	0,007
Weight loss	0,0017
Minor pain	0,07
Reflux symptoms	0,106
Irritable bowel syndrome	0,07

Table VII. Association between endoscopic findings and hp infection

ENDOSCOPIC FINDINGS	HP INFECTION (p value)
Esophageal tumors	0,21
Hiatal hernia	0,48
Erosive esophagitis	0,01
Ring	0,102
Barrett esophagus	0,206
Erosive gastritis	0,127
Gastric ulcer	0,24
Gastric cancer	0,000029
Duodenal ulcer	0,0000000028
Erosive duodenitis	0,000071
Biliary reflux	0,167
Remnant stomach	0,00153
Other gastritis	0,008
Nonerosive duodenitis	0,121

Table VIII. Association between histological diagnosis and HP infection

HISTOLOGICAL DIAGNOSIS	HP INFECTION (p value)
Active gastritis	0,000000000....
Intestinal metaplasia	0,0025
Dysplasia	0,056
Atrophic gastritis	0,052

Table IX. Association between symptoms and endoscopic findings

SYMPTOMS	Hiatal hernia	Esophageal erosions	Erosive gastritis	Gastric ulcer	Gastric cancer	Gastric polyps	Duodenal ulcer	Remnant stomach	Other gastritis
GI bleeding	0,34	0,4	0,29	0,008	0,15		0,017	0,062	0,0106
Major pain	0,108	0,017	0,0013	0,000025	0,0017	0,35	0,00000018	0,132	0,039
Dysphagia	0,25	0,401	0,463	0,216	0,0003	0,21	0,06	0,34	0,407
Nausea/Vomiting	0,062	0,26	0,31	0,14	0,016	0,03	0,0016	0,24	0,009
Inapetence	0,37	0,41	0,28	0,11	0,0000...	0,48	0,46	0,31	0,49
Weight loss	0,13	0,075	0,052	0,45	0,000000001	0,302	0,43	0,005	0,42
Minor pain	0,07	0,001	0,004	0,0006	0,00007		0,0000019	0,28	0,0041
Reflux symptoms	0,03	0,0000019	0,056	0,089	0,103		0,04	0,31	0,17
Anemia	0,36	0,0015	0,008	0,19	0,36		0,28	0,40	0,30

Table X. Association between endoscopic findings and age over 45 years

ENDOSCOPIC FINDINGS	AGE OVER 45 YEARS (p value)
Esophageal tumors	0,152
Hiatal hernia	0,08
Esophageal erosions	0,45
Erosive gastritis	0,041
Gastric ulcer	0,024
Gastric cancer	0,264
Duodenal ulcer	0,036
Gastric polyps	0,03
Remnant stomach	0,008
Other gastritis	0,465

Table XI. Association between histological diagnosis and age over 45 years

HISTOLOGICAL DIAGNOSIS	AGE OVER 45 YEARS (p value)
Active gastritis	0,32
Intestinal metaplasia	0,001
Dysplasia	0,094
Atrophic gastritis	0,00009

The bioptic changes like active gastritis and intestinal metaplasia were strongly associated with the presence of HP infection (Table VIII).

The association between clinical complaints and endoscopic findings was performed (Table IX). Major pain, GI bleeding, dysphagia, nausea, vomiting were found to be predictors for major endoscopic lesions. Most of the alarm symptoms were associated with gastric cancer. We also have found that the age over 45 was associated with the presence of erosive gastritis, gastric ulcer, duodenal ulcer, gastric polyps and remnant stomach after surgery (Table X). The association between the age over 45, gastric atrophy and intestinal metaplasia was statistically significant (Table XI).

By using the logistic regression, we established that patients with major clinical symptoms have an increased risk to present major endoscopic findings, regardless the age. (RR 2,39; 95% CI: 1,57 – 3,64). Patients with minor symptoms, under the age of 45, have a lower risk to develop major endoscopic lesions. (RR 0,3; 95% CI: 0,21 – 0,42)

DISCUSSIONS

In this study, the detection of HP infection using the biopsy based test was lower than using the serological method. Intestinal metaplasia and patchy distribution of the bacteria are thought to be factors causing false-negative diagnosis of HP infection. By obtaining biopsy samples from not only the gastric antrum, but also from the gastric corpus, may raise the accuracy of the diagnosis.[9]

In our study group, the HP infection was strongly associated with the remnant stomach after surgery. The need of treatment in this category of patients was revealed by the results of previous studies. Gastrectomy for benign disease and HP infection are risk factors for the development of gastric cancer. HP eradication has also been found to reduce the risk of carcinogenesis in patients who had undergone distal gastrectomy for early gastric cancer.[3]

HP infection was associated with the active gastritis and intestinal metaplasia.There was a poor correlation with gastric atrophy (p=0,052). False negative histological results might be obtained for gastric atrophy or HP infection. However, it is difficult to take a biopsy specimen from the diffuse lesions of chronic active gastritis or atrophic gastritis, when there is not target observed to perform an aiming biopsy.[4] By raising the number of biopsies the accuracy of the diagnostic will improve.

The gastric cancer was associated with most of the alarm symptoms. Patients with erosive gastritis, gastric ulcer and duodenal ulcer also showed alarm symptoms. Major pain, nausea and vomiting were associated with minor endoscopic findings (other gastritis).This correlation should be evaluated in the context of the presence of associated pathologies, like other severe organic diseases, psychiatric disorders. The same symptoms may hide a variety of pathological conditions, that could be identified only by performing endoscopy and biopsy.

Abdominal pain, nausea and vomiting are predictors for a major gastric or duodenal disease. This result is similar to others found in the literature. Stephan M. Wildi et al. have performed a study on 175 patients and they demonstrated that daily abdominal pain, nausea combined with an ulcer history, are strong predictors for major gastric or duodenal diseases.[11]

The association between patients with reflux symptoms and a major endoscopic finding was rarely revealed (statistical significance was obtained only for duodenal ulcer). The idea of treating only the reflux symptoms without performing endoscopy, especially in young patients, should be taken into consideration. However, the diagnosis of Barrett esophagus in these groups of patents requires an endoscopic and bioptic follow-up.

In this study, symptoms, endoscopic findings and the presence of the HP infection were correlated with the age of patients. We couldn't find any statistically significant difference between the distribution of the HP infection in patients under and over the age of 45. However, the management of the disease after the detection of the HP infection in all category of patients should be the treatment of the infection. HP eradication has the potential to prevent future peptic ulcer and the potential to reduce the incidence of gastric malignancy, and it may cure symptoms in one of 15 patients with functional dyspepsia.[6]

In the study group, the age over 45 years was associated with the presence of gastric ulcer, duodenal ulcer, remnant stomach, erosive gastritis, atrophic gastritis, intestinal metaplasia, dysplasia. There were few cases of gastric cancer, but among these patients there were a large number of patients under the age of 45 years. Therefore, this lesion was not statistically

associated with the age of the patients. Gastric atrophy and intestinal metaplasia are strong associated with the age over 45. Atrophy and metaplasia are implicated in the pathogenesis of gastric cancer of the intestinal type. Individuals who have severe atrophy and intestinal metaplasia in the gastric mucosa have the highest risk of gastric cancer.[5]

The association of the symptoms with the age and the major endoscopic findings, has confirmed the presence of major endoscopic findings in patients with alarm symptoms, which indicates the need of endoscopic evaluation of this group of patients. According to the Maastricht Consensus, a "test and treat" approach is recommended in adult patients under the age of 45 years, presenting in primary care with persistent dyspepsia, without alarm symptoms.[8]

There is controversy about the appropriate role of endoscopy during the evaluation and management of dyspeptic in the evaluation and management of dyspepsia in the absence of alarm symptoms. Some experts have argued that all patients with chronic reflux symptoms should be screened with endoscopy to determine whether they have Barrett esophagus or early adenocarcinoma. Other investigators have been suggested that this would be costly and not improve patient outcomes. Patients with non-reflux dyspepsia may initially receive acid suppression therapy, HP treatment, or endoscopy.[7] Some studies show that a prompt endoscopy strategy for the initial management of dyspepsia confers a clinically small, but statistically significant benefit, in terms of patients' symptom resolution compared with a "test and treat" approach, although this is not a cost-effective strategy.[2]

In summary, the true impact of endoscopy, aside from the psychological benefit, derived from a definite diagnosis, lies in the discovery of gastrointestinal malignancies. However, for many patients with dyspepsia, whether young or old, the fear of cancer or other serious underlying illness is a major reason for seeking consultation with a specialist. An endoscopy with normal findings may thus relieve anxiety and fear. There is evidence that endoscopy provides reassurance for many of these patients and therefore confers a therapeutic benefit.[10]

A complete gastroenterological diagnosis can be established using the clinical data, endoscopic evaluation, histological exam, completed with HP-status evaluation.

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The young people attitude in connection to dento-facial aesthetics

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Impactul social al fizionomiei faciale influenţează foarte mult atitudinea pacientului legată de estetica sistemului dento- maxilar.
Scopul lucrării este de a studia impactul anomaliilor dento- maxilare la tînăr. Este foarte important pentru dentist să cunoască structura psihică a pacientului, în scopul obţinerii unor rezultate bune din punct de vedere terapeutic.
Cuvinte cheie: estetică, tânăr, anomalii dento- maxilare

The social impact of facial physiognomy influences very much the patient attitude related to the harmonious restoration and in point of aesthetics of dento -maxillary system. The aim of this paper is to study the psychological impact of dento-maxillary anomalies on the teen-agers and the young pacients. It is very important for the dentist to know the psychic side of the pacients , their specific features for the successful end of the treatment.
The psychological importance of the aesthetic treatment relies on the observation that the oral sphere is the primary place of the manifest for many emotional conflicts.
***Key words**: aesthetics, teen-ager, young people, dento-maxillary anomalie*

The patient possibility to improve his facial aspect is the most important psychological factor for him to accept orthodontic rehabilitation, The third international dictionary Webster's defines aesthetics as: "the assessment of the beauty or the aspiration to the beauty, but also the sensibility for the beauty, elegance, remarkable culture", Each people has this sensibility. The manifestation and the interpretation of this sensibility award him personality.[1,2]

Different investigations (De Witt, Lucher, Schaw) demonstrated the salutary effect of the attractiveness in relationship between people. The general attractiveness is the most frequent correlated with the face's one. The eyes and teeth represent the face's attractive points during communication.[3,4]

The wish of looking well or better has become a real necessity, imposed by social, economic and sexual raports. The face is the part of the body the most represented and the lips, the proeminent appearances.[6] "The psychological aspects of the representation, the image which the patient has about himself and his body play a decisive role in aesthetics", said Burns.

The personality, the motivations, the wishes, the expectations, the capacity to accept changes and the wish to cooperate are important factors for the successful end of the treatment.[5]

Psycho-somatic specific features of the teen-agers and the young patients.

Adolescence (16-20 year old) is considered the period of passing between childhood and maturity. Now it takes place the personality crystallization's process of the young people, In this period, facial aesthetics is very important and the teen-ager is more and more interested in his external aspect, in the way how he looks, how he smiles, The psychological changes are: self-control, well-balanced behaviour, great opening to the social-human area, independence, autonomy, Teen-agers don't accept values or rules imposed by the older people.

The young people – the youth (18-35 year old) - in this period there is an harmonious equilibrium between wishes and realities. The young people have a well outlined personality, with a great capacity of decision, a good control of emotions and a strong motivation. They are psychological prepared for life, being attracted by different confrontations and competitions.[5]

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MATERIAL AND METHODS

We worked out a questionnaire which we gave to the teen-agers and the young patients to complete it and we achieved a clinical-statistical investigation about the psychological evolution of the young people during orthodontic treatment with different kind of fixed appliances, The research was performed on a group of 90 patients, 60 girls(66,66%) and 30 boys(33,33%) between 16 and 31 year old.

The parameters which we used in this analysis are:

-the motivation of the patients;

-the wishes and the expectations;

-the type of the fixed appliances which the patient chose;

-the choice of the treatment from their own initiative;

-the opinion regarding the inclusion of their case in the research;

-the accept to take photos and radiographs;

-how long the patient supports the appliance;

-which is the most painful stage during the orthodontic treatment,

RESULTS AND DISCUSSION

After we evaluated the answers and we analyzed them, we saw the results: from the number of patients which were questioned (90) -50 are teen-agers (55,55%) and 40 are young people (44,44%), 34 from the teen-agers are girls (68%) and 26 are boys (32%), 26 young people are girls (65%) and the rest -14 (35%) are boys,

During the time they completed the questionnaire, the patients were self-assured, confident or reserved, inquiring (Table I)

Depending on the parameters, we can say the following things:

-The motivation of the young patients to succed an orthodontic treatment is aesthetics in 97% of cases and only for 3% of them functional disorders are the reason for coming at the dentist. (Figure 1)

-89% from the patients are convinced of the necessity to rectify dento-facial disturbances and they ask for the dentist to be professional man, 5 % ask for patience and 6% from the people who were questioned, considered that the understanding is the most important for the success of the treatment (Figure 2)

-Regarding the inclusion of the own case in analysis and achievement of photos and radiographs , 58% didn't agree to this thing, the rest of 42% answering in the affirmative (Figure 3)

-The teen-agers and the young people, in a rate of 56 % chose ceramics' brackets, 17% lingual technique and 27% accepted metallic brackets (Figure 4)

-78 % from the patients which were questioned came to the treatment from their own initiative and 22 % at the recommendation of the other persons (Figure 5)

-Regarding how long the patient is prepared to support an orthodontic appliance , 80% from the patients who answered the questions support 6 months and 20% a year or more (Figure 6)

-98% consider that the stage of sealing the orthodontic band is the most painful during the orthodontic treatment (Figure 7).

Table I. Number, rate and specific features (confident/ reserved)of the young patients

Patients	Number of patients	Girls No→%	Boys No → %	Confident No → %	Reserved No → %
Total	90	60→66,66%	30→33,33%	70→77,77%	20→22,22%
Teen-agers	60	34→68 %	26→32 %	45→ 75 %	15→ 25 %
Young people	30	26→65%	14→35 %	25→83,33%	5→16,66%

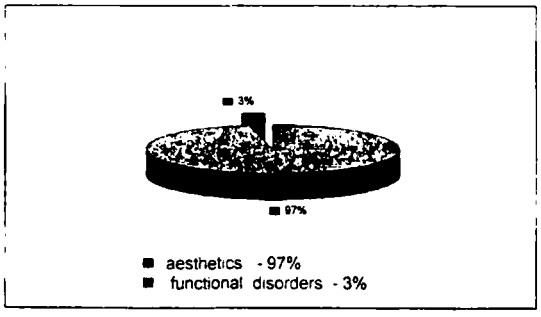

Figure 1. Motivation

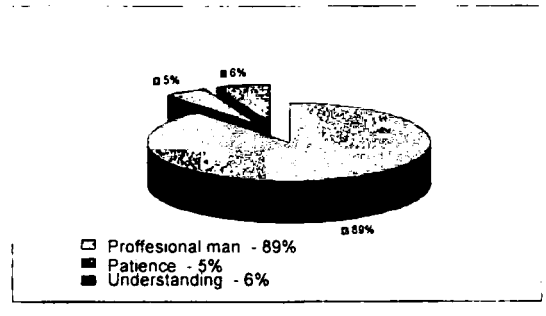

Figure 2. Wishes and expectations

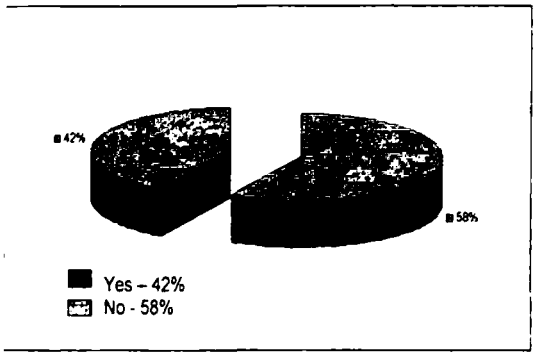

Figure 3. Patient's accept

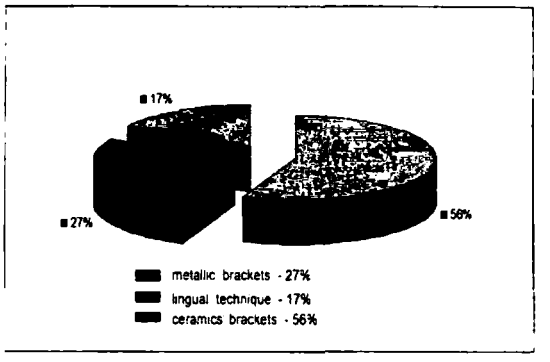

Figure 4. Type of fixed appliance

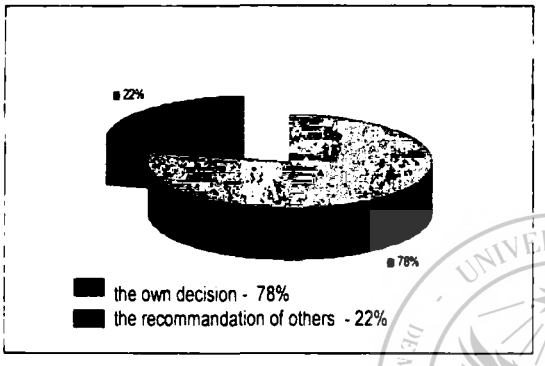

Figure 5. The choice of the treatment

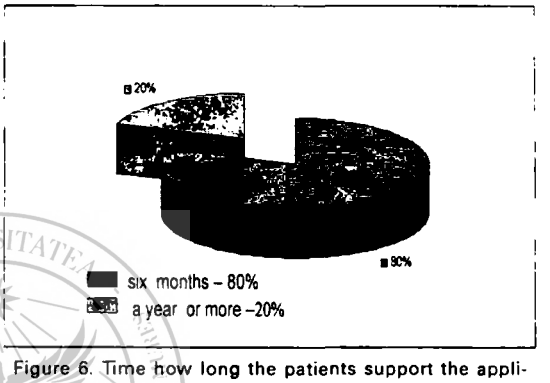

Figure 6. Time how long the patients support the appliance

CONCLUSIONS

1.Intervening in the oral sphere, with many psycho-emotional investments, the dentist must consider the therapeutical act very important from the view point of aesthetics. The aesthetic motivations represent the major factor for the patients to request orthodontic treatment.

2.Most of the teen-agers and the young patients with different anomalies want the armonious restoration and aesthetic of dento-maxilary system. The people associate the beauty to the success, happiness, friendship and autoconsideration.

3. Although young people want very much to rectify the dento –maxillary anomallies through orthodontic treatment with fixed appliance, they are reticent regarding the inclusion of their case in research and the accept to take photos and radiographs for using in analysis, They want treatment to end in a short time and with less visible methods.

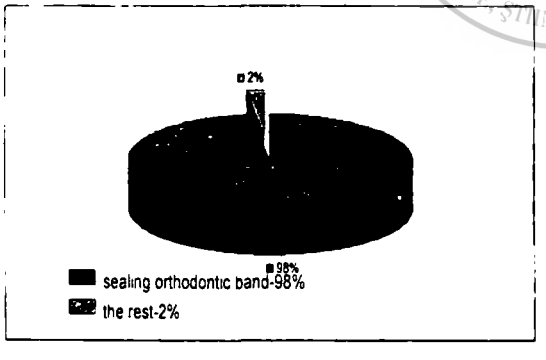

Figure 7. The most painful stage of the treatment

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The evaluation of cerebral vasoreactivity in carotidian stenoses and oclusions by the use of acetazolamide test

I. Macavei

Scopul acestui studiu îl reprezintă aprecierea variaţiilor vitezelor de debit sanguin cerebral (DSC) înainte şi după vasostimulare cu acetazolamidă (ACZ), determinate bilateral la nivelul arterelor cerebrale medii (ACM), la un lot de 30 de pacienţi şi la un lot de referinţă de 20 subiecţi sănătoşi. Pentru evaluarea vitezelor de debit, înainte şi după vasostimulare cu acetazolamidă s-a utilizat metoda transcranial Doppler (TCD). Datele obţinute au fost sintetizate în tabele care ne arată că după administrarea de acetazolamidă vitezele de debit sanguin cerebral au crescut foarte semnificativ atât ipsilateral cât şi controlateral la lotul martor faţă de lotul de pacienţi. Vasoreactivitatea cerebrală (VRC) se exprimă prin variaţii ale vitezelor de flux la nivelul principalelor artere intracraniene, cel mai frecvent fiind utilizată artera cerebrală medie.

Cuvinte cheie: acetazolamida, viteze de debit sanguin cerebral, artera carotida internă.

The aim of this study is to measure the blood flow velocity variations, before and after acetazolamide stimulation, determined on the middle cerebral artery, in a group of 30 patients, a control group and 20 healthy subjects. For the assessment of blood flow velocities, before and after acetazolamide stimulation, we used the transcranial Doppler method. The obtained data were summarized in tables, which show that after acetazolamide administration, the cerebral blood flow velocities, significantly increased both ipsilateral and controlateral, in the control group versus patients group. The vasomotor reactivity is expressed by the variations of the blood flow velocities of the main intracranial arteries, most frequently on the middle cerebral artery.

Key words: acetazolamide blood flow velocity; internal carotid artery,

Acetazolamide (ACZ) belongs to the sulphonamide class and is an inhibitor of carbonic anhydrase (CA). Carbonic anhydrase is an enzyme discovered in 1932 by Meldrum and Roughton, with a molecular weight of 30 kDa (kilodalton), with one zinc atom in the molecule. It catalyses one of the most simple reactions, the one between CO_2 and H_2O.[4,10]

An essential particularity of the hydration reaction of CO2 is that, unlike most enzyme catalysed reactions the participant reagents are inorganic compounds and the reaction takes place without catalyst, but more slowly. Hydration occurs in fractions of seconds and is followed by the spontaneous and instant dissociation of H_2CO_3 in H^+ and HCO_3 according to the following reaction:

$$CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3$$

Fundamental studies carried out, some on animals and others on humans have shown that ACZ has a pronounced cerebral vasodilator effect.[4,10,17]

In humans, ACZ administered intravenously (iv) in doses of 10-15 mg / kg body is sufficient for AC inhibition, inhibition that occurs primarily in red blood cells and later in the central nervous system (CNS) because of slower penetration of the substance in the hematoencephalic barrier (HEB). This produces an increase of PaCO2, with consequent local acidosis, which induces arteriolar vasodilation.[2,15,17]

CVR represents the property of the cerebral arterioles to actively modify the lumen surface by involving vasodilation or vasoconstriction, in response to changes in cerebral perfusion pressure or because of physiological or pathological stimuli.[1,5,19]

In recent years several techniques of the assessment of cerebrovascular reserve capacity have been described. The most used are: computerized tomography with single photon emission (CTSPE), with positron emission tomography (PET), Xenon based Computer Tomography and transcranial Doppler ultrasonography with, which measures the blood flow speed. Most techniques require intracerebral arterioles stimulation to produce their dilation. This is attained either by increased arterial pressure of CO2, or by intravenous administration of acetazolamide.[1,8,15,19]

The objective of the study was the assessment of cerebral vasoreactivity (VRC) in patients with internal carotid artery stenosis and occlusion by the aid of transcranial Doppler ultrasonography and acetazolamide test (ACZ).

The objective of the study was the evaluation of DSC velocities before and after vasostimulation with ACZ determined bilaterally in ACM and also the assessment of the unilateral carotid stenosis effect on intracranial blood circulation.

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MATERIAL AND METHODS

The study was conducted on a batch of 30 patients with various degrees of stenosis and / or occlusions of the ACI in the cervical segment and some subtypes of cerebral ischemic stroke. Out of the 30 patients 23 (76.6%) were male and 7 (23.3%) women aged between 30 and 80 years.

There was also a control group of 20 healthy subjects studied who did not have a history of vascular or neurological diseases and presented no risk factors and the clinical and neurological examination performed before this study was between normal limits.

The extra-cranial Doppler examination, included the duplex examination and spectral analysis of the Doppler signal of the arteries with cerebral destination in the extracranial segment using 7.5 MHz transducers of the HITACHI EUB 515A and VINGMED-CFM 800 devices and CW 4MHz transducers of the MEDASonics//CDS device and TCD examination.

For TCD examination we used transducers working at a frequency of 2MHz pulsating emission of the MEDASONICS//CDS device.

In order to assess the intracranial hemodynamics, the M1 segments of bilateral ACM were transtemporally vocalized by using an exploration setting of 50-60 mm.

For each artery the following hemodynamic parameters were recorded: systolic velocity (Vs), mean velocity (Vm), diastolic velocity (VD), bilaterally.

For vaso-stimulation we used a dose of 1 g ACZ (DIAMOX ®). This amount was dissolved in 10 ml distilled water, then it was administered by slow i.v. infusion over a period of 5 minutes, under the strict monitoring of hemodynamic parameters, continuing observation and recording them for a period of 25 minutes from administration.

In order to perform an analysis of the increase of debit rate (VD, Vs, Vm) regarding ACZ we calculated the maximum increase of rate over baseline values, using the formula:

(Vmax-Vbas) / Vbas

RESULTS

Debit velocities (VD, Vs, Vm) were measured at the level of ACM in the control group and in the group of patients under baseline conditions and after vasostimulation with ACZ.

Variations of the diastolic velocity of debit values under baseline conditions and after vasostimulation with ACZ were recorded at the controlateral level (Table I).

Mathematical-statistical analysis reveals that the increase of VD after vasostimulation with ACZ in the patient group is much lower than the control group, the difference is highly significant ($p < 0.0046$).

In order to analyze the increase in VD after ACZ the increase of maximum velocities was calculated over the baseline. Thus, VD in patients increased by 25% after ACZ and in the control group it increased by 69%.

At ipsilateral level (left side in the control group and the affected side in patients) the VD variations were registered under baseline conditions and after vasostimulation with ACZ (Table II).

Mathematical -statistical analysis reveals that VD at the controlateral level (opposite the wound) increases markedly in the control group (69%) compared to the patients group (25%), after ACZ the difference statistically being highly significant. At ipsilateral level (same side of the lesion) these values of velocity increased in the control group (62%) more than in the group of patients (23%), the difference being also very significant (Figure 1).

Table I. Diastolic velocities at the level of ACM baseline controlateral and after vasostimulation with ACZ

Diastolic contralateral (right – control group)							
Type of group	Baseline	5 min	10 min	15 min	20 min	25 min	Significance
Control	47,50	62,30	74,75	80,40	73,75	-	
Patients	31,07	33,37	35,50	37,80	38,83	37,20	0,046

Table II. Diastolic velocities at the level of ACM baseline ipsilateral and after vasostimulation with ACZ

Diastolic ipsilateral (left - control group)							
Type of group	Baseline	5 min	10 min	15 min	20 min	25 min	Significance
Control	47,50	60,80	70,90	77,50	70,65	-	
Patients	26,23	27,50	29,30	30,90	32,27	30,53	0,0019

Table III. Sistolic velocities at the level of ACM baseline controlateral and after vasostimulation with ACZ

Sistolic contralateral (right - control group)							
Type of group	Baseline	5 min	10 min	15 min	20 min	25 min	Significance
Control	92,60	108,00	121,20	127,60	120,65	-	
Patients	69,70	73,27	77,47	81,97	85,77	62,00	0,0013

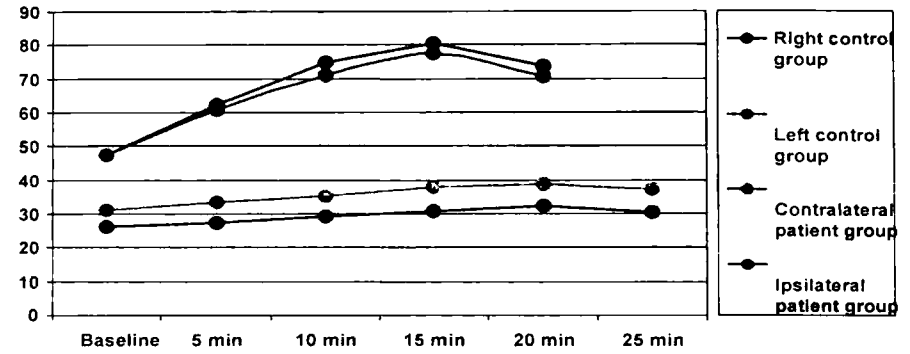

Figure 1. Evolution in time of Vd at the level of ACM after vasostimulation with ACZ

At controlateral level the values of systolic velocities in baseline conditions and after vasostimulation with ACZ are represented both for patients and for the control group in a table (Table III)

Mathematical-statistical analysis reveals that the increase of Vs after vasostimulation with ACZ in the patient group is much lower than in the control group, the difference is highly significant (p <0.0013).

To analyze the increase of Vs regarding ACZ we calculated the maximum increase of Vs over baseline values, using the formula:

Vmax-Vbas/Vbas.

Thus mean value of Vs in the patient group has increased by 23% after ACZ. In the control group this increased by 37%.

At ipsilateral level (left side in the control group and the affected side in patients) Vs values in baseline conditions and after vasostimulation with ACZ are represented in a table (Table IV).

Mathematical-statistical analysis reveals that the increase of Vs after vasostimulation with ACZ in the patient group is much lower than in the control group, the difference being highly significant (p <0.0004), much more significant than in the case of contralaterale artery (p <0 , 0013).

To analyze the increase of Vs after ACZ the maximum increase of the Vs value over the baseline values were calculated, using the formula:

Vmax-Vbas/Vbas.

In the patient group this increase was 24%. In the control group this increase was 33.20% (Figure 2).

At the controlateral level, the average velocities in baseline conditions and after vasostimulation with ACZ (Table V).

Table IV. Sistolic velocities at the level of ACM baseline ipsilateral and after vasostimulation with ACZ

Sistolic ipsilateral (left - control group)

Type of group	Baseline	5 min	10 min	15 min	20 min	25 min	Significance
Control	94,05	107,20	118,10	127,30	120,00	-	
Patients	56,60	58,40	61,97	67,20	70,23	63,69	0,004

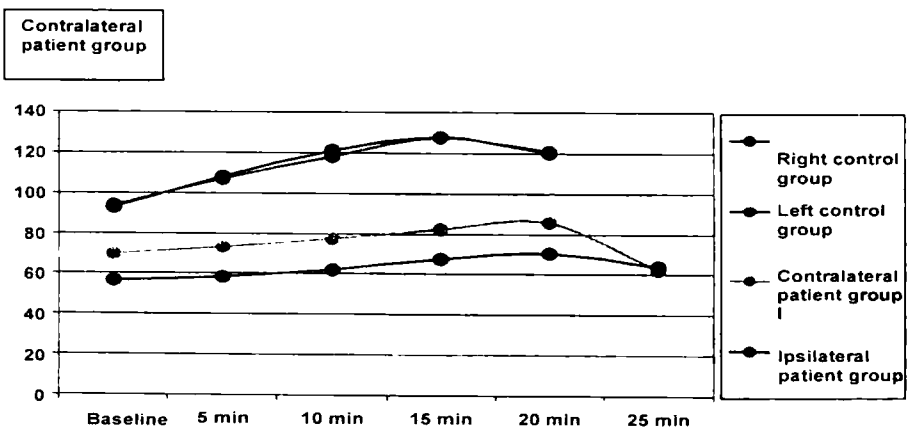

Figure 2. Evolution in time of Vs at the level of ACM after vasostimulation with ACZ

Table V. Mean velocities at the level of ACM baseline controlateral and after vasostimulation with ACZ

Contraleteral Mean Velocity (right - control group)							
Type of group	Baseline	5 min	10 min	15 min	20 min	25 min	Significance
Control	92,60	108,00	121,20	127,60	120,65	-	
Patients	69,70	73,27	77,47	81,97	85,77	62,00	0,0013

Table VI. Mean velocities at the level of ACM baseline ipsilateral and after vasostimulation with ACZ

Ipsileteral Mean Velocity (left - control group)							
Type of batch	Baseline	5 min	10 min	15 min	20 min	25 min	Significance
Control	94,05	107,20	118,10	127,30	120,00	-	
Patients	56,60	58,40	61,97	67,20	70,23	63,69	0,0004

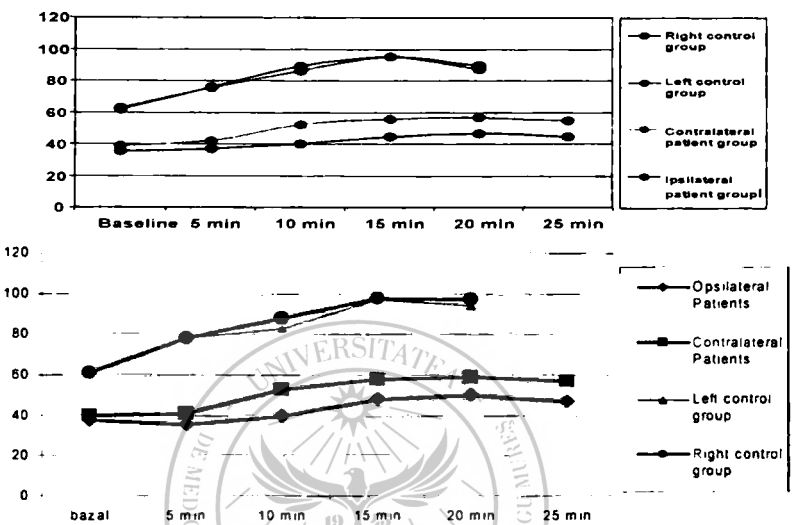

Figure 3. Evolution in time of Vm at the level of ACM after vasostimulation with ACZ

Mathematical-statistical analysis reveals that the increase of Vm after vasostimulation with ACZ in the patient group is much lower than in the control group, the difference is highly significant ($p < 0.0013$). To analyze the increase of Vm after ACZ we calculated the maximum increase of Vm over the baseline situation, using the formula:

Vmax-Vbas/Vbas

Thus, VM in patients increased by 23% after ACZ

In the control group, the increase was 35%.

At ipsilateral level (left side in the control group and the affected side in patients) Vm values in baseline conditions and after vasostimulation with ACZ (Table VI).

The mathematical-statistical analysis reveals that the increase of Vm after vasostimulation with ACZ in the patient group is much lower than in the control group, the difference being highly significant ($p < 0.0004$), much more significant than in the case of contralaterale artery ($p < 0,0013$) (Figure 3)

To analyze the increase of Vm after ACZ the maximum increase of Vm values over the baseline situation was calculated, using the formula:

Vmax-Vbas/Vbas.

In the lot of patients, the increase was 23%.

In the control group, the increase was 35%

DISCUSSIONS

This study confirms that ACZ administered intravenously at a dose of 1g, in physiological conditions, induces cerebral arteriolar vasodilation which produces an increase in debit velocities and implicitly, an increase of DSC.[2,6,15,18]

These results are in line with other studies in the specialty literature. Most studies published in reference to CVR have been conducted in patients with carotid stenosis and occlusion.[1,2,7,8,9]

Hayashida et al. [cit.[8]] studied the effect of a dose of 1 gram ACZ administered iv in group of patients with occlusion and / or unilateral stenosis of the extracranial ACI. In order to measure the DSC they have used the PET method. Measurements were made in a state of relaxation and after injecting ACZ at 10, 20 and 30 minutes. The authors of this study have reported the effect of ACZ up to 10 minutes subsequent to i.v. administration. Thus they concluded that the work indice of 10 minutes is the most appropriate duration to measure DSC.[8,15]

In our study, the largest increase in the flow speeds (Vd, Vs, Vm) was recorded at 15 minutes in the reference group and at 20 minutes in the patient group.

The explanation is that in the control group the cerebral vasomotor response is much faster in time than

in the patients group. This is due to the fact that in diseased persons the arteries on the ipsilateral side of the stenosis is in a certain degree of compensatory vasodilation. Thus, the vasodilatation answer to vasostimulation with ACZ will be more diminished and more persistent in time.

Hojer Pedersen studied the effect of a dose of 1 g ACZ administered i.v. in a group of 17 patients with subacute and chronic ischemic cerebral-vascular disease. The DSC measurement was performed in baseline conditions, before ACZ injection and 20 minutes after injection, using the inhalation method of ^{133}Xe. The author of this study reported that after injecting a dose of 1 g ACZ, DSC value starts to increase within an interval up to 15 minutes, reaching a maximum value in about 25 minutes and then gradually decreasing to half in approximately 95 minutes.[3,6]

The data of our study show that debit velocities increase much less on the ipsilateral side of the stenosis and/or occlusion compared to the controlateral side after vasostimulation with ACZ.

Kuwabara et al., in a study on patients with occlusions of ACI observes that the effect of a dose of 1g ACZ administered i.v., appears late in the ipsilaterale hemisphere of the occlusion compared to the unaffected hemisphere. This can be explained by the slow release of the substance and a slow metabolism of the glucose (CO2 and H2O in small amounts) on the ipsilateral side of the occlusion compared to the non- occlusion controlateral side.[8,11,12,14]

CONCLUSIONS

After administrating ACZ, the bilaterally determined DSC velocities in ACM behaved as follows:

1. Vd increased highly significantly both ipsilateral and controlateral in the control group compared to the patients group, when the increase index of Vd was almost equal in both sides. This suggests that Vd, reflecting cerebral vascular resistance, is not a reliable indicator to evaluate DSC differences.

2. Vs increased significantly both ipsilateral and controlateral in the control group compared to the patients group, and the increase index of Vs was significantly higher ipsilaterally than controlaterally, suggesting that the Vs, reflecting DSC in correlation with the cardiac debit, is an important indicator for evaluating the DSC difference.

3. Vm increased significantly, both ipsilateral and controlateral in the control group compared to the patients group, when the increase index of Vm was significantly higher ipsilaterally than controlaterally, which displays a similar Vs behaviour.

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The diagnosis of renal artery stenosis with Doppler ultrasound

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Scop: Obiectivul nostru a fost diagnosticare rapidă şi cu cât mai mare acuratete a stenozei de arteră renală cu ajutorul examinării ecografice Doppler în sistem duplex, care furnizează şi informaţii funcţionale, evidenţiind leziunile stenotice semnificativ hemodinamic (cu reducere mai mare de 60% a diametrului arterial).
Material şi metodă: S-au inclus în studiu 122 hipertensivi, internaţi şi urmăriţi în perioada 2000-2007 în Clinica Medicală III şi Policlinica Atlas Târgu Mureş, Romania. Toţi pacienţii au avut aspecte semnificative anamnestic, clinic şi paraclinic pentru stenoza de arteră renală.
Rezultate: Din cei 122 de pacienţi hipertensivi introduşi în studiu, în funcţie de viteza maximă sistolică măsurată (VmaxS>1,8m/sec este caracteristică ptr. SAR semnificativ hemodinamic, măsurată ecografic Doppler), au rezultat două loturi: fără SAR - 86 de pacienţi (70,49%) şi cu SAR - 36 de pacienţi (29,51%). Media valorilor tensiunii arteriale sistolice a fost semnificativ mai mare(p<0,001), în lotul cu SAR(194mmHg) comparativ cu lotul fără stenoză(160mmHg
Concluzii: Raportarea la angiografie, confirmă şi în studiul nostru, că ultrasonografia Doppler vasculară este o metodă eficace, relativ ieftină, reproductibilă , în diagnosticul SAR.
Cuvinte cheie: stenoză de arteră renală, ecografie doppler

Objective: Detecting the renal artery stenosis (RAS) is extremely important because its consequences, especially high blood pressure and kidney failure are curable by revascularization. Our objective was swift diagnosis with maximum accuracy of renal artery stenosis using Doppler ultrasound examination in duplex mode, which provides functional information and reveals hemodynamically significant stenosis (over 60% reduction in arterial diameter).
Material and method: The study was performed on 122 patients with high blood pressure, hospitalized between 2000-2007 in Clinica Medicală III and with follow-up in Policlinica Atlas Târgu Mureş, Romania. All patients revealed significant data for renal artery stenosis during anamnesis, clinical and paraclinical examination.
Results: The 122 patients with hypertension included in the study, were included in two groups according to the maximum systolic speed (maximum systolic speed over 1.8m/s measured by Doppler ultrasonography is characteristic for hemodynamicaly significant RAS): 86 patients (70.49%) without RAS and 36 patients (29.51%) with RAS. The average blood pressure was significantly higher (p<0.001) in the RAS group (194mmHg) compared to the group without RAS (160mmHg
Conclusions: The comparison to renal angiography confirms that vascular Doppler ultrasonography is an efficient, relatively inexpensive, reproducible method for RAS stenosis and useful for screening purposes.
Key words: renal artery stenosis, doppler ultrasound

The renal artery stenosis can have important clinical repercussions, for example high blood pressure, acute pulmonary edema and kidney failure [1, 10]. It is also associated with elevated risk of cardiovascular morbidity and mortality [6,8].

Renovascular hypertension is the result of a significant decrease in renal flow secondary to a severe arterial stenosis (unilateral or bilateral). This article is focused on the renal artery stenosis which is the most frequent cause of renovascular hypertension [21].

One of our objectives was the quick diagnose and with grater accuracy of the renal artery stenosis with the help of duplex mode Doppler ultrasonographic examination, which also provides functional information, revealing the hemodynamicaly significantly stenotic lesions (with grater decrease of the arterial diameter) [16,20].

We have also evaluated the improvement in the detection of renal artery stenosis, by comparing the characteristics of patients who were diagnosed with this pathology and of those with normal ultrasonographic features.

Directing the screening for renovascular disease implies the attempt of determining the strongest predictive factors that can be associated with this pathology, as well as the association with other vascular affectations (coronaries, carotids, peripheral arteries) [13,14].

MATERIALS AND METHODS

We included in this study 122 patients diagnosed, admitted into hospital and with a follow-up between January 2000 - December 2007 in Medical Clinic III

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Târgu Mures and Atlas Policlinic Târgu Mures. We included in the group of 122 , patients with suspicion of renal artery stenosis, all with hypertension and having one or more of the following features [5, 15, 19]: hypertension onset: below 35 years and above 55 years of age, sudden rise in blood pressure, the acceleration of a previously well controlled hypertension, high blood pressure uncontrollable with at least 3 drugs, fast evolving retinopathy (stage III and IV retinopathy), malignant hypertension, abdominal systolic-diastolic murmur, sudden onset of acute pulmonary edema in a hypertensive with no apparent reason, or the development in the same conditions of cardiac failure, acute kidney failure after the administration of angiotensin conversion enzyme inhibitors (three times the initial value after treatment) or after the administration of angiotensin receptor blockers, unexplained hypokalemia, unexplained azotemia in a hypertensive, small unilateral kidney.

For the ultrasonographic examination we used initially an Interspec and subsequently an Aloka SSD-1700 ultrasonograph, having duplex transducers with variable frequency between 2-5 MHz. With the help of Doppler echography in duplex mode we measured a series of parameters: (the top systolic speed, pulsatility and resistivity indexes) in the renal artery and in the interlobar arteries [3, 7, 9]. The ultrasonographic results were validated with the help of intraarterial digital substraction angiography.

Statistical analysis was performed with the help of the Student's t test and the Chi-square test.

RESULTS

From the 122 hypertensive patients included in the study, two groups were formed according to the measured top systolic speed, determined by Doppler ultrasonography (maximum systolic speed > 1,8m/s is characteristic for the hemodynamicaly significant renal artery stenosis (RAS). One group without RAS 86 of patients (70.49%) and one with RAS 36 of patients (29.51%). In the group with the stenosis 30 patients had unilateral stenosis and 6 patients had bilateral stenosis or unilateral renal artery stenosis on single functional kidney.

We calculated the average of the maximal systolic speeds measured in patients from both groups with or without the renal artery stenosis. In the group with the renal artery stenosis we obtained an average of the maximal systolic speeds of 2.3741m /sec, and in the lot without the stenosis an average of the maximal systolic speeds of 1.3022m /sec ($p < 0,001$).

We calculated the average of resistivity index (RI)in both groups ($p < 0,001$):

- the average of the resistivity index in the RAS group is 0,536
- the average of the resistivity index in the group without RAS is 0,829 (Chart 1)

Despite the blood pressure lowering treatment, blood pressures were constantly elevated (Systolic BP ≥ 160mmHg and Diastolic BP≥ 110mmHg) specilay in the RAS group 17 patients (47.22%) compared to 5 patients (5.81%) in the group without RAS.A larger proportion of patients needed a combination of ? 3 blood pressure lowering drugs in the RAS group (31 patients - 86.11%) compared to the group without RAS (49 patients - 58.98%) $p<0.001$ (Chart 2).

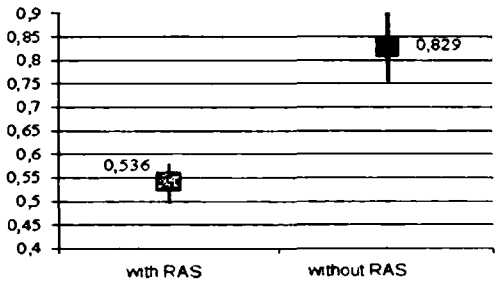

Chart 1. Comparison between the averages of RI in the groups with /without RAS p<0.001

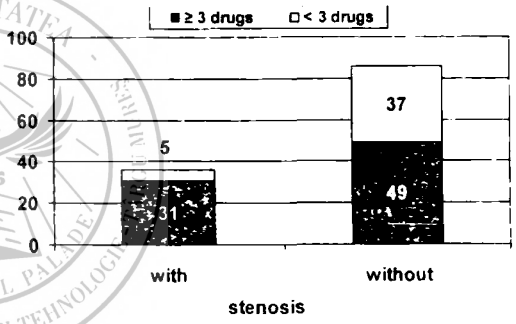

Chart 2. The distribution of patients with 3 or more Blood pressure lowering drugs p<0.001

In the group with renal artery stenosis the average systolic BP was 194mmHg and in the group without RAS it was 160mmHg ($p<0.001$) (Chart 3).

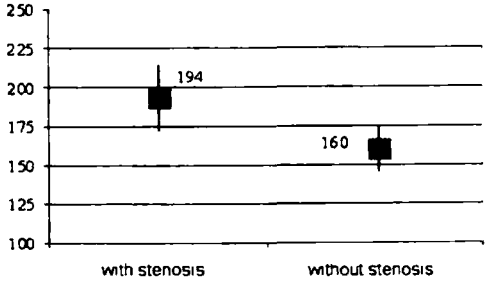

Chart 3. The averages of systolic blood pressures in the group with/without stenosis p<0.001

We recorded 21 patients (58.33%) with coronary hearth disease in the group with RAS and 17 patients (19.77%) with coronary hearth disease in the group witout RAS, revealing a statistically significant difference of the coronary heart disease in the two groups (p <0.01). (Chart 4)

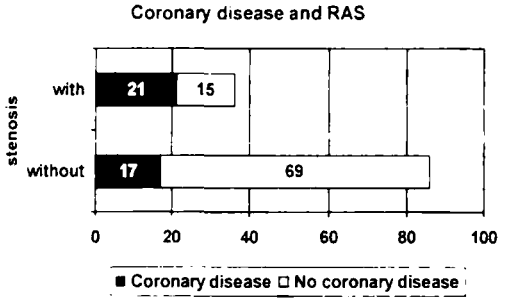

Chart 4. The proportion of patients with coronary heart disease in the two groups p<0.01

In the group with RAS cerebro-vascular disease was (carotid stenosis and/or history of stroke) was present in 15 patient (41.67%) compared to 15 patients (17.44%) in the group with no RAS (p <0,001). (Chart 5)

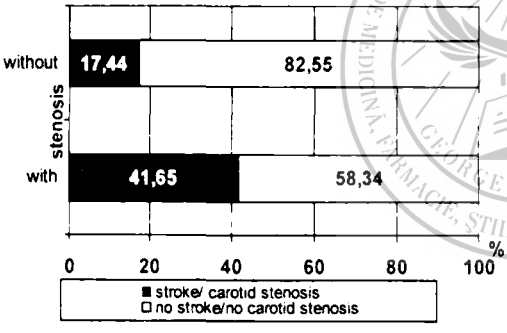

Chart 5. Association of cerebrovascular disease in patients with/without renal artery stenosis p<0.001

DISCUSSION

With the aid of duplex mode Doppler ultrasonography (color and pulsated) we can determine several parameters: maximum systolic speed, pulsatility and resistivity indexes.

Maximum systolic speed>1.8m/sec is characteristic for the renal artery stenosis (RAS) due to its hemodinamic significance being associate to a stenosis over 60%.

Duplex mode Doppler ultrasonography (color+ pulsated) [4] can be used to evaluate the severity of SAR, noticing the alteration of the flow speed as well as the characteristics of the flow in the stenotic segment of the renal artery. The sensitivity of the method [2] varies from 92 to 98%, also confirmed by our study.

The resistivity index below 0.6 is considered suggestive for a renal artery stenosis with hemodinamic significance. The resistivity index can be measured through Doppler ultrasonography and many studies have confirmed the utility of the RI as a marker of prognosis for kidney function after revascularization [17,18].

In patients with atherosclerotic vascular disease, a high value of RI, measured in the opposite kidney to the one with RAS, is a predictive factor for kidney function after revascularization. Thus this high RI indicates a poor response of blood pressure and of kidney function, after angioplasty, due to a severe and irreversible intrarenal alteration [3,12], also confirmed by our study.

Our study assessed whether there is a connection between coronary disease and the renal artery stenosis and found a statistically significant association between the two.

This association increases the risk of cardiovascular morbidity and mortality for these patients. In a group of patients undergoing coronary angiography and evaluated in a study [6] for RAS the survival rate over 4 years was 57% in patients with RAS ? 75% in at least one renal artery, compared to 89% in those with no significant RAS. Most fatalities in this study were of cardiovascular origin.

Suggestively for our study was the association between the presence of the carotid stenosis and/or the history of stroke and the renal artery stenosis. In a retrospective study [11] where 346 cases with cerebral infarction at autopsy were evaluated it was found that severe renal artery stenosis (over 75%) was present in 10.4% of the subjects and carotid stenosis in 33.6%. The patients with the carotid stenosis were more often affected by the renal artery stenosis than those without carotid level injury. The process of general arteriosclerosis is involved in both cases.

The American guides [22] state the importance of the Doppler ecographic examination in the diagnosis of RAS.

CONCLUSIONS

The values of systolic and diastolic blood pressure in the case of renovasculare hypertension are larger than in the witness group with essential hypertension. It also requires a in a larger proportion the use of more the 3 blood pressure lowering drugs, which is statistically significant.

The presence of coronary heart disease, cerebrovascular disease and peripheral vascular disease is significantly higher in the group with RAS.

Renal duplex mode Doppler ultrasonography (color and pulsed) is considered as initial screening test in the diagnosis of RAS, with the best cost/efficiency ratio. Compared to angiography our study confirms and that vascular Doppler ultrasonography is an efficient, relatively cheep, reproducible examination for the diagnosis of RAS. Renal Doppler ultrasonograph is based on morphological as much as functional criteria.

The top systolic speed and the resistivity index (RI) are prediction factors in the diagnosis of RAS. These measurements besides the diagnosis value, offer information about the prognostic of renal revascularization (the resistivity index).

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Distributional tipologies of the aferrent vascularization of the caudate lobe

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În acest articol este prezentat un studiu anatomic descriptiv, pe un lot de 50 de piese hepatice, al principalelor tipologii de distribuţie spaţială intraparenchimatoasă a elementelor vasculare aferente ale lobului caudat, bazat pe studiul iniţial macroscopic al pieselor hepatice cu identificarea principalelor surse vasculare hepatice cât şi a celor accesorii, cu preponderenţă cele arteriale, urmat de o analiză distributivă a pieselor de coroziune rezultate din preparatele iniţiale.
Piesele anatomice hepatice au fost corodate cu acid clorhidirc tehnic, după o injectare prealabilă cu Technovit 7143. Analiza de ansamblu a pieselor de coroziune a demonstrat variabilitatea mare a surselor vasculare aferente (glissoniene), atât portale dar şi arteriale. Arterele lobului caudat au provenit într-un număr de 28 de cazuri din ramura dreapta a arterei hepatice proprii, 16 cazuri din cea stângă dar şi din surse arteriale accesorii cum sunt artera hepatică accesorie dreaptă, ramură a arterei mezenterice superioare într-un număr de 4 cazuri respectiv cea stângă într-un număr de 2 cazuri. În ceea ce priveste originea ramurilor caudate portale, acestea au provenit din bifurcaţia venei porte într-un număr de 4 cazuri, din ramura stângă a venei porte în 36 de cazuri respectiv din ramura dreaptă în 10 cazuri.
Cuvinte cheie: artere lobului caudat, ramurile caudate ale venei porte hepatice, artere hepatice accesorii, vena portă hepatică

In this article we present a descriptive anatomical study on a number of 50 liver pieces of the main tipologies of intraparenchymal spacial distribution of the aferrent vascular elements of the caudate lobe, a study based on the initial macroscopical observation of the hepatic pieces with the identification of the main vascular sources of the liver as well as of the accessory ones,mainly the arterial ones, followed by a distributive analysis of the corrosion pieces which resulted from the initial ones.
The hepatic anatomical pieces were corroded with technical chlorhydric acid after previously being injected with Technovit 7143. The overall analysis of the corrosion pieces demonstrated the large variability of the aferrent (glissonian) vascular sources both portal and arterial. The arteries of the caudate lobe derived in a number of 28 cases from the right branch of the proper hepatic artery, in 16 cases from the left one, but also from accessory arterial sources like the right accessory hepatic artery,a branch of the superior mesenteric artery,in a number of 4 cases and from the left accessory hepatic artery in a number of 2 cases. Regarding the origin of the caudate portal branches, these derived from the bifurcation of the portal vein in a number of 4 cases, from the left branch of the portal vein in 36 cases and from the right branch in 10 cases.
Key words: caudate lobe arteries,caudate branches of the hepatic portal vein, hepatic accessory arteries,hepatic portal vein

The work has as a purpose to study descriptively the vascular elements,arterial and venous (portal),of the aferrent pedicle corresponding to the caudate lobe. The motivation of this study is the lack of morphological aspects and of the spacial distribution tipology of these elements destined to a small volume hepatic segment, these elements being considered per se and without really being described.[3,4]

The study of the cadaver material started with the morphological analysis of the caudate lobe on unfixed anatomical pieces, on pieces fixed with 25% formol and consequently with the analysis of a number of pieces obtained by corrosion.[13,14,15] After this observation we analysed the spacial distribution of these vascular elements, their number, origin, distributional pattern.[15,17]

The study material included a number of 50 hepatic anatomical pieces obtained from the prosecture service on the basis of a protocol with The University of Medicine and Pharmacy - Targu-Mures. The original pieces were studied macroscopically, afterwards they were washed with a saline flush. We only used fresh pieces,26 in number, obtained from recent necropsies. The batch was completed with a number of 24 pieces fixed in 25% formol. After being washed, the pieces were cannulated, both the portal and the arterial components, and were thus prepared for being injected with a rapidly polymerisable substance called Technovit 7143.[3,5,7]

The injection procedure was taken from the prosecture service of the Anatomy and Embriology Department of The University of Medicine and Pharmacy – Timisoara, being conceived by Professor Petru Matusz.[5,8,16] We modified this procedure in the sense that we accelerated the polymerisation process by using a bath of liquid injection at a high temperature, approximately 50°C. The polymer we used is prepared according to a variable formula corroborated with the final details which are desired. We used a 3/2 and a 2/1

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polymer/diluant ratio. The cannulated hepatic piece is introduce in a liquid injection environment because it must not be diformed after the polymerisation process; we used a 10-litre container with warm water at approximately 45-50°C. The diluted polymer is poured rapidly in a 50 ml Guyon seringe, for the portal vein a volume of 80-90 ml being necessary, and in a 20 ml seringe for the hepatic artery because this one necessitates around 20-30 ml of polymer. After the injection of the vascular elements at the level of the hepatic hilus,a waiting time of 30 minutes for the solidification of the injected piece is required,afterwards this piece is introduced in a bath of technical chlorhydric acid, a special attention needed to be payed to this acid wich is extremely irritant for the airways and which has to be manoevered under the niche.[13,15] Because we used technical chlorhydric acid, the corrosion is extremely quick and is completed in maximum 72 hours for a piece in which we want to study the 3rd and 4th order ramifications. After obtaining the corrosion pieces they are washed intensely with a water jet, carefully so that the minute ramifications are not destroyed, and then they are left to dry.[9] Then follows the macroscopical descriptive analysis of the intraparenchymal distribution of the portal and arterial branches destined to the caudate lobe.[14,15,17]

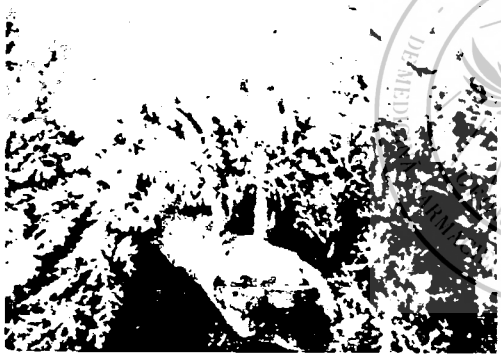

Figure1 Arterial caudate branches which derive from the right hepatic artery.

Figure 2 Arterial caudate branches which derive from the right hepatic artery.

Figure 3. Arterial caudate branches which derive from the left hepatic artery.

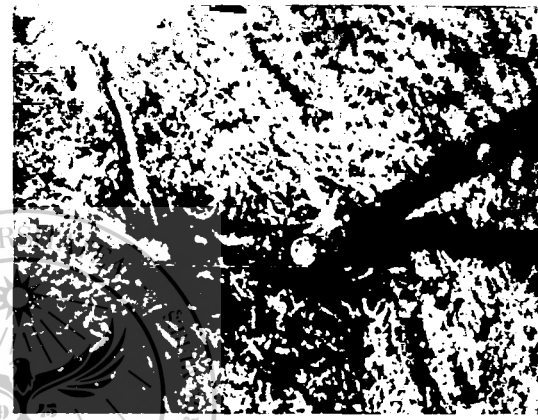

Figure 4. Arterial caudate branches which derive from the right accessory hepatic artery.

Figure 5. Arterial caudate branches which derive from the left accessory hepatic artery

The results obtained were initially analysed macroscopically and the data were corroborated with the ones obtained after the corrosion of the pieces.

Thus, the sources of arterial origin were in 88% of the cases the classical ones, caudate arterial branches from the right hepatic artery – 28 cases, 56% (Figure 1,2) and from the left one – 16 cases, 32% (Figure 3), but we also put into evidence caudate branches which derived from the accessory hepatic arteries ; the left accessory hepatic artery, 2 cases, 4% (Figure 5), a

branch of the left gastric artery and the right accessory hepatic artery respectively, 4 cases,8% (Figure 4), a branch of the superior mesenteric artery. In these cases the arterial sources were put into evidence macroscopically on original pieces and cannulated separately.

Regarding the origin of the portal caudate branches, we classified these according to their origin and number in 3 types : type 1 – 1-2 caudate branches which derive from the bifurcation of the portal vein in a total number of 4 cases, 8% (Figure 5) ; type 2 – 2-4 caudate branches which derive from the left branch, 36 cases, 72% (Figure 6) ; and type 3 – 10 cases, 20% in which the caudate venous branches are represented by 1-3 elements which derive from the right branch of the portal vein (Figure 7).[13]

Figure 6. 2-4 caudate branches which derive from the left branch of the portal vein

Figure 7. 1-3 elements which derive from the right branch of the portal vein.

The conclusions of our study are the following : the caudate lobe has aferrent, distinct arterial and venous vascular sources in the form of aferrent (glissonian) pedicles respecting Couinaud's description; the variability of the vascular sources is significant but there exists a specific tipology; the venous caudate elements, which we included in type 2, representing 72% in the real situation, practically justifies the classical descriptions[1,2,3,4] in which it is specified that the portal caudate branches derive from the left branch of the portal vein; we underline the fact that there exists the possibility to find the other variants also[1,2,17] which are not neglectable and which can constitute key elements in the surgical treatment of the tumoral pathology anf of liver transplants. Our study actually achieves a review of the main arterial and venous sources also adding practically particular situations but which are necessary in the formation of a liver-transplant surgeon.[10,11,12] And last but not least we wish to put an accent on the importance of studying on corrosion pieces and on their practical and demonstrative utility.

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Correlation between the severity of erectile dysfunction and clinical heart disease

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Introducere. În literatura de specialitate există în ultimii ani o mare preocupare pentru evaluarea pacienţilor cu disfuncţie erectilă, în special de relaţia istorică între disfuncţie erectilă şi a bolilor cardiovasculare.
Obiective. Obiectivul principal al acestui studiu este de a stabili o corelaţie între gradul de disfuncţie erectilă şi de la debutul clinic a bolilor cardiovasculare.
Material şi metodă. Un număr de 215 de pacienţi (n=215) au fost incluşi în studiu care au fost internaţi în Institutul Inimii Cluj-Napoca, în perioada 01.01.2008-31.08.2008 şi care ua asociat afecţiuni cardiovasculare şi de un grad de disfuncţie erectilă. Ei au fost evaluaţi cu ajutorul Indicelui Internaţional al Funcţiei Erectile (IIEF). Pacienţii au fost interogaţi despre momentul de debut al disfuncţie erectilă faţă de debutul bolilor cardiovasculare şi dacă aceste două patologii au apărut în acelaşi timp sau în momente diferite (6 luni, 1 - 2 ani înainte, etc). Ei au fost au împărţiţi în 6 subgrupuri.
Rezultate. Lotul investigat a cuprins subiecţi de sex masculin cu vârste cuprinse între 32 ani şi 77 ani (55,4 ani). Disfuncţia erectilă de diverse grade (severă, moderată, uşoară) a fost întâlnită la 60,5% din pacienţii de 30-39 ani şi a crescut progresiv pentru ca 85,2% din pacienţi cu vârste cuprinse între 70-79 de ani să prezinte disfuncţie erectilă.
Există corelaţie semnificativă statistic între debutul a bolilor cardiovasculare şi de disfuncţie erectilă severitate.
Concluzii. Am concluzionat că gradul de severitate al disfunctiei erectile este cu atat mai mare cu cat debutul disfunctiei este mai precoce, respectiv cu cat debutul disfunc'iei erectile a fost inainte de debutul bolilor cardiovasculare.
Cuvinte cheie: disfuncţie erectilă, boli cardiovasculare, corelaţie

Introduction. In the literature, there is in recent years a great concern for the evaluation of patients with erectile dysfunction, especially the historical relationship between erectile dysfunction and cardiovascular disease.
Objectives. The primary objective of this study is to establish a correlation between the degree of erectile dysfunction and the onset of clinical heart disease.
Material and method. A number of 215 patients (N = 215) were included in the study from the the patients admitted in The Heart Institute from Cluj-Napoca, during 01.01.2008-31.08.2008, who associate a cardiovascular disease and a degree of erectile dysfunction. They were evaluated using the international index of erectile function (IIEF). Patients were questioned about the moment of erectile dysfunction debut over the onset of cardiovascular disease and if this two conditions appeared simultaneously or at different times (6 months, 1 - 2 years before, etc.) and were divided in 6 subgroups.
Results. The investigated group includeed male subjects aged between 32 years and 77 years (55.4 years). Erectile dysfunction of various degrees (severe, moderate, mild) was met at 60.5% of patients aged 30-39 years increasing progressively to 85.2% of patients aged between 70-79 years.
There are statistically significant correlation between the onset of cardiovascular disease and the erectile dysfunction severity.
Conclusions. We concluded that the severity of erectile dysfunction is even higher as the beginning of erectile dysfunction is early, respectively, as onset of erectile dysfunction was before the onset of cardiovascular disease.
Key words: erectile dysfunction, cardiovascular disease, correlation

Male erectile dysfunction (ED), previously known under the term impotence, is defined as the inability to achieve an erection sufficient for a satisfactory sexual act.[1] Although erectile dysfunction is considered a benign pathology, it has a significant negative impact both on patients, their socio-professional performance and couple relations.

In the last 50 years have made considerable progress for understanding the ED ethiopathology and comorbide conditions. Researchers have concluded that ED and diabetes mellitus (DM) had common risk factors (endothelial dysfunction, autonomic neuropathy, cardiovascular and hormonal abnormalities) and often coexist in this patients.[5]

Erection is a complex phenomenon that requires a perfect coordination between nervous system centers, arterial and venous sistems. A located defect at any of these levels may cause erectile dysfunction.

Vascular ED it is considered the clinical manifestations of vascular penile disorder, as pectoris angina is the manifestation of coronary disorder, thus becomes increasingly necessary to a common approach of the patient with the ED and subclinica coronary disease.[7]

In the literature, there is in recent years a great concern for the evaluation of patients with erectile dysfunction, especially the historical relationship between these two diseases. Today it is known that most

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times, vascular ED preceding the installation of ischemic heart disease or are at most a time validates in the some time.[2]

Objectives. The primary objective of this study is to establish a correlation between the degree of erectile dysfunction and the onset of clinical heart disease.

MATERIAL AND METHOD

A number of 215 patients (N = 215) were included in the study. They were selected from the the patients admitted in The Heart Institute from Cluj-Napoca, during 01.01.2008-31.08.2008, who associate a cardiovascular disease and a degree of erectile dysfunction. They were evaluated using the international index of erectile function (IIEF). We investigated also the comorbide conditions that these patients had, if they present life partner or not, the degree of and correlation between erectile dysfunction and heart disease.

This group was analyzed in terms of IIEF value for determining the degree of erectile dysfunction (severe ED-IIEF score under 20, moderate ED-IIEF score between 21 and 40, mild ED - IIEF score between 41 and 60 and without the IIEF - score between 60 and 75).

To be able to make a correlation between the onset of erectile dysfunction and the onset of cardiovascular disease, patients were questioned about the moment of erectile dysfunction debut over the onset of cardiovascular disease and if this two conditions appeared simultaneously or at different times (6 months, 1 - 2 years before, etc.).

Thus a total group was divided in 6 subgroups divided according to the time of the beginning of the two diseases:

Group "0" - ED (erectile dysfunction) and CVD (Cardiovascular disease) have started concurrently.

Group "1" – the ED debut was less than 6 months before CVD

Group "2" - the ED debut was 6 months - 1 year before CVD

Group "3" - the ED debut was 1 -2 years before CVD

Group "4" - the ED debut vas 2 - 4 years before CVD

Group "5" - the ED debut with more than 4 years before CVD

Group "6"- we do not have data on ED onset, either because patients do not have ED (the IIEF score > 61) or for that this condition began after heart disease and then they are not compatible with our study. Group "6" have 87 subjects and will not enter into further statistical analysis.

RESULTS

The investigated group included male subjects aged between 32 years and 77 years. Total group was divided into 5 subgroups by age as follows: 30 - 39 years with 38 patients, 40 - 49 years with 30 patients, 50 - 59 years 45 patients, 60 - 69 years to 75 patients and 70 - 79 years 27 patients.

The average age of the group is 55.4 years, other statistics descriptive data are detailed in the table below (Table 1). The coefficient of variation (CV), one of the dispersion indices, calculated by Stand.Dev. / Mean is 22.3%, which shows that the population taken in the study is relatively homogeneous (homogeneous populations are defined in terms of the statistical CV below 10%).

Table I. Age group characteristics

Mean	55.43255814
Standard Error	0.844517356
Median	57
Mode	60
Standard Deviation	12.38305522
Sample Variance	153.3400565
Kurtosis	-1.024701523
Skewness	-0.281745016
Range	45
Minimum	32
Maximum	77
Sum	11918
Count	215
Confidence Level(95.0%)	1.664637627

Joined is a graphic representation on the prevalence ED degrees of severity and age groups studied (Figure 1).

The prevalence of severe erectile dysfunction has a serious upward trend with age. The prevalence was 7.9% in the younger subjects of the group, increasing slightly to 8.8% in the age group of 50-59 years. Then we see an rapidly increasing prevalence to 25.9% in patients over 70 years.

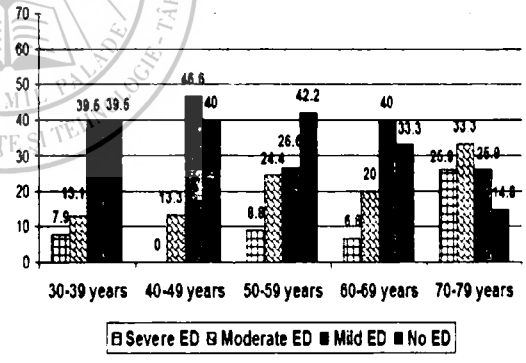

Figure 1. The prevalence of erectile dysfunction

Moderate erectile dysfunction has a similar upward trend, being 13.1% at age group 30 - 39 years, 24.4% in group 50 - 59 years and atingang a maximum of 33.3% in the most elderly patients.

For each group we separately calculated the average IIEF scores (Figure. 2)

Group "0" - includes 32 patients and the average

IIEF is 45.9

Group "1" - includes 18 patients with an average IIEF is 44.1

Group "2" - includes 25 patients with an average IIEF is 37.0

Group "3" - includes 25 patients with an average IIEF is 46.9

Group "4" - includes 20 patients with an average IIEF is 37.8

Group "5" - includes 19 patients with an average IIEF is 22.9

The chart above, were we draw the trend line,

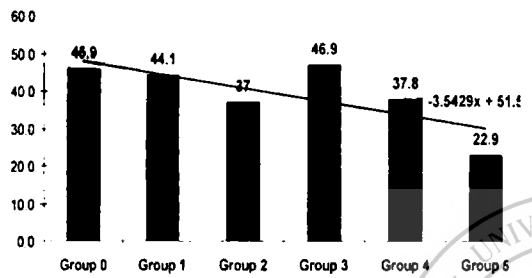

Figure 2. Medium IIEF on the 6 groups

which is downward, allows us to say that the average IIEF score decreases as early the onset of erectile dysfunction is. The group "0", were the onset ED is concurrently with CVD debute, have an average of 45.9, while the group "5", were the onset ED is more than 4 years before beginning BCV has an average of 22.9 points on IIEF test, that means less than half.

To determine if there is statistically significant differences between the 6 groups it was calculated the t-test, version: Two-sample Assuming Unequal Variances. In a first stage we compared group "0" with the other 5 groups. In the table below are found the t values, which must be greater than 2 and p value, which should be below 0.05, for a statistically significant difference (Table II).

Table II

	0 with 1	0 with 2	0 with 3	0 with 4	0 with 5
t	0,55	2,69	-0,33	1,79	3,775131
p	0,59	0,0097	0,74	0,08	0,003631

Note that there are statistically significant differences between group 0 and group 2 and between group 0 and group 5.

Then compared the group 1 with the other groups (Table III).

Table III

	1 with 2	1 with 3	1 with 4	1 with 5
t	3,39372	-0,85014	1,334077	3,39372
p	0,005995	0,400866	0,191897	0,005995

Here is observed statistically significant difference between group 1 and group 2 and between group 1 and group 5.

Comparison between group 2 and other groups shows that there are statistically significant differences between group 2 and group 5 (Table IV).

Table IV

	2 with 3	2 with 4	2 with 5
t	-2,99063	-0,17602	2,238889
p	0,004461	0,861355	0,046792

Comparison of group 3 and other shows that there are statistically significant differences between both group 3 and group 4 and between group 3 and group 5 (Table V).

Table V

	3 with 4	3 with 5
t	2,009671	3,936728
p	0,053852	0,00279

And finally the comaparison between group 4 and 5 show that there are statistically significant differences between the two groups (Table VI).

Table VI

	4 cu 5
t	2,132106
p	0,048844

DISCUSSIONS

It can be said under the data above that any patient with DE must be considered at risk to cardiovascular risk, up to the contrary.

Recent studies show that up to 75% of patients with effort pectoris angina have ED also. Most early sign in patients with atherosclerosis is the diminishing of coronary reserve, meaning decreased ability to increase blood flow to the effort. Non-invasive determination of coronary reserve is a reliable method in the evaluation of endothelial dysfunction. Recently studies demonstrated a decrease of the coronary reserve in patients with diabetes mellitus also.[6]

Currently are increasingly more evidence that ED may be a clinical sign of early coronary disorder and that the connection is the endothelial dysfunction. Determination of coronary reserve is indeed a marker of coronary disorder in patients with DE and without diabetes mellitus, arterial hypertension or other cardiac disease. Using the questionnaire of the international index of erectile function shown that it correlates with the overall level of plaque in the aterom at the coronarography.[2] When these data will be check in larger studies, this questionnaire will be used as a predictive factor in identifying men at risk for endothelial dysfunction and likely silent coronary impairment, without having evidence of clinical cardiovascular disease.[2]

To explain the link between cardiac damage and erectile dysfunction was issued "vessel size hypothesis".[4,7] In this sense, considering the adverse impact of systemic atherosclerosis, all vascular territories would be affected in the same mesure.Still, symptoms rarely appear in the same time. This difference of vascular impairment leed to assumption that larger vessels more easily bear the same amount of plaque, than do the small vessels.

According to this hypothesis, because penile arteries are smaller than coronary arteries, patients with erectile dysfunction rarely have symptoms of ischemic cardiopathy, while patients with coronary disease have frequently erectile dysfunction.

The "COBRA" study, which examined the association between this two diseases - the prevalence of ED in patients with ischemic cardiopathy, depending on their clinical presentation - showed that the erectile dysfunction severity is correlated with coronary disorder expansion and that ED precedes coronary ischemia in most patients with 2-3 years.[3]

CONCLUSIONS

After comparing the 6 subgroups by applying t-test, version: Two-sample Assuming Unequal Variances, we concluded that the severity of erectile dysfunction is even higher as the beginning of erectile dysfunction is early, respectively, as onset of erectile dysfunction was before the onset of cardiovascular disease.

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Infective endocarditis in children with restrictive ventricular septal defect - case report

Amalia Făgărăşan

Endocardita infecţioasă este una dintre complicaţiile serioase apărute la pacienţii cu boli cardiace congenitale, ea fiind definită ca o infecţie localizată la nivelul suprafeţei endocardului. Zona lezată are risc ridicat de colonizare bacteriană. Defectul septal ventricular este o malformaţie cardiacă congenitală frecventă în patologia cardiacă a copilului, evoluţia şi abordarea terapeutică depinde de mărimea shuntului, de gradul de hipertensiune pulmonară şi de anomaliile cardiace asociate. Riscul de endocardită bacteriană la copiii diagnosticaţi cu defect septal ventricular nu depinde de mărimea defectului, astfel problema ridicată de necesitatea sau nu a închiderii defectelor mici, restrictive rămâne deschisă. Prezint cazul unui copil în varstă de 6 ani, diagnosticat cu defect septal ventricular restrictiv perimembranos complicat în evoluţie cu endocardită bacteriană cu Staphilococcus aureus.
Key words: defect septal ventricular, copil, endocardită bacteriană.

Infective endocarditis is one of the serios complications of congenital heart diseases, defined as a microbial infection of the endocardial (endothelial) surface of the heart. The damaged area has a high risk of bacterial colonization. Ventricular septal defect (VSD) is a common congenital heart disease in children, the evolution and therapeutical approach indicated by the location of the defect, the magnitude of the shunt, the degree of pulmonary hypertension and the associated cardiac anomalies. The risk of bacterial endocarditis in children diagnosed with VSD does not depend on the size of the shunt, therefore, the problem of closing a restrictive VSD remains open to discussion. We willl be presenting the case of a male child, 6 years old, diagnosed with restrictive perimembranous VSD and bacterial endocarditis with Staphylococcus aureus.
Key words: ventricular septal defect, child, endocarditis.

Case presentation

F.D., male, 6 years old, comes from a rural environment.

Diagnosis: febril state of unknown etiology. Restrictive VSD.

Without signs of cardiac or genetic disorders.

Born at term, weighing 3,40 Kilograms, after an uneventful pregnancy and normal delivery. Neuropsychomotory development according to age. Vaccinated accordingly.

Diagnosed with perimembranous VSD at 6 months, various upper airway infections.

History: the pacient has been transfered to our department from the Territorial Service of Pediatrics due to prolongued febril state, of about 22 days (hyperpyrexia- temperature elevations of up to 40° C, chills, profuse nocturne sweating, asteny, inappetence). The patient was treated with antibiotics (second and third generation cephalosporin and aminoglycosides) and symptomatics. Due to the persistence of the febile state and the biological inflamatory syndrome, the patient is transfered to us. He has been traced with a restrictive VSD since infancy.

Physical examination uppon admittance: fever (39,8° C), altered general status, marked mucotegumentary palour , cardiac tachycardia, AV 140/min, a holosystolic murmur graded 3 from 6 with large irradiation, bilateral palpable perypheral pulse, blood pressure 90/46 mmHg. Hepatomegaly, no splenomegaly, SO2 96%.

Paraclinical examination: laboratory: elevate acute phase reactants: leukocytosis- 18.700/mmc; anemia: red blood cell: 3000000/mmc, Hg 7,8 g/dl, platelets: 311000mmł. Differential white blood cell count (DIFF): Neutrophilis 79%, Eosinophilis 3%, Monocytes 2%, Basophils 1%, Lymphocytes 14%. Erythrocyte sedimentation rate (ESR) elevated - 70/h). Routine urinalysis: color yellow, turbidity clear, specific gravity 1,015; pH 4,8, glucose negative, ketones negative, blood-microscopic hematuria+. Presence of rheumatoid factor. Electrolyte tests normal. Seric creatinine, uric Acid – normal values. AST 65u/L, SGOT 89 u/L. Nasal culture: Staphylococcus aureus MSS, annexed antibiogram.Throat culture negative. Positive blood culture: staphylococcus aureus coagulase-positive methicillin-susceptible.

ECG: sinusal tachicardya, 130/min.

The chest X-ray showed a increase in heart size and increased pulmonary vascular circulation.

Two-dimensional ecocardiography, spectral and color Doppler, with Sonos 5500, transducer 4 MHz,

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showed a situs solitus, with normal atrio-ventriculary and ventriculo-arteriary connexions, and a small perimembranous defect of about 5 mm, and the jet velocity of 70 mmHg, with a left side shunt. Four-chamber projection (apical) and short axis images show vegetations of 10/6 mm on the tricuspid leaflets, mobile and with high risk for embolic events (Figure 1,2). Apical four-chamber projection shows a severe tricuspid insufficiency (Figure 3). Spectral and color Doppler identified a large tricuspid stenosis (Figure 4,5).

Figure 1. Apical four chamber - large vegetations on tricuspid leaflets

Figure 2. Short axis scan – large vegetations on tricuspid leaflets

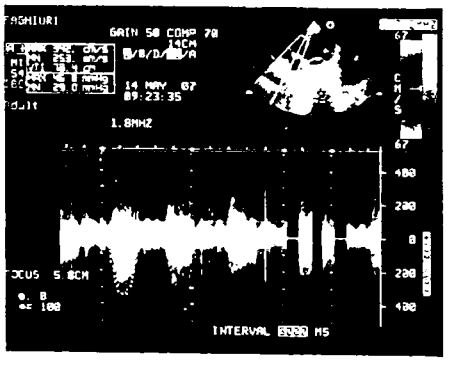

Figure 3. Spectral Doppler - severe tricuspidian insufficiency

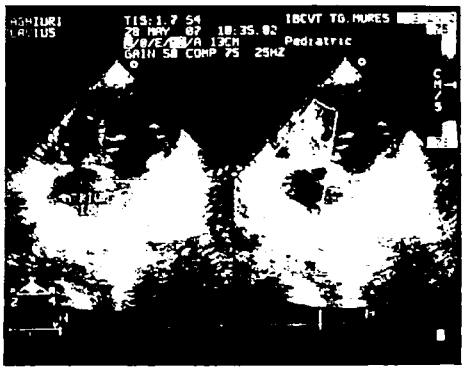

Figure 4. Apical four chamber - Doppler and color flow examination

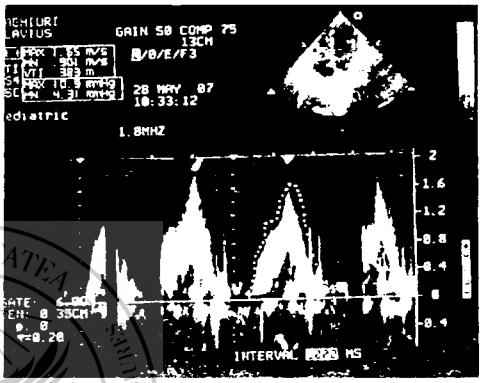

Figure 5. Apical four chamber, spectral Doppler - large tricuspid stenosis

Clinical development: the purpose of the treatment was antiinfectious (according to the antibiogram) and symptomatic. Control by antiinfectious treatment has prevented complications determined by the location of the vegetation – tricuspid leaflets (high risk of embolism, significant tricuspid failure). The clinical, paraclinical and blood culture development under treatment has been favorable. Post-antibiotic evaluation (4 weeks) shows a significant regression in the size of the vegetation with persistent tricuspid regurgitation. The patient benefitted from surgical correction – the excision of the vegetation and the closing of the VSD; a favourable evolution, upon release a minor tricuspid stenosis was detected. Spectral Doppler evaluation permits the grading of the residual tricuspid leaflet stenosis.

DISCUSSION

The particularity of the case consists of the presence of bacterian endocarditis (staphylococcus aureus coagulase-positive methicillin-susceptible) in an cardiac asymptomatic child with small, restrictive VSD. Ventricular septal defect is the most common congenital heart disease diagnosed at birth, the spontaneous closing of the defect occuring frequently (an event we

need to consider in therapeutic approach).[6] The rate of spontaneous closing depends on the location and size of the defect (most defects close during the first year, especially the restrictive muscular defects).[7,10] The possibility of closing or shrinking in size of a VSD is diverse (most frequently in perimembranous VSD the septal tricuspid leaflet attaches itself to the defect, closing it).[7] Therefore, the therapeutic approach will depend on the location and size of the defect, associated lesions and the age of the patient.[5,6,8,9] With the aforementioned arguments, the risk of bacterian endocarditis is still present regardless of the size and location of the defect, especially in children in kindergartens and schools where the percentage of bacterial carriers is high (such as the case of our patient), who suffer from frequent acute respiratory infections. Bacterian endocarditis remains one of the serious complications of congenital heart disease, defined as a grafting of a bacterial or micotic germ on the endocardial surface, especially damaged endocardial surface (in congenital heart disease with shunt lesion), by forming an aseptic thrombus. The damaged area has a high risk of bacterial colonization.[2] The presented case has another particularity, that postendocarditis bacteriana remains a large tricuspid stenosis which represents a risk factor for the reccurence of the endocarditis. In conclusion, the antimicrobial prophylaxis for endocarditis remains a mandatory requirement in all children diagnosed with congenital heart disease with a shunt, regardless of its size.[1,3,4]

CONCLUSIONS

The opportunity of closing restrictive VSD depends on a series of considerations related to: age of the patient, location of the defect, associated lesions (aortic failure associated to VSD constitutes a precocious closing argument) and the risk of bacterial endocarditis must not be neglected, seeing as how children in groups are exposed to respiratory infections caused by staphyloccus or streptococcus, bacterial agents involved in infectious endocarditis etiology.

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Reflux esophagitis, cause of esophageal stenosis – a clynical case

Oana Mărginean[1], Ana-Maria Pitea[1]

Mecanismele care determină reflux gastroesofagian La copil includ incompetența sfincterului esofagian inferior, prelungirea clearence-ului esofagian și întârzierea evacuării gastrice, adaugându-se si factori favorizanți.
Prezentare de caz: pacient de 6,11 ani, cunoscut cu reflux între 1-3 ani, netratat, cu frecvente intercurențe respiratorii, care se prezintă pentru dificultăți alimentare, vărsături postprandial precoce și în contextul intercurențelor.
Gastroscopie: mucoasa esofagiană congestionată, friabilă, posibilă stenoză esofagiană Bariu-pasaj: esofag cu pereți supli, progresia substanței de contrast până la nivelul 1/3 inferioare; stomacul dilatat superior (aer în cantitate mare). În poziție Trendelemburg nu se evidențiază reflux gastro-esofagian. Spasm esofagian.
Evoluție favorabilă sub tratament și alimentație cu semisolide, intermitent imposibilitatea administrării de lapte, vărsături matinale practic absente în ultimele 5 luni; curba ponderală ascendentă.
Ulterior la esofagoscopie: mucoasa esofagiană intens congestionată, friabilă, cu tendință la sângerare, false membrane, stenoză circumferențială a esofagului.
La pasajul baritat se constată stenoza 1/3 inferioare a esofagului cu păstrarea elasticității parietale.
Concluzii: Întotdeuna în fața unui caz cu dificultăți alimentare, tulburări de deglutiție și antecedente de tuse și infecții respiratorii, trebuie să ne gândim la un reflux gastroesofagian cu posibilă stenoză esofagiană consecutivă. Când esofagita este consecința refluxului acid, motilitatea esofagiană și disfuncția sfincteriană se agravează și apare un cerc vicios între reflux și injuria mucoasei.
Cuvinte cheie: esofag, stenoza, copil, reflux

At children, the mechanisms that cause gastroesophageal reflux are the incompetence of lower esophageal sphincter, the prolongation of inferior esophageal clearance, the delay of gastric evacuation and favourable factors.
Case presentation: We present a 6,11 year-old patient, known with gastroesophageal reflux, without treatment, with many respiratory infections; he presented for difficulties during alimentation and vomiting.
Gastroscopy: congestion of esophageal mucosa, friability, possible esophageal stenosis. Barium passage: esophageal sleazy walls, with the progression of contrast substance till the inferior third. The stomach is distended superior by a large quantity of air. In Trendelemburg position there is no gastroesophageal reflux marked out; esophagean persistent spasm.
The evolution is favourable under alimentation with semisolid-food and treatment, with intermittent impossibility of drinking milk; no vomiting, ascending ponderal curve.
Subsequently at esophagoscopy: intense congestion of the esophageal mucosa, friability, tendency of bleeding, circumferential stenosis. At barium passage a stenosis of the lower 1/3 part of esophagus is detected.
Conclusion: in front of a case with feeding difficulties, trouble swallowing and antecedents of cough and respiratory infections, we have to think about a gastroesophageal reflux with possible consecutive stenosis. When esophagitis develops, esophageal motility and sphincterian function are impaired further, creating a cycle of reflux and esophageal injury.
Key words: stenosis, esophagus, child, reflux disease

Gastroesophageal reflux is defined as the effortless retrograde movement of gastric contents upward into the esophagus or oropharynx.[2,3]

At children, the mechanisms that cause gastroesophageal reflux are the incompetence of lower esophageal sphincter as well as favourable factors such as: the transient relaxation of the sphincter, esophagitis, increased intra-abdominal pressure, cough, persistent respiratory difficulty and hiatal hernia.[1,3,10,11]

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After the gastroesophageal reflux settlement, it maintains the incompetence of lower esophageal sphincter which causes failure of motor mechanisms, with prolonged contact of esophageal mucosa with gastric pepsin, biliar salts and proteolytic pancreatic enzymes; in time - the esophageal mucosa erodes and appears the peptic esophagitis disease.[3,10,11]

Esophagitis are inflammatory esophageal diseaes. They can be acute (bacterial, caustic or traumatic), as well as they can have a chronic evolution (also bacterial, traumatic, chemical – in case of gastroesophageal reflux disease, drug associated or secondary to esophageal varix).[1,4,7]

Clinic, the child presents retrosternal burns and pain, exacerbated in supine position, occasionaly Sandifer syndrome.[2,8,9]

The following can be complications of peptic esophagitis:[1,4,10,11]

- esophageal stricture
- bleedings
- failure to thrive
- Barett's Esophagus

The superiour digestive endoscopy (Esophageal endoscopy) allows the visualization of esophagitis injuries, the prelevation of bioptic material for histological diagnostic and the diagnostic of complications as stenosis.[5,7,12]

In peptic esophagitis the following aspects are characteristic:[6,12]

-hyperemia (red colour of esophageal mucosa, with dissapearance of vascular draw)

-longitudinal erosions, sometime covered by white-grey material, from fibrin and leucocytes; the erosions are partly or total joining;

- the mucosal thickening, loosing it's sheeny aspect, gut, without possibility of vascularity visualization.

Endoscopic Classification of Reflux Esophagitis in big child according to Savary and Miller[7,8,9]

-Stage I - one or more non confluent lesion with erythema and edema

-Stage II - confluent erosive and edematous lesions not covering the complete esophageal circumference

-Stage III - the lesion covers the complete esophageal circumference

-Stage IV - Esophageal ulcer, Barrett´s epithelium, strictures and other chronic mucosal lesions

The esophageal mucosa biopsy is performed in 1/5 part of esophagus, usually not in the last 2 cm of esophagus – because this area can contain inflammatory cells in children with minimal Gastro-esophageal Reflux Disease.[2,5,6,7]

In children with susceptibility of reflux disease, without macroscopic detectable esophagitis, at least two biopsies are performed, 2-3 cm upon Z-line.

Treatment of Gastro-esophageal Reflux Disease associated to reflux esophagitis includes tacky food, eating in proclive position, prokinetics (as Cisapride 0,2 mg/kg/day - 20-30'minutes before meal, Metoclopramid 0,1 mg/kg before meals, Eritromicyn 5-8 mg/kg/day), proton pump inhibitor (Omeprazole, Pantoprazole, Lansoprazole 0,7 mg/kg/day); surgical treatment when complications appeared.[2,10,11]

The aim of work

We present a 6,11 year old patient known with gastroesophageal reflux between 1 and 3 years old, with no treatment meantime, who developed consecutive esophageal stenosis.

Case report

Patient C.H. 6,11 years old at the moment of presentation in our clinic, presents for difficulties during alimentation with solid-food, vomiting, especially precocious aftermeal, often during acute respiratory episodes.

Heredo-colateral antecedents are not important for present acuses.

Personal physiological antecedents: the first-born child, (pregnancy affirmatively phisiologic), weight at birth 3300 g, Apgar 7/1min, 9/5min, breastfeeded 1 month.

By personal pathological antecedents we note that the patient presented many intercurrent respiratory infections.

After 1st year of life he was diagnosed with Gastroesophageal Reflux, without treatment in territory, with apparent amelioration till 3 years old.

October 2007

The patient presents for

- vomiting early in the morning and after meal
- disphagy, especially at liquids

Symptoms:

- pains in epigastric region
- vomiting early in the morning, often with abundant mucus

Clinic – phisical examination does not detect signifiant pathological aspects.

Digestive endoscopy shows congestion of 1/3 inferior esophageal mucosa, friability, possible esophageal stenosis, esophageal spasm which does not allow the complete endoscopic exploration.

Barium-passage: esophageal thin walls, with the progression of contrast substance till the inferior third. The stomach is distended superior by a large quantity of air. In Trendelemburg position there is no gastroesophageal reflux marked out; esophageal persistent spasm.

Diagnostic: Esophageal persistent spasm. Esophagitis

The case is interpretated as esophageal persistent spasm, without the possibility of excluding an esophageal stenosis.

Recomandations: eviction of stimulating and irritating food, 5 meals/ day.

Treatment: proton pump inhibitors, prokinetics, antispastics.

2008 MARCH

The patient presents with:

- early vomiting much rare (almost absent since october)
- alimentation is possible especially with semisolid-food
- intermittent appears the impossibility of drinking milk

Clinic – phisical examination does not detect signifiant pathological aspects.

Laboratory

Haemogram, ESR: normal confines.

Biochemistry – normal findings.

Coagulogram – normal values.

At Barium-passage a stenosis of the lower 1/3 part of esophagus is detected, with the maintenance of the wall's elasticity.

Figure 1. Radiologic images at Barium passage: A - PA aspect, B - Bevel view: Stenosis of lower 1/3 part of esophagus

Esophagoscopy reveals intense congestion of the esophageal mucosa, friability, with tendency of bleeding, false membranes, circumferential stenosis which does not allow the complete endoscopic exploration. Esophagitis Degree IV (After Endoscopic Classification of Reflux Esophagitis according to Savary and Miller).

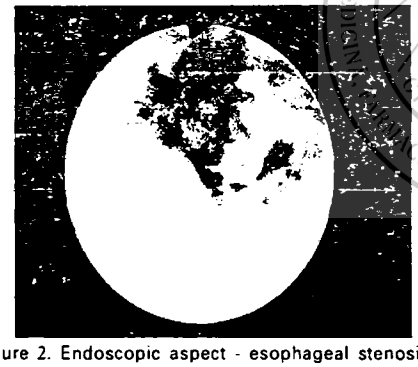

Figure 2. Endoscopic aspect - esophageal stenosis with false membranes

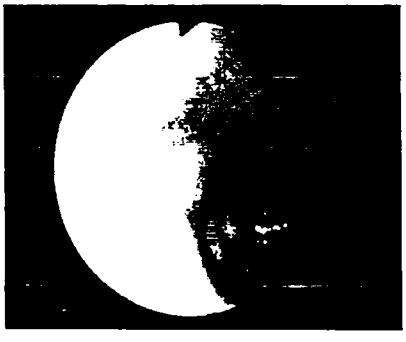

Figure 3 Endoscopic aspect - stenosis with false membranes and bleedings

Diagnostic: Esophagitis Degree IV. Esophageal stenosis

Recommendations. diet, food without spices, no toasted, smoked, acide nourishment; 5 meals/ day.

Treatment: proton pump inhibitors and prokinetics.

Surgical consult recomands procedures of esophagian progressive dilations.

Conclusions

In front of a case with feeding difficulties, trouble swallowing and antecedents of cough and respiratory infections, we have to think about a gastroesophageal reflux with possible consecutive stenosis.

When esophagitis develops as a result of acid reflux, esophageal motility and sphincterian function are impaired further, creating a cycle of reflux and esophageal injury.

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48,XXYY syndrome- a case presentation and review of the literature

Ionela Pascanu, Claudia Banescu, Katalin Csep, Ana Maria Butila Todoran

Descriem cazul unui băiat de 17 ani, investigat datorită unui test Barr pozitiv şi unui sindrom dismorfic minor. Examenul obiectiv evidenţiază ginecomastie bilaterală moderată, penis de dimensiuni normale şi testicoli de dimensiuni reduse (volum testicular drept 10 ml şi respectiv stâng de 15 ml). Gonadotropinele bazale au prezentat valori crescute iar testosteronul seric total a fost scăzut (hipogonadism hipergonadotrop). Efectuarea cariotipului folosind culturi de limfocite periferice a evidenţiat 48,XXYY. Se discută strategia terapeutică a acestui caz, problemele cognitive şi comportamentale frecvent descrise în aneupoidiile ce implică heterozomi şi importanţa unui climat familial suportiv. Testul Barr are numai valoare orientativă şi de screening în acest sindrom. Efectuarea cariotipului e importanta în toate cazurile în care se evidenţiază un hipogonadism hipergonadotrop, mai ales daca se asociază modificări comportamentale şi/sau sindrom dismorfic.
Cuvinte cheie: 48,XXYY, anomalii cromozomiale, modificări comportamentale

We report a case of a 17 years old boy referred because of a positive Barr body test and minor dysmorphic features. Endocrine examination shows mild bilateral gynecomastia, normal size penis and small testis with right testis volume of 10 ml and left testis volume of 15 ml. Basal gonadotropins were elevated and serum testosterone low (hypergonadotropic hypogonadism). Cytogenetic analysis of cultured peripheral blood lymphocytes shows 48,XXYY We discussed the clinical management and also the cognitive and behavioral problems and the importance of a supportive family and a healthy environment for this case. Barr bodies counting in a buccal smear, still in use in many cytogenetic laboratories in our country, cannot differentiate this syndrome, so it is important to perform karyotype for every hypergonadotropic hypogonadism especially if there is other dysmorphic features or/and behavioral problems.
Key words: 48,XXYY, sex chromosome abnormalities, behavioral problem

Sex chromosome aneuploidies are the most frequently occurring chromosomal abnormalities with an incidence of 1 in 400 births[3]. These aneuploidies involve the addition or deletion of an X or Y chromosome to a normal female or male chromosome karyotype, resulting in the well-described 47,XXX, 47,XXY, 47,XYY, or 45,X abnormalities. In contrast, the addition of more than one extra sex chromosome occurs rarely and information in the literature is generally limited to isolated case reports. Although neither is associated with a distinct phenotype, a proportion of individuals with such aberrations are more liable to have impaired speech development, limited learning ability, and behavioral problems.[7,10]

Our purpose is to present an unusual case of aneuploidy affecting heterosomes and to summarize current knowledge and implications regarding the moment of the diagnosis in the management of this case.

Case report

A.A, a seventeen year old boy, was referred to our outpatient's clinic because of a positive Barr body test. He was the first child of unrelated parents, born after a full term pregnancy and a normal delivery, with a birth weight of 3.150 kg and a length of 51 cm. There was no family history of intellectual handicap or mental illness. He could sit without support at 11 months and walked at 18 months. His developmental and intellectual functioning during early childhood had not been formally tested but was suspected to be low-average. He was able to speak only few words at 24 months and he was confronting with speech and language delay, receiving long term speech therapy. His mother reported also moderate behavioral concerns: he was always been an anxious, immature, and sensitive child, preferring friends younger than himself, but without signs of aggressiveness. He attends a normal school.

At the moment the patients measure 175, 6 cm in height and weights 83 kg, with a BMI of 27, 1 kg/m^2. His head circumference is 56, 2 cm, his sitting height 78, 9 cm and his arm spam 179,5 cm. His facial appearance is coarse with mild dysmorphism consisting of macrocephaly, prominent forehead and supraorbital ridges, dense scalp hair. The external ears are placed above the eye-line and the nasal bridge appears broad. The intercanthal distance is 3.6 cm. We notice also a short philtrum with a thick lower lip and prognathism. Abdomen examination shows no organomegaly. On the hips and anterior portion of the abdomen there are striae. Hand findings include single transverse crease and bilateral clinodactyly of the fifth finger. There is also mild genu valgum and the veins in his legs is prominent, but no skin ulcer. The neurologic examination is normal. The I.Q. is 92.

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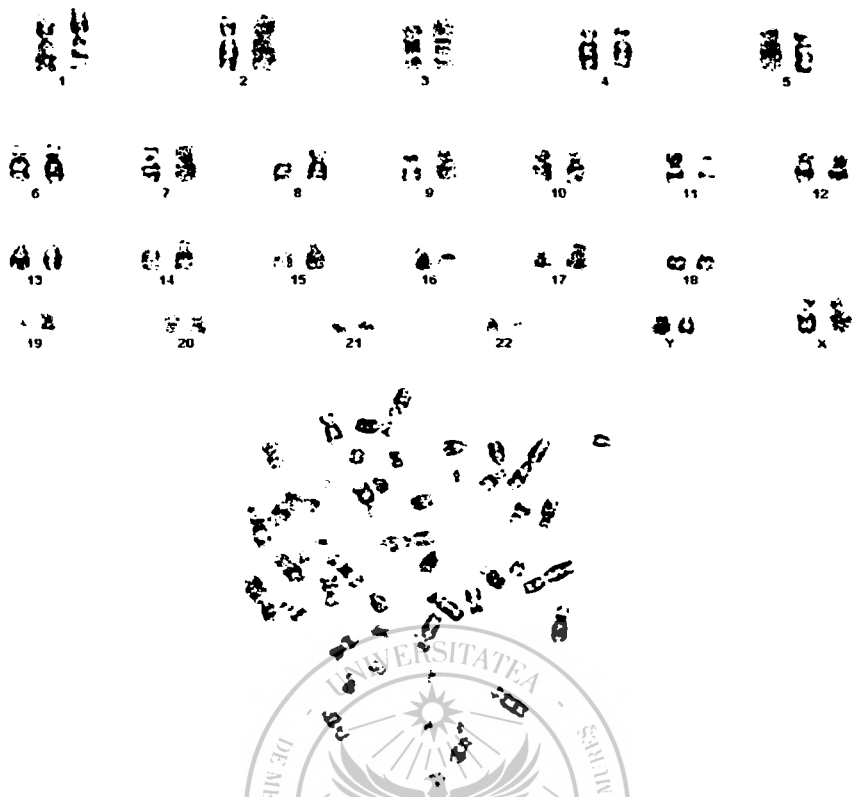

Figure 1. Metaphase and karyotype (standard G-banding) of the patient A.A., showing 48,XXYY

Endocrine examination shows mild bilateral gynecomastia, with normally set nipples. His penis is of normal size but his testis are small with right testis volume of 10 ml and left testis volume of 15 ml. Axillary hair was sparse and pubic hair was Tanner IV.

The karyotype -standard G banding method- was performed on lymphocytes from peripheral blood (20 metaphases examined) and resulted homogeneously 48,XXYY. (figure 1).

Hormonal analysis revealed:

-Plasma level of prolactin, estradiol, cortisol in the normal range,

-Low level of testosterone and increased level of both FSH and LH hormones

- LH 35,6 mIU/ml (0-18)
- FSH 30,84 mIU/ml (0-18)
- testosterone 1, 206 ng/ml (2,4-12ng/ml)

DISCUSSIONS

The first description of this aneuploidy was published by Muldal and Ockey[4] in 1960 as a cytogenetic variant of Klinefelter syndrome in a 15 year old boy with mental retardation. Nowadays, it is accepted as a distinct clinical and genetic entity.[6] The incidence ranges from 1 in 17,000 to 1 in 50,000 males[5,8] and is not associated with advanced parental age, patients as old as 70 have been described. Sorensen et al[8] have published a prevalence of 48,XXYY amongst institutionalized mentally retarded individuals of 1/300.

There is still a controversy whether this syndrome is associated with recognizable physical features or not. Some authors, like Borghraef et al[1] reported that at least 50% of the 48,XXYY boys was referred for a chromosomal investigation because of one or more clinically evident abnormalities. These include truncular obesity, macrocephaly, and maxillary hypoplasia. Despite this, many authors agree that facial characteristics are variable in this syndrome and skeletal findings are generally minor. Our patient is overweight and has many minor dysmorphic features, some of them specific to heterosomes aneuploidy. Regarding skeletal findings we noticed genu valgum and clinodactily in our patient, other skeletal abnormalities including radioulnar synostosis or pes cavus may also be present.[3] Zelante et al[11] reported a 48,XXYY karyotype in a 35 year old adult with a very particular "pugilistic" facial appearance witch is very similar to our patient's face. This appearance seems to be correlated to the Y polysomy.

Phenotypically, men with 48,XXYY are usually tall with a final adult height greater than 170 cm, and they are thus exceeding males with 47,XXY. They have long,

thin legs, often the upper segment-to-lower segment ratio is decreased (<1), with and a eunuchoid habitus being characteristic.[3]

In addition to the physical features of Klinefelter Syndrome, boys with 48,XXYY have been thought to have more severe cognitive and behavioral problems, determinate by the addition of an extra Y chromosome or by double sex chromosomes anueploidy. The behavior problems, frequently psychotic reactions have been reported in most 48,XXYY patients.[10] However, a bias of ascertainment exists, because at least one third of the more than 100 worldwide reported cases were obtained from mental and behavioral hospital screenings in the 1960s and 1970s.[3] Problems in the 48,XXYY males range from anxiety and withdrawal to aggressive and delinquent behaviors. Visootsak et al[12] hypothesizes that males with 48,XXYY are more prone to these problems then other males with sex chromosomes aneuploidy because their higher cognitive functioning provides more opportunities to interact in social settings.

The IQs in this syndrome range from 60 to 80, with 10% having an IQ above 80, and IQs up to 111 have been reported.[8] The intellectual development, that varies from nearly normal to moderate/severe mental retardation in this aneuploidy is attributed mainly to the X polysomy and, probably, to a skewed X-inactivation.[11] It's well described the effects of extra X chromosomes on physical and mental development, each X reduces the overall IQ by 15-16 points, with language most affected.[3] Global developmental delay and language disability, with receptive skills better than expressive skills, are common in 48,XXYY males. Motor delay and decreased coordination are similar to that observed in 47,XXY. In a study of 16 males with 48,XXYY compared to 9 males with 47,XXY between the ages of 5 and 20, findings indicate that 48,XXYY males have verbal and full scale IQ's significantly lower than males with 47,XXY. 48,XXYY males are also prone to have problems with hyperactivity, conduct and depression compared to males with 47,XXY. Their mean scores in these areas are in the clinically significant range and males with 47,XXY have scores in the average range. Furthermore, 48,XXYY males have significantly lower adaptive functioning than males with 47,XXY.[9] Our patient, despite the delay in language acquisition and behavioral problems described, was never referred to a genetic department until his sexual development was suboptimal. He is not mentally retardate and with optimal testosterone treatment the long term prognosis good. This conclusion is in agreement with Linden regarding an ascertainment bias existing in screening individuals for X and Y chromosomes abnormalities. Whether more benign phenotypes of heterosomes polysomy and tetrasomy kayotypes are possible has not been established. It is also true that our patient came from a very educated and supportive family and has received early and ongoing speech and language therapy. The parents have been actively involved in their child's development and education though interactions with school personnel. This fact seems to assist our patient in maximizing his potential.

We noticed vein dilatations in both leg in our case, but no other modifications. The skin trophic ulcers are very common in the 48,XXYY subjects as well as in Klinefelter's syndrome. Their etiology has been attributed to varicose vein and chronic edema of the legs, to a thromboembolism tendency and/or arteriolar restriction.[2] Other different pathogenetic hypotheses include increased platelet aggregation and a deficit of fibrinolysis which is liable to correction by androgen substitution. We indicated an arterial and venous Doppler examination in our patient, which we think it would help us to understanding the pathogenic role in ulcers formation and will allow us to take preventive measures .

Since additional Y chromosome is accompanied by an additional X chromosome in our case we consider that it is difficult to pinpoint specific features in these phenotypes that are unique to either the X or Y chromosome.

Hypergonadotrophic hypogonadism is similar to that of 47,XXY men: increased follicle-stimulating hormone and luteinizing hormone, decreased testosterone, small testes, and sparse body hair. Because testicular volume in our case is not so reduced compared with testicular volume described in literature we suspected a mosaic, which can be evidenced with fibroblast cell culture. Only half of 48,XXYY cases have been reported to have small penises, the others like our case can have penis with normal size. Testicular histology in 48, XXYY has been reported to be similar to those in 47,XXY and includes hyalinization of the seminiferous tubules, hyperplasia and fibrosis of Leydig cells and lack of spermatogenesis. There is also a similarity in testosterone therapy to that prescribed for Klinefelter syndrome. The presence of gynecomastia has been reported frequently and is not prevented by testosterone supplementation.

CONCLUSION

Our case confirms that, in this very rare gonosomal aneuploidy, minor and nonspecific dismorphyc anomalies can be present together with delay in language acquisition and behavioral problems but mentally retardation is not mandatory. Barr bodies counting in a buccal smear, still in use in many cytogenetic laboratories in our country, cannot differentiate this syndrome, so it is important to perform karyotype for every hypergonadotropic hypogonadism.

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Interdisciplinary approach of the neurologic patient with multiple arterial lesions

Andreea Bârsan[1], Jerzicska Erno[2], A.A Șchiopu[3], A. Șchiopu[4]

Ateroscleroza este o boală inflamatorie cronică caracterizată prin acumularea de lipide, calciu şi ţesut fibros la nivelul intimei arteriale, cu formarea plăcii de aterom (aterosclerotice) şi îngustarea concomitentă a lumenului arterial. Plăcile ateromatoase sunt localizate în special la nivelul arterelor medii şi mari (aortă, carotidă, coronare, femurale, artere mezenterice).
Principala complicaţie a plăcii aterosclerotice o constituie ruptura, urmată de tromboză. Trombul poate opri fluxul sanguin local sau la distanţă, prin formarea de ateroemboli. Acest mecanism stă la baza majorităţii evenimentelor ischemice; aspectul clinic depinde de teritoriul vascular afectat şi de severitatea stenozei.
Ateroscleroza este o boală plurivasculară. La nivelul carotidei, poate genera evenimente ischemice sau infarct cerebral, complicaţie cu consecinţe grave şi definitive. În acelaşi timp, pacientul poate prezenta infarct miocardic sau evenimente ischemice periferice acute, având ca şi rezultat scăderea dramatică a calităţii vieţii sau chiar decesul pacientului.
Prezentăm un caz clinic care a necesitat o abordare terapeutică complexă, finalizat cu rezultate excelente.
Cuvinte cheie: ateroscleroză, boală plurivasculară, accident vascular ischemic

Atherosclerosis is a chronic inflammatory disease which is characterized by the accumulation of lipids, calcium and fibrous tissue in the arterial intima. The result of this process is the atheroma (atherosclerotic plaque) with concomitant narrowing of the arterial lumen in various degrees. Atheromatous plaques are localized mainly in the large and medium arteries (aorta, coronary, carotid, femoral, mesenteric arteries).
The main complication of the atherosclerotic plaques is their rupture, followed by local thrombosis. The thrombus may block the blood flow locally or at distance, through the formation of thrombemboli. This mechanism underlies the majority of ischemic diseases which clinically depend on the affected vascular territory and the severity of the stenosis.
Atherosclerosis („the silent killer") is a plurivascular disease. At carotid level, this may trigger cerebral vascular ischemic stroke or cerebral infarction, a devastating complication with definitive and debilitating consequences. At the same time, the patient is a candidate for the occurrence of myocardial infarction and acute peripheric vascular disease, determining a dramatic lowering of the quality of life and even possible death. This is why we consider the presentation of a clinical case which necessitated a complex therapeutic approach with excellent results to be extremely useful.
Key words: atherosclerosis, plurivascular disease, ischemic stroke, teamwork.

Atherosclerosis is a chronic inflammatory disease determined by the deposition of lipoprotein particles (LDL, VLDL) in the arterial wall. In the subendothelial space, the LDL particles are oxidized and transformed in oxLDL, the latest being a powerful proinflammatory factor which activates the endothelial cells and favors leukocyte diapedesys into the arterial intima layer. If the cholesterol influx overcomes the capacity of the macrophages to phagocytose oxLDL, the inflammation becomes chronic and determines the formation of the atherosclerotic plaque. Atherosclerotic plaques are localized in large and medium sized arteries (carotid, coronary, aorta, femoral, mesenteric arteries), developing different degrees of stenosis and, in consequence, interruption of blood flow in the corresponding territory.[9,15,16]

Ninety percent of the carotid diseases are determined by atherosclerosis. The atherosclerotic process is progressing insidiously, being conditioned by the presence of specific risk factors: dislipidaemia, diabetes, arterial hypertension and smoking. An important role is also played by age, gender, genetic background, obesity, sedentarism, stress and some infections (Chlamydia pneumoniae, Cytomegalovirus, Herpes Virus).[10,11,12,13,14,15]

The clinical symptoms occur in the case of severe carotid stenosis (60-70%) or at the moment of plaque erosion or rupture. In these situations carotid artery thrombosis or occlusion develops locally or downstream of the lesion, through emboli or consecutive thrombembolic complications in the intracerebral arteries.[6,15,17]

The clinical manifestations are represented by ischemic stroke in the affected carotid territory, or by cerebral infarction. Amongst the possible clinical findings the most common are: hemiparesis, paresthesias, visual disorders (amaurosis fugax), speech

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impairment (aphasia). These may have variable duration: transient ischemic attack (TIA: persistence of symptoms to maximum 1 hour); reversible ischemic stroke (persistence of symptoms up to a maximum of 24 hours) and progressive stroke until the constitution of cerebral infarction (definitive clinical signs).[5]

The coronary stenosis determines myocardial alteration and is manifested clinically by: angina pectoris, myocardial infarction, arrhythmias or sudden death.[2,5,13,15,20]

The stenosis of the peripheral arteries occurs more frequently in the lower limbs and may be clinically manifested by intermittent claudication and trophic disorders.[1,3,15]

The stenosis of the mesenteric arteries stenosis may cause mesenteric angina, with postprandial periumbillical pain, haematemesis or melena, diarrhea and weight loss.[3]

In conclusion, the clinical manifestations of atherosclerosis impose an interdisciplinary approach (neurologist, cardiologist, angiologist) and the exploration of the whole vascular bed. We exemplify with a case which reflects the severity of this disease, the consequences that it may have and the real benefits of interdisciplinary teamwork.

Case report

Patient GI, 56 years old, was admitted in our Neurology clinic (Clinica Neurologie I, Spitalul Clinic Judetean Targu-Mures) in emergency, with the clinical signs of right sylvian ischemic stroke: motor deficit of the right limbs with sudden onset, facial asymmetry and speach disorders.

Personal pathologic history: smoker (30-40 cigarettes/day); arterial hypertension (untreated); ischemic cardiopathy, stable angina pectoris (precordial constrictive pain at moderate efforts, fatigue, dispnea); lower limbs obliterative arteriopathy (intermittent claudication, ID 100 m).

The clinical neurological evaluation showed central left facial paresis, left hemiparesis (3rd degree), augmented osteotendinous reflexes in the left upper limb, negative plantar stimulation, Toulouse's sign, bilateral Rossner's sign, superficial left hemihypoestesias (predominant brachial), disarthria, conscious, orientated, apathy.

An emergency cranial CT scan was made which revealed an area of hypodensity (infarction in evolution) in the territory of the right cerebralis media artery. In order to establish the etiology of this cerebral infarction, a carotidian echoduplex scan was made, which showed the following alterations: w severe stenosis of the right ICA (internal carotid artery), poststenotic modifications in the right CMA (cerebral medial artery), w brachicephalic trunk thrombosis (BCTr). An angiographic evaluation was imposed, which revealed: w suboclusive stenosis of the BCTr, w right common carotid artery (CCA) occlusion, w suboclusive left CCA stenosis (at origin), w left vertebral artery suboclusive stenosis (V1) (Figure 1,2).

Figure 1. Brachiocephalic trunk suboclusion. Right CCA amputation

Figure 2. Left CCA stenosis

Cardiological clinical evaluation: arterial blood pressure (BP) 170 / 100 mmHg; rhythmical cardiac sounds, pulse rate 80 beats / min, systolic murmur at the aorta (II / 6 degree). ECG evaluation revealed diffuse ischemic changes; effort testing was contraindicated due to the peripheric arterial occlusive disease;

echocardiography showed parietal calcifications of the ascending aorta, minimal atherosclerotic changes of the mitral valve, I/II degree regurgitation of the mitral valve; left ventricle ejection fraction normal (LVEF 55%). Coronarography revealed: w occlusion of the LAD (left anterior descending artery), w severe stenosis of the circumflex artery (proximally), w right coronary artery (RCA) occlusion, rich collateral circulation from the RCA, which loads the whole LAD. Ventriculography demonstrated left ventricular anterior wall abnormal motion (left ventricular aneurism).[2,4,18]

Angiologic evaluation: pale and cold extremities of the lower limbs, diminished pulse amplitude in the right upper limb, diminished right femoral pulse, absent right popliteal pulse, systolic left femoral murmur. Oscilometry indicated a 0 oscilometric index at the right inferior limb and diminished oscilometric index at the left inferior limb.[1,5] The peripheric arterial angiography revealed: w suboclusive lesion of the external iliac artery (EIA, at origin) and w right superficial femoral artery (SFA) occlusion.

The patient was then transferred to the Cardiovascular Surgery Clinic, where the following interventions were indicated:

1st intervention: left subclavio-carotid by-pass (Figure 3,4). The postoperative evolution was favorable, the patient healed surgically "per primam intentionem". After 30 days, the patient did not have any neurological or cardiological symptoms, only the intermittent claudication of the right lower limb persisted. After 3 months, an angiographic reevaluation was done (Figure 5,6), which revealed functional left subclavio-carotid by-pass, 50% left internal carotid artery stenosis, coronary lesions and left ventricular anterior wall abnormal motion.

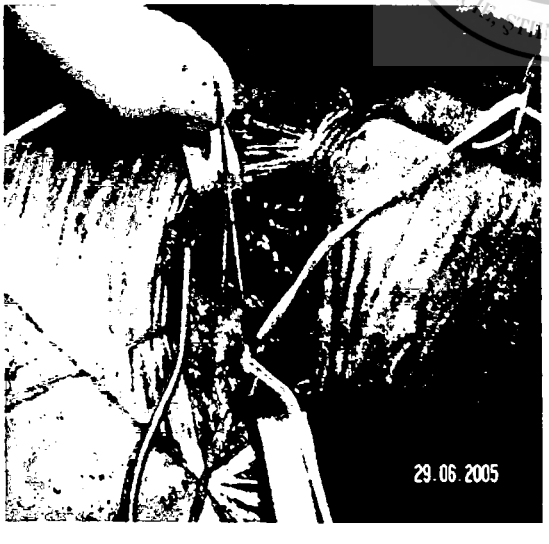

Figure 3. Intraoperativelly, left subclavian artery and the emergence of the vertebral artery

Figure 4. Intraoperativelly, suclavio-carotid by-pass

Figure 5. Functional left subclavio-carotid by-pass (Gore-Tex prosthesis 6mm); left vertebral artery suboclusion.

Figure 6 Functional left subclavio-carotid by-pass; left ICA stenosis.

2nd intervention: coronary artery by-pass grafting (LAD, RCA), left ventricular aneurism resection-suture. The immediate postoperative evolution was favorable, the patient healed surgically "per primam intentionem". After 30 days, the patient remained asymptomatic from a neurological and cardiological point of view. The intermittent claudication in the right lower limb persisted.

After 6 months, the 3rd intervention was indicated, percutaneous right external iliac artery angioplasty, also with a favorable post procedural evolution and the diminishing of the intermittent claudication.

DISCUSSION

The patient, lacking a functional cerebral vascular axis, with extreme coronary lesions, becomes postoperatively asymptomatic from a neurological and cardiological point of view, the quality of life being affected only by the intermittent claudication which was favorably influenced post procedurally by angioplasty.

The patient is continuously monitored in the neurological and cardiological departments ambulatory. Left ICA lesion is monitored through ecoDoppler periodic evaluation, discussing the possibility of ICA endarterectomy in case of stenosis progression. Also, if the intermittent claudication persists, the possibility of a femuro-popliteal by-pass is considered.[3]

We have prescribed a chronic treatment with antiagregants, hypotensives and statins, while also controlling the other cardiovascular risk factors.[7-19]

In conclusion, this case confirms the fact that atherosclerosis is a generalized process. One should never consider only the cerebral vascular lesions, even if the patient is asymptomatic from a cardiological point of view in the moment of CVA occurrence. Conversely, one cannot consider only coronary lesions in a cardiac patient without evaluating the cerebral circulation.[3] In fact, is very well known that almost half of the patients with history of ischemic CVA are candidates in the following 5 years to the occurrence of acute myocardial infarction. This is why we consider useful such an approach to the investigation plan and the interdisciplinary therapeutic strategies. We consider that this approach allowed an ideal outcome of the case, at present the patient having a more than satisfactory quality of life.

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