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The new journal of TSU in medicine



The development of classical medicine has a long history in Georgia. Even the ancient Greeks recognized the high level of the Georgian-Colchis healing art, which is reflected in their myths (Argonauts, Ceres, Medea). Georgia, which was the crossroad of Eastern and Western cultures, was naturally adopting new ideas, theories, medical knowledge, was making the synthesis and used it in practice with the original Georgian achievements. A clear sign of this are the works of thinkers of antique or middle ages, which clearly show that they were familiar with the former eastern or western understanding of the human body structure, psychology and disease causes. Even the immortal work of medieval Georgian poetry and philosophy „The Knight in the Panther's Skin” shows mentioned concepts which indicate that biomedical knowledge was common not only to the narrow circle of physicians and philosophers. Perhaps this was due to the academies which were founded by the King David the Builder where, like in many Western Universities of those times, an obligatory subject (in the current sense - faculty) was medicine. Here they received not only theoretical but also practical knowledge. There was a hospital in Gelati Academy, where teachers and students of the Academy gained practical experience. The system is still relevant in the form of the university clinics.

Considering such development of medicine, there existed manuscripts on medical issues. The oldest Georgian medical book that has come down to us is Canaanite's "Incomparable Carabadine". Its origination coincides with the establishment of the "Medical Faculty" in Gelati Academy and it discusses general issues in medicine – anatomy, physiology, and pharmacology concepts. Since then, in each next era, this knowledge was perfected and this was reflected in the original Georgian or translated books (Hodja's "Book of medicine" XIII century; Zaza Panaskerteli-Tsitsishvili's "Book of healing" etc.)

A kind of continuation of this history, as well as the Georgian academic education in general, was the foundation of the Medical Faculty at Tbilisi University in 1918. It was initiated by the doctor's union of that time -"The Society of Georgian Doctors and Naturalists" and its chairman Mr. Spiridon Virsaladze.

Outstanding Georgian doctors and researchers of that time, who had graduated not only from the Universities of the Russian Empire but also from Europe's leading medical and scientific schools, were invited as the teaching staff of the Medical Faculty of Tbilisi State University. Afterwards, the professors of this faculty founded lots of Medical Research and Natural Science Research Institutes. Their scientific achievements were recognized in the world scientific circles. In 1929, based on the Medical Faculty of Tbilisi State University, the Tbilisi Medical Institute was established, which continued the history of the above mentioned faculty.

Re-establishment of Medical Faculty at Ivane Javakhishvili Tbilisi State University was due to this historical experience. From the beginning, the reason of establishment of this faculty was not only giving the modern medical education, but also the growing interest in medical and biological sciences in the world and therefore, the education of new generation of Georgian scientists.

At present up to 80 academic staff and 112 doctoral students, conduct the academic and scientific activity of the faculty. In addition, Tbilisi State University integrates medical-biological and scientific research institutes. Their scientific achievements are important for increasing academic and scientific potential of the University. The only way for developing modern science is in internationalization. Serious scientific research activity is impossible without the study of scientific results obtained by the representatives of various countries.

For this purpose, it's my great pleasure to announce that with the joint effort of the Faculty of Medicine, TSU and the Georgian Medical Association a peer-reviewed multi-profile journal "Translational and Clinical Medicine - Georgian Medical Journal" was founded. It should support increasing the visibility of scientific results of researchers, working within the TSU and affiliated research institutes, especially young investigators and PhD students.

The founders of the journal will do their best for quick indexing of the journal in such international scientific databases as Research gate, Google Scholar, Global Impact Factor, SCImago Journal & Country Rank, Scopus. PubMed, etc.

It is noteworthy that the journal was founded in 2015, announced by TSU as "Science Year", and its first issue appears in the first quarter of 2016

Considering that academic staff of the Faculty of Medicine is widely recognized in the field of medical sciences, I am convinced that the new journal "Translational and Clinical Medicine - Georgian Medical Journal" will be an impressive project.

I wish success to this joint great endeavor of the Faculty of Medicine, TSU and the Georgian Medical Association!

*The Rector of Ivane Javakhishvili Tbilisi State University
Academician Mr. Vladimer (Lado) Papava*



It is my great pleasure and honor to welcome the birth of a new biannual electronic medical journal “Translational and Clinical Medicine-Georgian Medical Journal“. The idea of the journal has come from professors and academic staff of the Faculty of Medicine of Ivane Javakhishvili Tbilisi State University expressing the need and long-lasting desire of having the faculty-affiliated high-quality scientific journal. The Editorial board consists of renowned experts of translational and clinical medicine not only from Georgia but also around the globe. Submitted manuscripts will be peer-reviewed by international experts, thus, ensuring the high quality of papers accepted for publication. I wish the journal “Translational and Clinical Medicine-Georgian Medical Journal“ scientific longevity and many enthusiastic authors as well as thankful readership.

Prof. Alexander Tsiskaridze
Dean, Faculty of Medicine
Ivane Javakhishvili Tbilisi State University (TSU)



Wonderful Gift for Scientists

Last year, on the traditional workshops in Bakuriani, with the participation of the medical professors and students, the idea was born concerning the establishment of the joint scientific, English-language online journal of the Faculty of Medicine, TSU and Georgian Medical Association. We all had the mood for seeking the innovations; this mood indeed came from the students, for whom there is no problem to make presentations and express their ideas, they easily go through the research labyrinths, and their fluent English allows them to use the newest data in different directions of medical research.

Today this dream comes true. Georgian medical scientific society as well as professors and students of Iv. Javakhishvili Tbilisi State University, especially PhD students, residents and young researchers, have the new wonderful opportunity to make visible the results of their researches. The editorial board will encourage publishing reviews, made by PhD students for their research theses.

In my thoughts, I went back to the past, in great history of XIV-XII centuries BC, when the myth about Golden Fleece in Colchis was created. According to the myth, the King Aeetes ruled Colchis, the richest kingdom in west Georgia. He had fantastic treasures. The most important from them was the famous Golden Fleece. According to many scientists, it was the symbol of divine wisdom on which the king had written some mysteries. Great part of these mysteries was “medical wisdoms”.

Of course, our students know this and I am happy about it... May be this is the start of the myths of classical medical development, Colchis-Iberian Medicine - Cura Mediana... According to some investigators of the history of Medicine, the term “Medicine” comes from the Aeetes’ daughter Medea who was skilled master in medicine.

Now Georgia meets spring, and our journal expects its spring too. I would like to wish good luck to the journal founded by the mutual efforts of Tbilisi State University and Georgian Medical Association.

Prof. Gia Lobzhanidze
Head of the Directors Board
Georgian Medical Association

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The study of behavior changes in growing rats under the conditions of halothane anesthesia and premedication with Midazolam

Dzidziguri D.¹, Mitaishvili E.¹, Aptsiauri A.¹, Bakuradze E.¹, Dzidziguri L.², Vadachkoria Z.²

Abstract

Background: Cleft of lip and palate is widespread pathology of development. These malformations are repaired with surgery. Inhalation anesthetics, for example halothane, are widely used in pediatric orthognatic surgery, causes side effects. For preventing these complications benzodiazepines (e.g Midazolam) are used, but based on last literature sources midazolam may cause long-lasting negative effects, such as high excitation and aggression. At same time, according to the literature, midazolam, which is used in sedation for infants, may have far-reaching adverse effects. For example, initiation of apoptosis in the developing brain, respiratory obstruction and other. The reverse data is obtained from adult white rats. It is determined that midazolam premedication does not react on behavioral characteristics and adaptation ability of experimental animals and reduces the halothane negative impact⁹. Relatively less is studied about far-reaching adverse effects of midazolam in growing organisms.

Aim of research: The effect of midazolam premedication (single injection) on behavior changes of growing rats under the conditions of halothane anesthesia after 1 week from the sham operation.

Methods: Open field test was used to assess behavior parameters and emotions in control and both test groups. We evaluated behavior changes in rats a week after the operation during 5 days. Each animal was explored during 5 minutes every day. There were registered following parameters: Vertical activity, sum of inner, external and center squares, time of staying in the center of the field, groomings, the grooming duration, defecation.

Results: It is shown that midazolam injections did not cause any negative effects on the growing rats' behavior parameters. The adaptation to environment has been revealed in all three groups a day after. Similar results were shown in the third and fourth days. The high level research activity has been determined in control and third groups, in comparison with halothane group. This fact is related to adaptation to environment and it proves decreasing of tension and fear level. The adaptation to environment and high space orientation of growing rats in third group has to be caused by midazolam premedication.

Conclusions: The reason for weak adaptation to environment after halothane anesthesia compared to intact animals may be the reducing of dendrite growth by halothane in growing animals and thus the inhibition of brain development. The fact that these effects are not revealed after midazolam premedication allow us to think that reducing the anxiety activity of animals after midazolam premedication provides to avoid the inhibition of dendrite growth and brain development. On the bases of our results it is established that a week after operation in growing rats under the halothane anesthesia midazolam premedication (single injection) doesn't cause any negative influence on behavior parameters of growing animals. (TCM-GMJ January 2016; 1:P8-P10)

Keywords: anesthesia, halothane, midazolam, premedication, behavior, rat.

Introduction

Inhaled anesthetics are widely used during surgical treatment of children with congenital defects of infants such as fissures of upper lip and palate. As it is known inhalation Anesthetic drugs are characterized by psyche damage impact.

In particular, it is determined that after their (e. g. halothane, which is mainly used in the above mentioned congenital defects) usage patients suffer from post-operative complications, such as nausea, high anxiety, disorder of synaptogenesis, in the early stages of brain development, which directly revealed with the

inhibition of behavioral activity and Other. The adverse effects of halothane on the responsible mechanisms of brain functioning is described also in experimental animals. In particular, it is shown that in the conditions of prolonged anesthesia, halothane causes inhibition of dendrites growth.^{1,2,3,4}

For the prevention of complications caused by halothane, increasing of sedation is recommended. For this purpose benzodiazepines drugs including midazolam is widely used in maxillofacial Surgery. Midazolam is known to be associated with ionotropic GABAA receptor, which leads to the opening of the opening Cl channels and transport of chloride ion from extracellular space to intracellular direction. Thus inhibitory postsynaptic potential is generated and sedation is increased.^{5,6,7}

At the same time, according to the literature, midazolam, which is used in sedation for infants, may have far-reaching adverse effects. For example, initiation of apoptosis in the developing brain, respiratory obstruction and other.⁸

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The reverse data is obtained from adult white rats. It is determined that midazolam premedication does not react on behavioral characteristics and adaptation ability of experimental animals and reduces the halothane negative impact.⁹ Relatively less is studied about far-reaching adverse effects of midazolam in growing organisms. For example, it is shown that the usage of midazolam in spinal anesthesia leads to decrease in locomotion activity in experimental animal only the first 24 hours. The negative impacts of midazolam are not occurring for late period.¹

Aim of research

The effect of midazolam premedication (single injection) on behavior changes of growing rats under the conditions of halothane anesthesia after 1 week from the sham operation.

Methods

Experiments were carried out on growing (20 days, average mass-26 g) rats. Animals (48 white rats) were divided into three groups: 1. Control group 2. First test group: This group includes animals, which has been operated (sham operation) under halothane anesthesia. 3. Second test group: This group includes rats, which has been operated (sham operation) under the conditions of halothane anesthesia and premedication with midazolam (midazolam injection- 200mg/kg, 30 minutes before surgery). Open field test was used to assess behavior parameters and emotions in control and both test groups. We evaluated behavior changes in rats a week after the operation. Research was lasted 5 days. Each animal was explored during 5 minutes every day. There were registered following parameters: Vertical activity, sum of inner, external and center squares, time of staying in the center of the field, groomings, the grooming duration, defecation.

Results and discussion

The high level research activity has been determined in all three groups in the first day of experiment (Vertical standing: the first group - $10,6 \pm 2,3$; the second group - $7,6 \pm 3,3$; third group - $15,1 \pm 2,7$ (fig. 1.a). sum of external squares: first group- $47,8 \pm 4,7$; second group- $45,6 \pm 5,8$; third group- $50,9 \pm 4$ (fig. 1.b). According to sum of inner (fig. 1.c) and center squares (fig. 1.d), and time of staying in the center of the field (fig. 2.a), revealed the higher level locomotion activity in the third group of animals, than in first and second groups (sum of inner squares: the first group - $4,8 \pm 1,3$; II group - $4,3 \pm 1,2$; III group- $9,2 \pm 1,7$; sum of center squares: the first group- $0,3 \pm 0,1$; the second group - $0,3 \pm 0,2$; the third group - $1,3 \pm 0,3$, time of staying in the center of the field: first group - $1 \pm 0,4$;

second group - $1,1 \pm 0,6$; third group- $3,6 \pm 1,1$), these results indicate decreasing of fear level (decreasing of fear in third group is connected to midazolam premedication).

Emotional tension disappeared in all three groups with short and seldom groomings (The first group (Fig. 2b) - $1,2 \pm 0,2$; the second group $1,7 \pm 0,5$; the third group- $1 \pm 0,2$). Grooming duration parameter showed following results: the first group- $15,9 \pm 3,8$; the second group- $10,7 \pm 3,9$; the third group- $9,4 \pm 2,7$ (Fig 2.c). According to defecation (Fig 2.d) fear level was equal in all three groups of rats (I group- $0,8 \pm 0,2$; II group - $1,2 \pm 0,6$; III group - $1,3 \pm 0,3$).

The adaptation to environment has been revealed in all three groups a day after. Similar results were shown in the third and fourth days. The high level research activity has been determined in control and third groups, in comparison with halothane group. This fact is related to adaptation to environment and it proves decreasing of tension and fear level. The adaptation to environment and high space orientation of growing rats in third group has to be caused by midazolam premedication.

Conclusions

The reason for weak adaptation to environment after halothane anesthesia compared to intact animals may be the reducing of dendrite growth by halothane in growing animals and thus the inhibition of brain development. The fact that these effects are not revealed after midazolam premedication allow us to think that reducing the anxiety activity of animals after midazolam premedication provides to avoid the inhibition of dendrite growth and brain development. On the bases of our results it is established that a week after operation in growing rats under the halothane anesthesia midazolam premedication (single injection) doesn't cause any negative influence on behavior parameters of growing animals.

Fig.1a

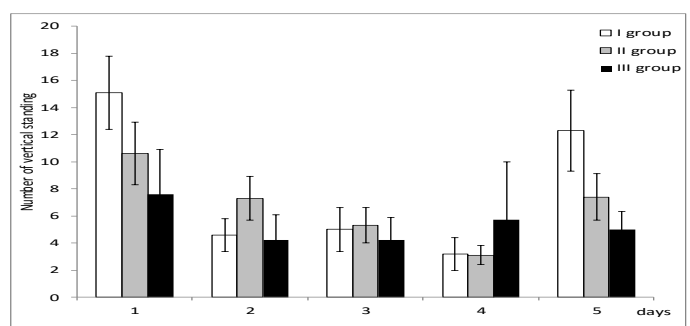


Fig.1b

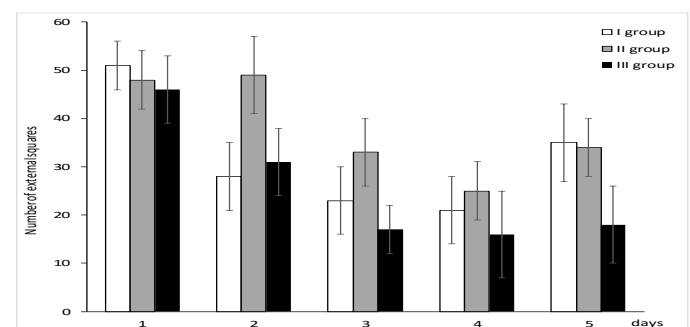


Fig.1c

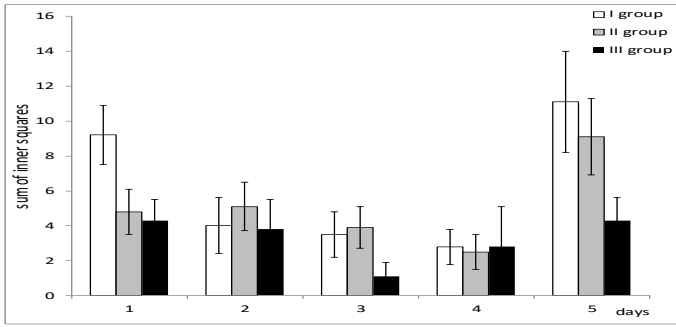


Fig.2d

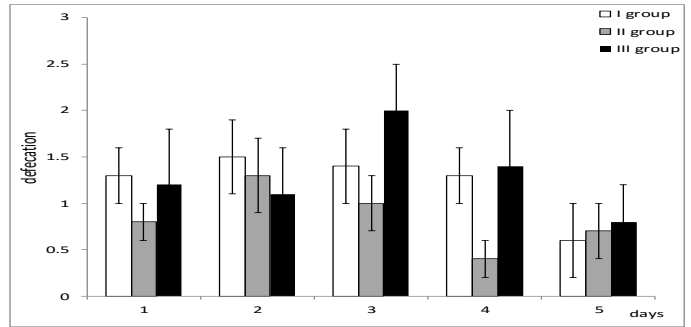


Figure 1. Behavior changes in growing rats in control and test groups under the conditions of halothane anesthesia and premedication with midazolam a. vertical activity. b. external squares c. inner squares d. sum of center squares

Figure 2: Behavior changes in growing rats in control and test groups under the conditions of halothane anesthesia and premedication with midazolam a. time of staying in the center of the field. b. groomings. c. the grooming duration. d. defecation

Fig.1d

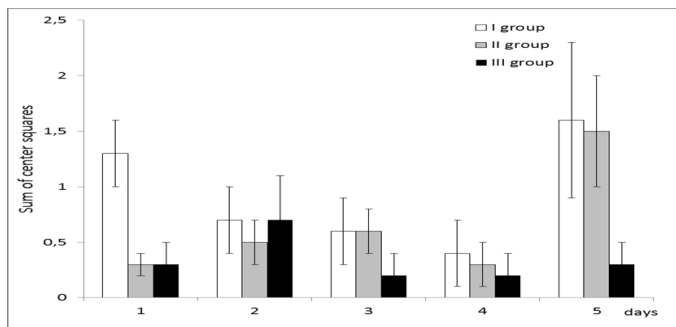


Fig.2a

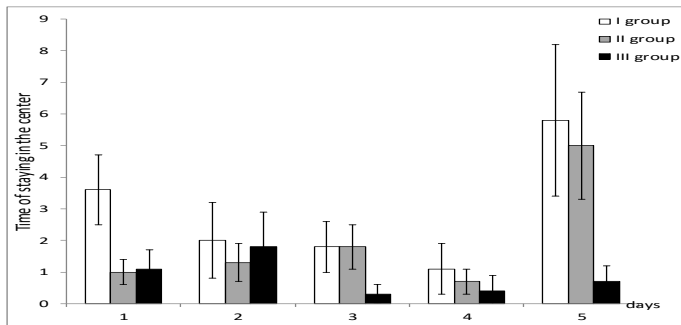


Fig.2b

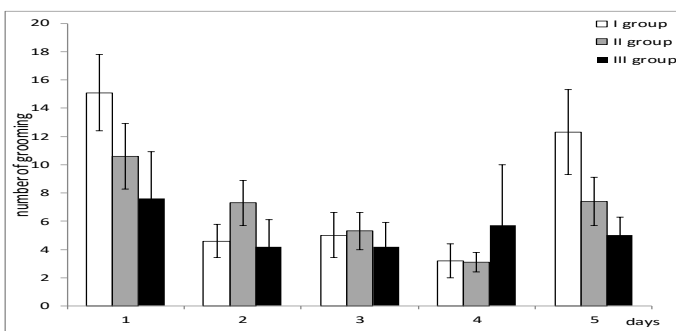
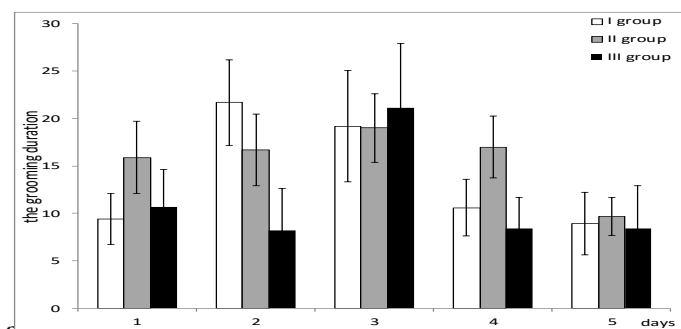


Fig.2c



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Late HIV diagnosis in Georgia: public health and economic implications

Chkhartishvili N.¹, Sharvadze L.^{1,2}, Gabunia P.¹, Abutidze A.¹,

Nikolaishvili M.¹, Tsertsvadze T.^{1,2}

Abstract

Background: Late HIV diagnosis has major individual and population implications in terms of patient survival, onward transmission of HIV and higher health expenditures. The objective of this study was to evaluate the problem of late diagnosis in Georgia, which since 2004 ensures universal to antiretroviral therapy (ART).

Methods: This was retrospective cohort study that included adult (age ≥ 18 years) HIV patients newly diagnosed during 2009-2011, who received care at the national referral institution for HIV diagnosis, treatment and care. Patient-level data were abstracted from medical and accounting records. Individuals were followed until death or July 1, 2012 whichever occurred first. Mortality rates were calculated for total follow-up period as number of events divided by the number of total person-years (PY) of follow-up. Costs per person-year were calculated as total costs incurred divided by the total number of PY contributed.

Results: Study included 1,002 patients (81% of total diagnoses). Among them the median age was 37 years and 71% were men. Majority was infected via either IDU (50%) or heterosexual contact (44%). A total of 702 (70.1%) patients were classified as late presenters (defined as CD4 < 350 and/or AIDS) and 512 (51.1%) patients presented with advanced disease (defined as CD4 < 200 and/or AIDS). Patients were followed for a median 1.2 years and contributed 1,305 PY of follow-up. Overall 137 late presenters and 8 non-late presenters died (mortality rates: 16.1 per 100 PY vs. 1.8 per 100 PY, $p < 0.0001$). Among patients presenting with advanced disease 129 died compared to 16 deaths among patients without advanced HIV diseases (mortality rates: 21.7 per 100 PY vs. 2.3 per 100 PY, $p < 0.0001$). Total expenditures per person-year for late presenters were 1,171 USD vs. 579 USD among those not presenting late ($p < 0.0001$). Total expenditures per person-year among patients presenting with advanced disease amounted to 1,394 USD vs. 606 USD ($p < 0.0001$).

Conclusions: The study provides evidence that late HIV diagnosis in Georgia negatively affects HIV epidemic both from public health and economic standpoints. Improving earlier diagnosis and supporting continued high engagement in the HIV care continuum will be critical for achieving success. (TCM-GMJ January 2016; 1:P11-P14)

Keywords: HIV, AIDS, late diagnosis, mortality, health expenditures

Introduction

Global roll-out of antiretroviral therapy (ART) resulted in dramatic reduction of HIV-related morbidity and mortality.^{1,2} In settings where ART is readily available life expectancy of HIV positive persons now approaches that of general population.^{3,4} Despite the successes HIV continues to claim millions of lives with an estimated 1.5 million persons living with HIV died in 2013 only.⁵ One of the major reasons for continued high mortality is late HIV diagnosis, which remains significant challenge across the continents with 40-60% of patients diagnosed at late stages of disease.^{6,7,8}

Late diagnosis has major individual and population implications: it negatively affects clinical outcomes, contributes to onward transmission of HIV and demands higher resource use.⁹

Georgia is an independent nation located in the Eastern European region between Russia and Turkey. The HIV epidemic in Georgia began in 1989 and the number of newly reported cases has been slowly growing annually, with the rate of new diagnosis reaching 11 cases per 100,000 population in 2013.⁸ According to UNAIDS in 2013 estimated 6,400 persons were living with HIV in Georgia and the estimated adult prevalence was 0.3%.⁵ The HIV epidemic in Georgia has been largely driven by injection drug users (IDU), accounting for nearly half of the total reported cases. Since 2004 Georgia made substantial progress in responding the HIV epidemic as a result of strengthened resource allocation from the Global Fund to Fight AIDS, Tuberculosis and Malaria. The country developed effective model of HIV treatment and care service delivery that ensures high patient engagement in clinical care that has translated into universal access to ART and reduced mortality.^{10,11}

The objective of current study was to quantify the problem of late diagnosis and evaluate its impact on patient survival and health expenditures.

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Methods

Design and settings

We conducted retrospective cohort study that included adult (age ≥ 18 years) HIV patients newly diagnosed during 2009-2011, who received care at the Infectious Diseases, AIDS and Clinical Immunology Research Center (National AIDS Center), which is the country's referral institution for HIV diagnosis, treatment and care.

Patient level-data were extracted from medical records using standardized data abstraction tool, including demographic (age, gender), epidemiologic (date of HIV diagnosis, mode of transmission), laboratory (CD4 count, viral load, co-infections) and clinical (AIDS-indicator diseases, co-morbidities, information on death if applicable) data.

Definitions for late diagnosis

Study used European consensus definition of late diagnosis,¹² which is as follows: *Late presentation*: Persons presenting for care with a CD4 count below 350 cells/mm³ or presenting with an AIDS-defining event, regardless of the CD4 cell count. *Late presentation with advanced HIV disease*: Persons presenting for care with a CD4 count below 200 cells/mm³ or presenting with an AIDS-defining event, regardless of the CD4 cell count.

Costs

Study collected information on health expenditures incurred by the National AIDS Center within the state funded National AIDS Treatment Program. These expenditures included costs related to patient hospitalization (in-patient care), out-patient care services such as treatment and prevention of opportunistic infections, laboratory and instrumental investigations, physician consultations and other human resource costs. Collected expenditure information did not include costs incurred through other programs, such as costs of antiretroviral drugs, costs of viral load test, CD4 count test and HIV drug resistance test. Information on costs were collected in local currency – Georgian Lari (GEL) and were converted to U.S. Dollars at the rate of 1 USD = 1.7135 GEL representing average of the daily exchange rate over the study period as per official rate set by the National Bank of Georgia.

<https://www.nbg.gov.ge/index.php?m=582&lng=eng>

Statistical analysis

All statistical analyses were performed using SAS v9.2 (SAS Institute Inc. Cary, NC). Individuals were included starting from the date of HIV diagnosis and were followed until death or July 1, 2012 whichever occurred first. Mortality rates were calculated for total follow-up period as number of events divided by the number of total person-years (PY) of follow-up contributed to the total period. Factors associated with mortality were assessed in modified multivariate Poisson regression analysis.¹³

Costs per person-year were calculated as total costs incurred divided by the total number of PY contributed. Bivariate comparisons were tested using Pearson's chi-square or Fisher's exact test as appropriate. All tests were two sided at significance level of 0.05.

Results and discussion

Of 1,238 adult persons newly diagnosed with HIV in Georgia over the study period, 1,002 (81%) received care at the National AIDS Center and were included in the study. Among 1,002 patients included in this study, the median age was 37 years and 71% were men. Majority was infected via either IDU (50%) or heterosexual contact (44%). Half of the patients had antibodies against hepatitis C virus (HCV). Overall, 45% and 68% of patients had CD4 count levels of < 200 cells/mm³ and < 350 cells/mm³ respectively (Table 1). Of 291 cases of AIDS-defining illness, 136 (47.1%) were due to tuberculosis (TB). A total of 702 (70.1%) patients were classified as late presenters and 512 (51.1%) patients presented with advanced disease. (Table 1).

Patients were followed for a median 1.2 (Interquartile range [IQR]: 0.5-1.9) years and contributed 1,305 person-years (PY) of follow-up. 702 late presenters contributed 850 PY and 512 patients presenting with advanced diseases contributed 594 PY of follow-up.

Both late presenters and those diagnosed with advanced HIV disease were at higher risk of death. Overall 137 late presenters and 8 non-late presenters died, translating into almost 90% increase in the risk of death (16.1 per 100 PY vs. 1.8 per 100 PY respectively, $p < 0.0001$, rate ratio [RR]: 9.16, 95% CI 4.52-21.64) (figure 1). Among patients presenting with advanced disease 129 died compared to 16 deaths among patients without advanced HIV diseases (21.7 per 100 PY vs. 2.3 per 100 PY, $p < 0.0001$, RR: 9.64, 95% CI 5.72-17.37) (figure 1). In multivariate models the strongest predictors of mortality were late presentation (RR 5.54, 95% CI: 2.73-11.22) and late presentation with advanced disease (RR 6.05, 95% CI: 3.60-10.17) (Table 2). Other factors associated with mortality included increasing age and history of IDU

Over the study period national AIDS treatment program expenditures for all patients included in the study totaled 1,259,460 USD, including 609,240 USD spent on in-patient care and 650,220 USD on out-patient care services. Late diagnosis was associated with higher expenditures. Particularly, total expenditures per person-year for late presenters were 1,171 USD vs. 579 USD among those not presenting late ($p < 0.0001$). Total expenditures per person-year among patients presenting late with advanced disease amounted to 1,394 USD vs. 606 USD ($p < 0.0001$). Differences were significant for in-patient and out-patient care costs separately (Table 3).

Our study revealed very high rate of late HIV diagnosis and demonstrated its detrimental health and so-

cietal consequences in Georgia. Late diagnosis remains worldwide problem and particularly in low- and middle income countries. A meta-analysis of 56 studies from Sub-Saharan Africa showed that mean estimated CD4 cell count at presentation did not increase over 2002-2013 period and remained below 350 cells/mm³.¹⁴ Large pan-European collaboration analysis showed that despite the decrease in the rates of late diagnosis from 2000 to 2011, more than half of newly diagnosed patients present late.⁶

CD4 cell count at the time of HIV diagnosis is a critical indicator measuring effectiveness of HIV testing programs. High rates of late HIV diagnosis seen in our study indicate deficiencies in testing efforts. Indeed latest bio-behavioral surveys among key population at risk showed low testing coverage in Georgia, with only 15% of IDUs reached in 2012.¹⁵ In addition, recent analysis of engagement in HIV care continuum showed that the major gap in the cascade of care is at the stage of HIV diagnosis, with more than half of people living with HIV remaining undiagnosed.¹⁰

Dramatic effect of late diagnosis on patient survival has been well documented in variety of settings.^{16,17,18} In our study late diagnosis, including presentation with advanced diseases was associated with 90% increased risk of mortality.

In multivariate analysis late presentation was associated with more than 5-fold increased risk of death (RR 5.54, 95% CI:2.73-11.22), while late presentation with advanced diseases increased risk of mortality by 6 times (RR 6.05, 95% CI: 3.60-10.17). High rates of late diagnosis and resulting mortality prevent the full realization of benefits of ART in terms of survival as well as prevention of new HIV infections.¹⁹ It also compromises cost-effectiveness of efforts towards universal access of ART that Georgia has been ensuring since 2004.²⁰

There is another important consequence of late diagnosis, which is contribution to ongoing HIV transmission. People who remain undiagnosed and unaware of their HIV positive status continue to engage in high risk behavior and unknowingly transmit the virus. It has been shown that people unaware of their infection contribute to majority of new transmissions.^{21,22}

Taking into account that estimated median time to from HIV seroconversion to CD4 cell count of 350 and 200 cells/mm³ is 4.19 and 7.93,²³ we can conclude that 45% of study population were infected for 8 years and additional 22% of patients were diagnosed after 4 years of infection. This is substantial period of time for spreading the virus deeper in the populations.

In addition to public health implications, late diagnosis represents significant economic problem. Studies in both industrialized and developing countries show increased economic burden associated with late diagnosis.^{24,25,26} In our study both total absolute expendit-

ures and per-person costs were significantly higher for patients diagnosed late or with advanced disease. Of 1,259,460 USD incurred during the study period 79% were spent on late presenters, while per person expenditures were twice as high. It should be also taken into consideration that late presenters spent less time in the study because of higher mortality rates (follow-up time for late presentation: 1.5 years vs. 1.1 years, $p < 0.0001$; follow-up time for late presentation with advanced disease: 1.4 years vs. 1.0 years, $p < 0.0001$).

Conclusions

In conclusion, our study provides evidence that late HIV diagnosis in Georgia negatively affects HIV epidemic both from public health and economic standpoints. Strengthened efforts are needed to expand HIV testing in Georgia including community-based approaches and health sector based provider initiated testing and counseling activities. Improving earlier diagnosis and supporting continued high engagement in the HIV care continuum will be critical for achieving success. This is proven cost-effective approach that saves lives and prevents new infections.

Table 1: Baseline characteristics of newly diagnosed HIV

n=1002	
Age, median years (IQR)	37 (32-44)
Sex, n (%)	
Men	707 (70.6)
Women	295 (29.4)
Mode of HIV transmission, n (%)	
Injection drug use	503 (50.2)
Heterosexual contact	446 (44.5)
Male-to-male sex	45 (4.5)
Blood transfusion	5 (0.5)
Unknown	3 (0.3)
Co-infection with viral hepatitis, n (%)	
anti-HCV+	508 (50.2)
HbsAg+	45 (4.5)
Anti-HBc+	462 (46.1)
CD4 count, median cells/mm³ (IQR)	215 (102-385)
CD4 count categories, n (%)	
<200	449 (44.8)
<350	679 (67.8)
AIDS-defining illness, n (%)	291 (29.0)
Presenting late, n (%)	702 (70.1)
Presenting late with advanced disease, n (%)	512 (51.1)

Table 2. Risk factors for mortality

	Univariate	Multivariate models	
		Presenting late	Presenting late with advanced disease
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Age (per year increase)	1.05 (1.04-1.07)	1.04 (1.02-1.06)	1.04 (1.02-1.05)
Men vs. women	2.33 (1.51-3.60)	1.11 (0.66-1.89)	1.14 (0.68-1.91)
IDU vs. non-IDU	2.60 (1.85-3.67)	1.90 (1.20-3.02)	1.86 (1.20-2.89)
Anti-HCV+	2.38 (1.70-3.34)	1.21 (0.77-1.91)	1.15 (0.74-1.77)
Presenting late	7.32 (3.63-14.73)	5.54 (2.73-11.22)	
Presenting with advanced disease	7.72 (4.66-12.78)		6.05 (3.60-10.17)

Table 3. National AIDS Treatment Program Expenditures

	Presenting Late					Presenting Late with Advanced Disease				
	Yes		person-year=850)			Yes		person-year=594)		
	(n=702, total		No			(n=512, total		No		
	Total costs	Cost per-person year	Total costs	Cost per-person year	p value	Total costs	Cost per-person year	Total costs	Cost per-person year	p value
In-patient care costs	507,251	597	101,989	224	<0.0001	447,708	753	161,531	227	<0.0001
Out-patient care costs	488,779	575	161,442	355	<0.0001	380,996	641	269,224	379	<0.0001
Total costs	996,030	1,171	263,430	579	<0.0001	828,705	1,394	430,755	606	<0.0001

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Modification of the method of corrosion casts for studying of bilio-vascular structures of liver

(Brief Communication)

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Abstract

The description of the original method for preparation of corrosion casts of intrahepatic vessels and bile ducts is provided. Readily available compositions, such as "Protacryl- M" set widely used in dental and neurosurgical practice and the Latex manufactured by "Geng" used in different constructions/repairs were applied for the casting. It is demonstrated that corrosion casts of blood vessels and bile ducts obtained from above-mentioned resins obviously reflect the architectonics and surfaces of studied structures and are completely convenient for the macro- and microscopic observation. (TCM-GMJ January 2016; 1:P15-P17)

Keywords: Hepatic blood vessels, Corrosion casts

Introduction

The study of spatial architecture of tubular structures – blood and lymphatic vessels, ducts, channels – by using the method of corrosion casts, belongs to one of the conventionally approved approaches. Application of the different stereo-microscopes (including scanning electronic microscope) make possible to study even the tiniest (capillary) branches with diameters of several microns.^{1,2,3,4}

We aim to study the transformation of hepatic biliary and vascular architecture in regenerating liver of rats after partial hepatectomy by using of this method. For the preparation of corrosion casts of hepatic biliary and-vascular beds of big animals (dog/pig/rabbit), we previously used the latex manufactured by "Nairit", which would coagulate in the acid - during the process of liver tissue corrosion.⁵ In smaller laboratory animals (rats) the cocktail including the monomer of methylmetacrilate, benzoyl peroxide and dimethylaniline was successfully applied for the same purpose.⁶

As observed recently, the production of Nairit's latex has been ceased. Widely used resins like "Batsom" and "Mercox" successfully applied by various investiga-

tors for obtaining of corrosion casts, are expensive and their purchase/importation to Georgia is related to technical difficulties.

Actually, the injectable mass used in the casting of tubular structures has to comply with the following demands: be non-toxic, have low viscosity but coagulate fast, be resistant to corrosion solutions (acids/bases), maintain structural configuration after drying and preferably be compatible for staining with different colors (e.g., in order to allow the simultaneous study of hepatic veins, arteries and bile ducts).

For this purpose, we have tested: 1. "Protacryl- M" set widely used in neurosurgical and dental practice, including liquid and powder components in addition to 3 different color pigments for staining. 2. Latex, manufactured by "Geng" used in different constructions/repairs, resembling "Nairit" latex and at the same time easily stained with different colors.

Preparation of hepatic tubular structure cast samples was performed as follows:

The abdominal cavity of Wistar rat, weighting 200-250 g was opened under general ether anesthesia. The catheters with appropriate diameters were inserted in the portal vein and common bile duct (directed towards liver), and fixed with ligatures. The liver vessels were washed out via portal vein catheter with the cocktail including 100 ml 0.9% NaCl, 1,0 ml Atropine, 1,0 ml No-Spa, 1ml Heparin and 1 ml 2% Novocain. Outflow was achieved through femoral vein, which was cut previously. After washing out the liver (as it turned white), 1% formalin solution was injected into the portal vein,

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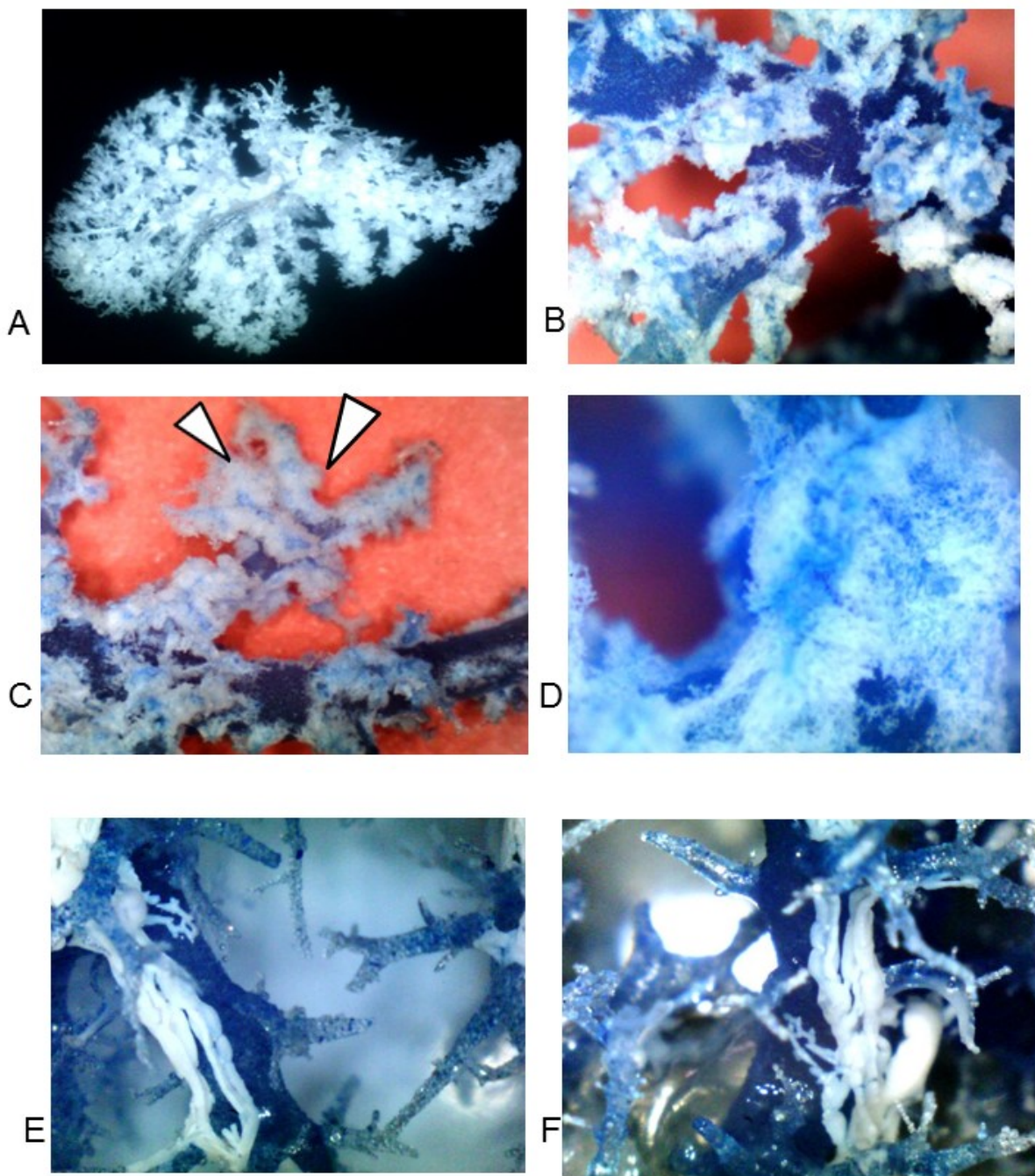
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followed by the injection of "Protacryl-M" cocktail ("Protacryl-M" powder 3 cm³ dissolved in 7.5 ml of its liquid component).

50-60 minutes later after injection of "Protacryl - M" (the term necessary for the solidifying of injected mass) the liver was excised and immersed into 20% NaOH solution for tissue corrosion, according to the previously described method.^{6,7} After complete dissolving of the liver tissue, the obtained plastic casts were rinsed under the water flow and let to be dried at the room temperature. The dried casts were ready to be used for macro-and microscopic study.

In several cases, the injection of "Protacryl-M" into the portal vein was followed by the injection of "Geng" latex via the catheter inserted into the common bile duct. In these cases, the excised liver was first immersed into the concentrated H₂SO₄ which led to the "coagulation" of latex. Later, the complete corrosion of liver tissue was done in 20% NaOH solution. It must be considered that immersion time in the concentrated H₂SO₄ for excised liver should not exceed 20 minutes, as the long-term storage of the specimen in the acid not only cause the coagulation of the latex, but can also dissolve the protacryl casts.

Fig1: Corrosion casts of rat's liver blood vessels. A) Portal vein branches ; B,C)Casts of portal vein branches and terminal portal venules; X 200; arrowheads indicate liver "lobules"; D) Casts of terminal portal venules and sinusoidal capillaries, X200; E,F) Corrosion casts of portal vein branches (blue)and bile ducts(white), X10;



The analysis of the casts prepared by the above mentioned method revealed that these casts evidently reflect the architecture of the studied structures; the obtained casts are sustainable, non-brittle and completely convenient for the relevant measurement of the volume or the length/diameters of the separate branches, including the measurement by stereo microscope. In cases of double injection, mobility (elasticity) of latex casts associated with the portal vein solid casts facilitates the better investigation of the relationship of these two structures.

The above mentioned demonstrates that the method of corrosion casts developed by us for modeling of tubular structures is completely relevant and can be successfully used in small laboratory animals for the assessment of architectural transformation of hepatic vascular bed and bile ducts in norm or pathology condition.

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Meckels diverticulum's injury after penetrating abdominal trauma

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Abstract

In 1595, for the first time, Hildanus described an ileal diverticulum, which was thoroughly scrutinized and defined by Johann Meckel in 1809. In most cases, Meckel's diverticulum does not cause any problems. In a small number of patients however, these diverticula can become infected (diverticulitis) cause an obstruction of the intestine, or cause bleeding from the intestine. We present a case of simultaneous rupture of Meckel's diverticulum and small bowel without abdominal pain following a penetrate trauma to the abdomen, sustained during a stab wound to the abdomen. (TCM-GMJ January 2016; 1:P18-P19)

Keywords: Meckels diverticulum, abdominal trauma

Introduction

In 1595, for the first time, Hildanus described an ileal diverticulum, which was thoroughly scrutinized and defined by Johann Meckel in 1809.¹ Meckel's diverticulum is one of the most common congenital abnormalities. It occurs when the connection between the intestine and the umbilical cord doesn't completely close off during fetal development. This results in a small out pouching of the small intestine, know as a Meckel's diverticulum. In most cases, Meckel's diverticulitis does not cause any problems. In a small number of patients however, these diverticulitis can become infected (diverticulitis) cause an obstruction of the intestine, or cause bleeding from the intestine. Diverticulitis or infection, of a Meckel's diverticulum (fig.1) is often mistaken for appendicitis. Meckel's diverticulum is generally seen as an incidental finding at laparotomy.² The symptomatic cases usually present with gastrointestinal bleeding, inflammation or intestinal obstruction which is the most common presentation in adults.²

Objectives

To present a case of simultaneous rupture of Meckel's diverticulum and small bowel without abdominal pain following a penetrate trauma to the abdomen, sustained during a stab wound to the abdomen.

Clinical Presentation

We present a case of a 37-year-old man presented at the emergency department (ED) immediately after a stab

wound in right side (fig.2) of abdomen with hemodynamic stability. The abdominal quadrants were not tender on palpation. On rectal examination no blood. Initial management of the patient involved intravenous fluid, routine blood tests and abdominal x-rays was normal. US of the abdomen didn't show free fluid in the peritoneal cavity and the patient was admitted in observation.

Six hours later the abdominal pain was increasing, and abdominal tenderness. An abdominal x-rays showed free air in abdominal cavity (fig. 3). In this situation an emergent laparotomy was decided. At the exploration, the peritoneal cavity was filled with 600 cc of blood-stained intestinal fluid, while numerous dilated loops of small bowel were present (fig. 4,6,). At approximately 90 cm from the ileo-cecal junction, there was an Injury of Meckel's diverticulum and jejunal injury 1.5m from Treitz.

Intervention

The ileum was repaired in two layers: a segmental bowel resection including Meckel's diverticulum and the gastrointestinal tube anastomosed without any tension. The patient has a normal postoperative course. The postoperative recovery was uncomplicated, and the patient was discharged on the fifth day postoperatively.

Discussion

The first case of ruptured Meckel's diverticulum was reported by Blanc in 1899.³ However, traumatic rupture of Meckel's diverticulum has been reported previously in few instances.^{4,5,6,7} Injury of Meckel's diverticulum after penetrate abdominal trauma is a rare cause in the adult and has been reported previously only in few cases. Meckel's diverticulum may also present with rupture secondary to blunt trauma^{1,8}, or as iron deficiency anemia with or without episodes of overt hemorrhage.

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Conclusion

This case shows that a Penetrating abdominal trauma can tear the mesodiverticulum and rupture the Meckel's

diverticulum base simultaneously, resulting in hemoperitoneum and chemical peritonitis.

Fig.1 Anatomy of Meckel's diverticulum

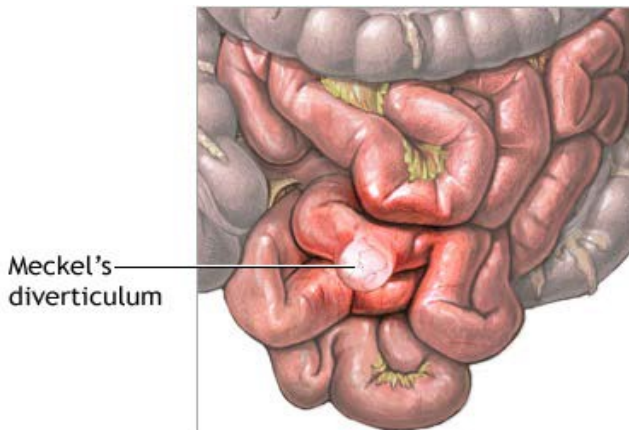


Fig.4 The injury of Meckel's diverticulum



Fig.2 Stab wound in right side of abdomen



Fig.5 The injury of Meckel's diverticulum

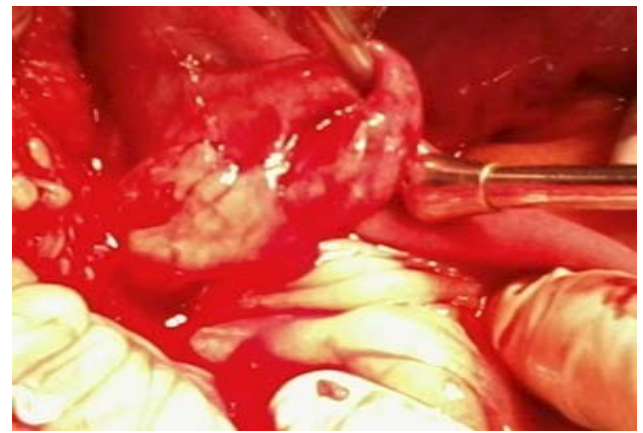


Fig. 3 Abdominal x-rays



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Early operative treatment for an enterocutaneous fistula after gunshot wound

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Abstract

Background: The successful treatment of an enterocutaneous fistula (ECF) is challenging even for experienced surgeons, as it is associated with potential complications such as infection, abdominal sepsis, fluid-electrolyte disturbances, septic shock and malnutrition. All of these conditions may congregate and lead to increased mortality in these patients, additional to the original trauma.

Case Report: We describe a 27-year old male who was shot once in the left thoraco-abdominal region without an exit wound. On laparotomy, multiple injuries to jejunum, ileum and sigmoid were identified. Primary repair of sigmoid was done as well as end-to-end jejunostomy and end-to-end ileostomy. At postoperative day 10, an ECF erupted as a low output fistula (100ml/24h). The patient was put on full parenteral treatment. Following work up including CT scan and fistulogram, the patient was taken back to the operating room for washout and diverting ileostomy with fistula tract resection. He fully recovered uneventfully following this second operation.

Conclusion: As shown in this patient without malnutrition and penetrating injury, early surgical treatment may work out advantageously and swift, compared to possible conservative treatment in this low output fistula following a gunshot of the thoraco-abdominal region. (TCM-GMJ January 2016; 1:P20-24)

Keywords: Enterocutaneous fistulas, trauma, abdominal trauma

Introduction

While enterocutaneous fistulas are rarely encountered in surgical practice, they are one of the most dangerous complications associated with abdominal surgery that may result in increased morbidity and mortality. This is especially and still true despite recent improvements in their treatment.¹ This treatment of enterocutaneous fistulas is particularly challenging, as surgeons must be cautious of hydro-electrolytic disorders, septic shock, and malnutrition. All of these conditions may add to the primary trauma and its' effects on morbidity and mortality.² Fistulas are defined as an abnormal communication between two epithelized surfaces, and enterocutaneous ones facilitate wanted or unwanted communication between skin and the bowel lumen. Enterocutaneous fistulas are well known a long time, and thus can be found within historical texts.³

The earliest record of an enterocutaneous fistula can be found in the Bible, Old Testament, in the book of Samuel, which is said to be timed between 1043 BC and 100BC.⁴

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Celsus first described the first attempt to surgical repair of a colocutaneous fistula. During the 18th century, John Hunter defended a conservative treatment technique reported that, in some cases that these fistulas have closed spontaneously.⁵

At the beginning of the 20th century, enterostomy of the obstructed colon in a healthy area was found to be an adequate solution. In some cases, fistulas closed spontaneously.⁶

Factors for an “easier” fistula closure are low output fistuli, a long fistula tract, and no obstruction within the aboral bowel section which drains the feeding sucus distally to the fistula.

Most of all enterocutaneous occur after laparotomy, and lead a long path down to cachexia and malnutrition. The degree of malnutrition is linked to the operative outcome in terms of intraoperative mortality, successful wound healing, uneventful recovery and finally discharge of patient with his EC fistula gone. Thus high caloric hyper alimentation before surgery has been proven to be of paramount importance before surgery, as the fistula may close spontaneously as well.¹

Closure rates up to 70 % with mortality rates coming down to 6 % were reported.⁷ This marked the milestone approach of EC fistula care that started with a dire 7% healing rate and 97% mortality with inadequate nutrition, as reported by Chapman et al.⁸

EC and trauma, especially after penetrating trauma to the abdomen, is a relatively new region of interest. As most of these patients are young, and time from trauma to surgical care is short, there is nearly no kachexia nor malnutrition. As such, hyperalimentation is not needed, and swift surgical closure of EC fistula with or without temporary stoma protection may be intended.

In this patient we argue and act using the non-malnutrition situation and decide for immediate surgical approach. There are several aspects that especially cases of enterocutaneous fistulas after traumatic injuries require aggressive treatment, because this gives the surgeon an advantage over conservative treatment: it is the good nutrition of the patient, the short time from trauma, there is no skin compromise or abdominal wall infection (which may arise after long standing fistula) and a low fistula output. The presence of a potentially septic condition (injury) which can be prevented is the ultimate reason that guided our decision in this patient.

Case Report

The patient was brought to our hospital with 19/12/2012 at night (09:00 p.m.). He had been shot and wounded one hour before by a single gunshot in the left thoraco-abdominal region. There was no exit wound detectable on clinical examination. The patient was hemodynamically stable, so we proceeded with diagnostics as follows: The abdominal X-ray revealed that the bullet lodged in the small pelvis close to the right acetabulum. Thus, the patient was swiftly taken to the operating room. On operation, large amount of jejunal and colonic contaminations were present within the abdomen, which were flushed out. The bullet had caused multiple perforations to the ileum, jejunum and sigmoid colon. The spleen was uninjured, as was the thoracic cave. No pelvic vascular lesion was present. A jejunal resection with end-to-end-anastomosis 100 cm after the ligament of Treitz was performed, followed by an ileal segmental resection 70 cm apart from the ileocecal valve (end-to-end anastomosis). Primary closure of the single hole in the sigmoid colon was judged feasible and was done. Post-operatively the patient recovered clinically uneventfully up to day 8, when he manifested a sigmoido-cutaneous secretion (enterocutaneous fistula). A CT scan with double contrast was performed, which demonstrated a leak of contrast to the skin. Additionally, there were multiple abscesses present between the intestinal loops, within the left sub-phrenic space, in the sub-hepatic area as well as in the retro-cecal area (Figure 1, 2). A fistulogram confirmed a fistula channel of about 20cm length (Figure 4, 5, 6). In these conditions we re-explored the patient. He was taken back to the operating room for thorough abdominal wash-out. No further bowel injury could be detected. The sigmoid fistula was resected, and the sigma fistula ostomy carefully debrided and closed primarily again. A temporary diverting ileostomy was fashioned in the right lower quad-

rant. Abdominal microbiology swabs were taken to correct i.v. antibiotic treatment as needed. Postoperative course was un-eventful, and the patient was discharged home after further five days later.

Discussion

Entero-cutaneous fistulas are one of the most feared and catastrophic complications following abdominal surgery,⁶ especially in the old and very sick patients. Their metabolic situation is typically not well equilibrated, their nutritional status may be compromised, and concomittant diseases as well as medication needed may hamper wound healing and recovery. It is thus imperative to initiate a most efficient treatment when EC fistula has been seen, which depends on a majority of factors. It is now best practice to treat any signs of malnourishment before any surgical procedure is allowed to follow in this patients. A proper and fast recovery is bound to fail if low albumin levels contradict any attempts of wound healing, as does a depressed immune system reaction in this patient already present with a chronic infectious complication. Chapmans priorities consist of 4 phases as follows (cited by ⁸):

Phase 1: Management of dehydration, sepsis, and fistula secretion fluids.

Phase 2: Initiation of electrolyte replacement and i.v. nutrition.

Phase 3: Institution of enteral feeding access and continued vigilance in the search for uncontrolled sepsis.

Phase 4: Major surgical intervention.

Thus the understanding of EC fistula pathophysiology has lead to further sub classifications in terms of fistula length, fistula volume output and severity of nutritional Dysbalance^{9,10,11} (Figure 6, Table 1, 2), but surgery has had its' place always after feeding and nutritional needs were corrected.

During long times of phase 1 to phase 3, substantial proportions of fistuli subsided, thus conservative treatment was postulated to be superior to surgical treatment. It took years to differentiate what treatment path was of most benefit for the individual patient, as conservative treatment is not always possible or advantageous (e.g. in high output ECF), as it may be associated with serious complications.^{4, 5}

For example, Sheikh et al. conducted a retrospective study of 213 patients who had received treatment for post-operative entero-cutaneous fistulae during 2001-2008.⁶ Based on a regression analysis of the data, they concluded that high output fistulae are not likely to close on their own and that early intervention surgery proved to be lifesaving.

As a result of treatment improvements and a more individualized treatment approach, a decrease in EC fistuli mortality was seen down to 5-25% within the second half of the last century.^{12,13,14,15}

This easy said, it was and is not always easy to correct any bowel obstruction in an abdomen where adhesions

have created a bowel block impossible to separate without injuring new adjacent bowel segments. This could be a recipe for disaster, creating new fistuli. Thus the insertion of foreign materials into the fistuli were tested, using vicryl mesh or vicryl plugs. Gelatine sponges, Histoacryl glue and biodegraded porcine pigs were applied, but with varying degrees of success. Even denaturation with phenol has been thought of, but as in perianal fistuli and pilonidal sinus disease, these approaches have not been showing to do consistently well, guaranteeing the absence of doing any harm.

Surgically speaking, several devices have been proposed to close the fistuli; these were wooden and metal buttons to be inserted into the fistula to stop the out-flow.^{16,17} Also externalization of the fistula has been proposed. When direct suture may repeatedly fail to heal, interposition of well perfused and immunocompetent tissue has been the most promising approach, as with muscle flaps or omentum flaps. These interposition flaps are not always possible though, as repeat abdominal surgery in a septic abdomen may have used up the omentum, or it may be resected or stuck to adjacent organs. Especially in situations with tense intraabdominal adhesions, the source of the bowel leak may be difficult to expose and to close without undue tension.

As small bowel secretions have toxic effects onto the skin, wound care has been improved using the knowledge of stoma therapists. Silicone polymer gels may protect the skin around the cutaneous fistula openings, as they may protect the skin around a stoma if needed. Continuous suction devices (negative wound pressure dressings) have been gaining ground in desperate cases with large open laparostomas or abdominal wall defects containing EC fistulas. They can contain (suction away) even large amount of aggressive fluids, but fluid and electrolyte replacement have to be kept in mind, as skin protection for the larger area covered with the opposite plastic sheet. A special danger arises if a negative suction dressing is placed into the abdomen onto the bowel. Here it needs only a few days that the bowel will build new fistula when being kept under direct suction contact. If a plastic sheet or a silicone sheet layer separate bowels and suction dressing, low pressure suction will not harm the bowel. The suction devices enable better and easier wound care, and they buy time for the fistula to close, but they keep sucking at the fistula channel. Do they keep it open?

Enterocutaneous fistulas remain a challenge for the surgeon treating the patient. He needs to know and to work the key decision elements to set the time and decision for the conservative strategy versus surgery.^{18,19} Numerous aspects from nutritional status, immune function, time since occurring and others have to be well known to guarantee best care for our pa-

tients with an EC fistula. Still today, these small tracts remain a challenge to the team.

Conclusion

Whereas correction of cachexia, malnutrition, immunocompromise and sepsis remain the mainstay in the weak old patient, early surgical treatment remains the mainstay of treatment in young patients with enterocutaneous fistulas resulting from penetrating trauma. There is still a substantial challenge in the patient with laparostoma and EC fistula to get the bowel leak closed.

Fig. 1 CT scanner abdomen with double contrast

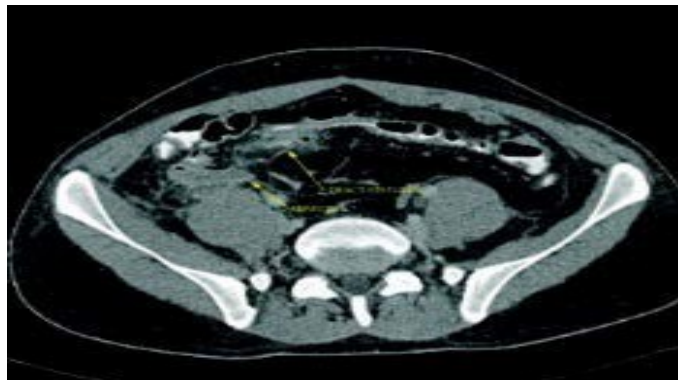


Fig. 2 CT scanner abdomen with double contrast

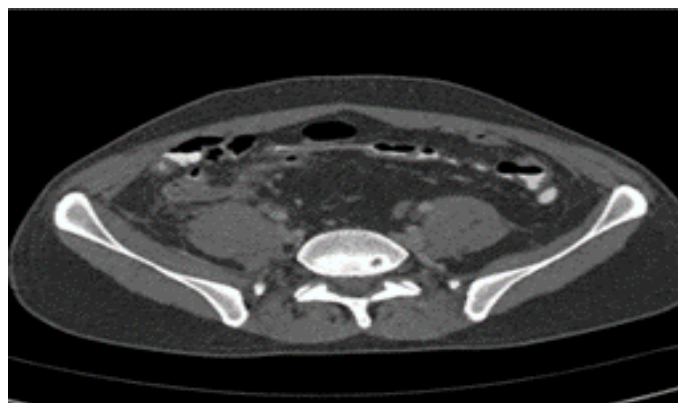


Fig. 3- Fistulogram in anterior direction



Fig.4 - Fistulogram in lateral direction



Fig. 5 Fistulogram in anterior direction and fistulas channels



Fig. 6 Anatomic classification

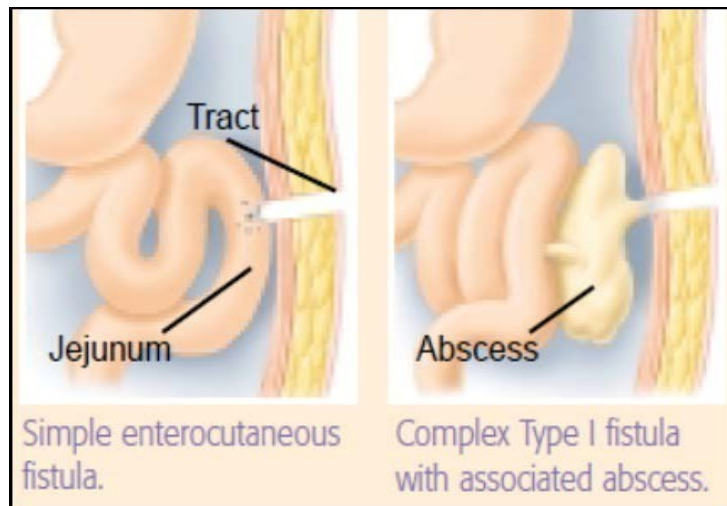
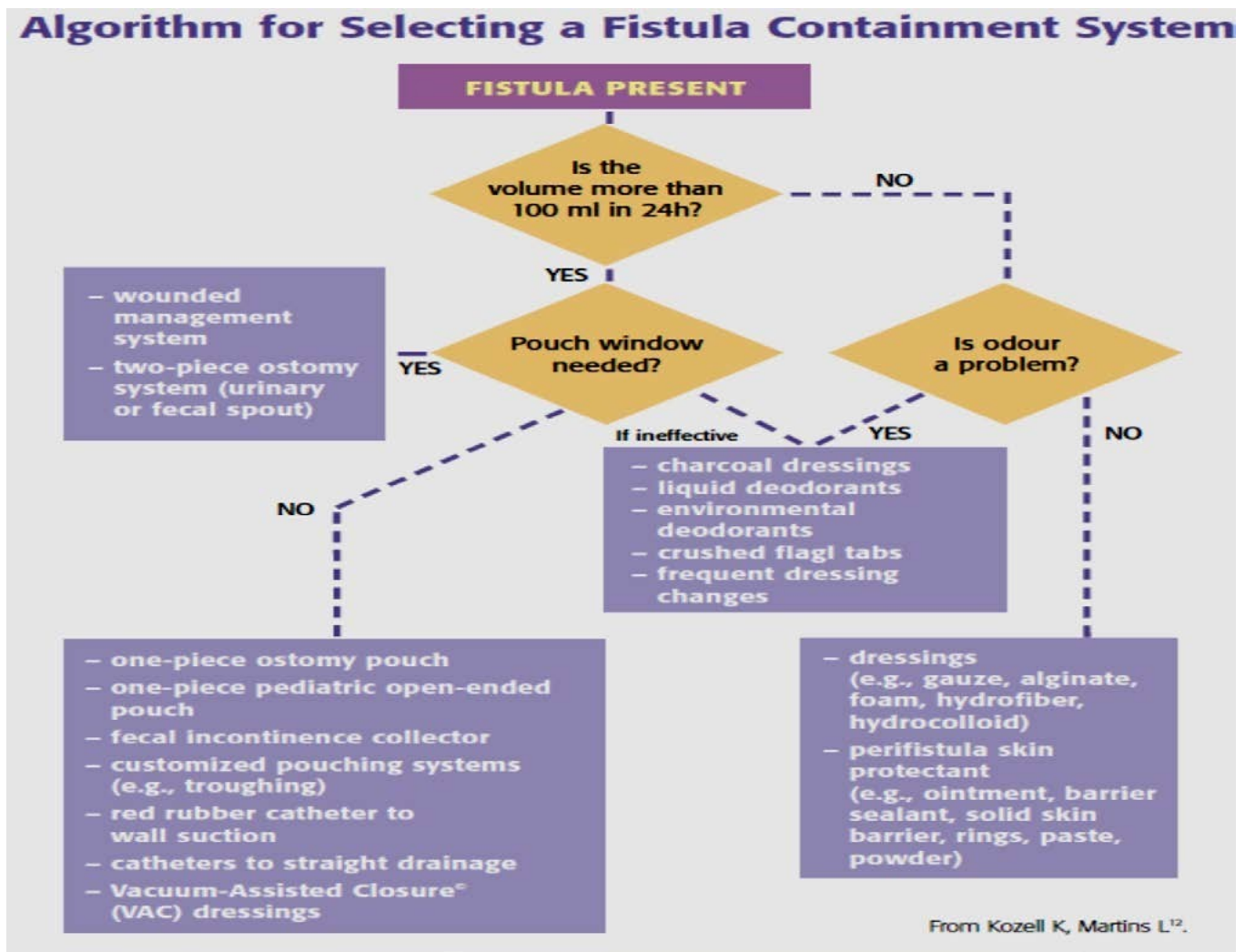


Table 1. Pathology classification

Fistula Classification		
Location	Internal	Tract contained within body
	External	Tract exits through skin
Involved structures	Colon	Colon
	Entero-	Small bowel
	Vesico-	Bladder
	Vaginal	Vagina
	Cutaneous	Skin
	Recto-	Rectum
Volume	High output	Over 200 ml per 24 hours
	Low output	Under 200 ml per 24 hours

Table 2 - Algorithm of ECF



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Diagnostic and treatment aspects of Lyme Neuroborreliosis

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Abstract

Lyme borreliosis is the most common tick-borne disease in Europe and North America. Nervous system involvement– neuroborreliosis – is the most common manifestation of the disseminated Lyme disease. In Georgia, there is no information about the prevalence of borreliosis even though it is considered as an endemic disease and there is enough evidence to suspect that it is underdiagnosed. This article reviews certain challenging aspects of clinical manifestation, diagnosis and treatment of Lyme neuroborreliosis. (TCM-GMJ January 2016; 1:P25-P27)

Keywords: Lyme borreliosis, neuroborreliosis

Introduction

Lyme borreliosis is the most common tick-borne disease in Europe and North America. It is caused by spirochetes of the *Borrelia burgdorferi* sensu lato genospecies complex. Human disease is mainly caused by three of the genospecies: *B. afzelii*, *B. garinii* and *B. burgdorferi* sensu stricto. All three are prevalent in Europe while the disease is most commonly caused by *B. afzelii* and *B. garinii*. In North America, *B. burgdorferi* is the exclusive causative agent of borreliosis.¹ *Ixodes ricinus* is the vector of Lyme disease in Europe and *Ixodes scapularis* – in North America. Lyme disease was first recognized in 1975 during an epidemic of arthritis in Lyme, Connecticut, USA.²

In Georgia, the prevalence of Lyme disease is unknown. Oral communication with clinicians reveals that they see Lyme disease in their practice. However, there is very little published information about it. Recent report lists borreliosis among endemic diseases in Abkhazia, a break-away region of Georgia.³

It is well known that Lyme disease is common in countries neighboring to Georgia – Turkey^{4,5} and Russia.^{6,7} The vector of Lyme disease, *Ixodes ricinus*, is detected at 67 locations all over Georgia.⁸ All these indicate that Lyme borreliosis an important and potentially underdiagnosed disease in this country.

Further development of eco-tourism, associated with increased exposure to the disease vector, might lead to more cases of Lyme disease in Georgia.

Lyme borreliosis can affect many organs and systems, mainly leading to dermatological, neurological, cardiac, and musculoskeletal disease. The most frequent manifestation, indicating to local infection and accounting for approximately 90% of cases, is erythema migrans; while the central nervous system (CNS) is the most frequent manifestation of a disseminated disease.⁹ Nervous system involvement is referred to as Lyme Neuroborreliosis (LNB). LNB accounts for 10-15% of Lyme disease patients and affects both CNS and peripheral nervous system (PNS).¹⁰ In this review we are focusing on challenges of diagnosis and treatment of LNB.

The incidence of LNB in Europe is 3-11/100 000 per year.¹¹ LNB is considered as a persistent infection. As Pachner described: “It has become clear that *B. burgdorferi* has joined *Treponema pallidum*, Herpes Simplex Virus, (HSV) and Human Immunodeficiency Virus (HIV) as an agent of persistent infection of the brain”.¹²

According to the time and location of manifestations, Lyme disease is classified into 3 stages. Stage I corresponds to the local infection, stage II – to the primary dissemination and stage III – secondary dissemination of the infection. The course of the disease may skip any individual stage, e.g., a patient with neuroborreliosis need not have had erythema migrans in the past.⁹

Clinical Features

Clinical features of LNB differ in European and American Patients. This is most probably due to the

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difference in bacteria species causing the disease in Europe and America - *B. burgdorferi* sensu stricto being the only causative agent in North America. It is not fully understood how *borrelia* disseminates from the site of the tick bite to other organs, including the nervous system. It has been suggested that *B. burgdorferi* disseminates predominantly via the blood, while *B. afzelii* and *B. garinii* migrate along other structures directly to the nerve roots.^{13,14} This explains the difference in clinical picture - in Europe, meningopolyradiculitis (Bannwarth's syndrome) predominates, while in North America, CNS disease is more diffuse with mostly meningitis or encephalopathy.^{9,14,15} Because of these differences, North American clinical studies are not automatically applicable to the situation in Europe, including Georgia.

In Europe, Meningoradiculoneuritis (Bannwarth syndrome) is the leading manifestation of the early disseminated disease. After erythema migrans, this is the second most common manifestation of acute Lyme disease in adults. Its main clinical features are lymphomonocytic meningitis, radiculitis, cranial nerve deficits (most commonly a peripheral facial palsy), radicular pain, and paresis. The protein concentration in the cerebrospinal fluid (CSF) is often relatively high, a finding that distinguishes this condition from a viral infection of the central nervous system.¹⁶

In late disseminated stage (stage III of Lyme disease) of the disease, chronically progressive meningoencephalitis and multifocal cerebral vasculitis can arise.⁹ The term "chronically progressive meningoencephalitis" is used when irreversible neurological damage is present and the course of the illness is not self-limited, as it is in acute *Borrelia*-induced meningoencephalitis.¹⁶

Another disease entity discussed in literature is Post Lyme Disease Syndrome (PLD). It is a condition persisting after treated Lyme Disease and is characterized by mostly mild and nonspecific symptoms, given that other causes have been excluded. PLD as a disease entity is not yet well defined and its pathophysiology is far from clear. Further studies on this topic are needed.^{17,18}

Diagnostic evaluation

The diagnostic criteria of LNB include three aspects: an appropriate clinical picture, a lymphocytic pleocytosis in CSF and an elevated specific *Borrelia* CSF-to-serum antibody index (AI), indicating intrathecal *Borrelia* antibody production (positive AI).¹⁹

Borrelia burgdorferi sensu lato can be very difficult to culture from body fluids and requires specialized laboratories. As to the polymerase chain reaction (PCR), it is of limited sensitivity because of a low bacterial count in samples and accordingly has a relatively low diagnostic value. Thus, routine diagnostic te-

sting of LNB is detection of *Borrelia*-specific antibodies.²⁰

In Europe, testing for Lyme disease must take the heterogeneity of the causative agents into consideration. It should be taken into account that there is a relatively high prevalence of antibodies against *Borrelia burgdorferi* (5% to 25%) even in healthy persons' serum, depending on their prior exposure to tick bites in their occupational and leisure-time activities. ELISA that differentiates IgG and IgM antibodies should be used as a screening test. Positive or borderline results should then be confirmed with an immunoblot, the interpretation of which is described in the guidelines.²¹ Antibodies against *Borrelia* are found in fewer than 50% of patients with erythema migrans.¹⁶ In contrast, when neurological manifestations arise, *Borrelia*-specific IgM or IgG antibodies are found in the serum of more than 90% of patients. Serology together with the corresponding clinical manifestations has a high diagnostic specificity. In neuroborreliosis, the CSF examination reveals pleocytosis, usually with a leukocyte concentration well below 1000/ μ L, in which lymphocytes predominate. The CSF protein concentration is often elevated to 1 g/L or higher.²¹

The clinical suspicion of neuroborreliosis is confirmed by the demonstration of CSF pleocytosis and intrathecally formed specific antibodies against *borrelia*. The *borrelia*-specific AI is determined for both IgG and IgM. It should be noted that an elevated *Borrelia*-specific AI does not mean an acute infection. Even when neuroborreliosis has been successfully treated, a positive *Borrelia*-specific AI can be found for years afterward.²⁰

There is a novel biomarker with a high diagnostic potential for LNB. It is the B-cell-attracting chemokine CXCL13, produced by monocytes and dendritic cells upon detection of intrathecal spirochetes and is a key factor for B-cell immigration into the CSF in LNB.^{22,23,24} The presence of this chemokine precedes the production of antibodies, and the sensitivity in early LNB is higher than the AI. However, highly elevated CXCL13 levels can also be found in the CSF in neurosyphilis, cryptococcal meningitis, cerebral lymphoma, tuberculous meningitis and HIV meningitis.²⁵ Due to the low incidence of the aforementioned diseases, the positive and, in particular, the negative predictive value of CXCL13 for acute LNB still appears to be high.²⁶ Thus, this test is promising but not yet included in the latest EFNS guidelines.²⁷

Treatment

Lyme disease generally has a good prognosis. Antibiotic treatment shortens the clinical course and prevents complications and rare chronic infections. On the other hand, reinfection is possible after another tick bite.²⁸

While the diagnosis of LNB might be challenging, the therapy is well defined. Several studies have documented a response to 14-day courses of intravenous ceftriaxone (2 or 4 g daily), intravenous penicillin (20 million units daily), intravenous cefotaxime (3X2 g or 2X3 g daily) or oral doxycycline (200 mg daily).²⁷

Significant resistance of *B. burgdorferi* to one of these antibiotics is reported to be very rare. It is recommended to treat for 14 days. There is no evidence that antibiotic treatment beyond 21-28 days is more effective, especially in the prevention of persisting syndrome.⁹

The outcome after antibiotic treatment is generally good. The pain, typical for Bannwarth's syndrome, reveals under antibiotic therapy, and patients might be free of complaints even after one antibiotic dose. A delayed treatment initiation in particular is considered a risk factor for developing persistent symptoms.²⁹

The prophylactic administration of antibiotics is not recommended as a routine measure.¹² There is debate about whether this might be of benefit in certain exceptional cases, e.g. multiple tick bites in a highly endemic area for the disease, but the necessary duration of antibiotic is unclear.²⁰

Conclusion

The knowledge about LNB is still incomplete even though in recent years, many aspects of this disease have been elucidated. In particular, the discovery of CXCL13 as an early and activity marker for acute LNB has a high potential to improve diagnostic procedures. It is important to remember about the differences in pathogenesis and clinical picture of LNB in Europe and North America, while reviewing the international literature. In Georgia, baseline surveillance studies are needed to define the prevalence and describe the clinical characteristics of LNB in our country.

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Acknowledgements

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