Editorial board

Editor-in-chief: Prof. Algidas Basevicius

MANAGING EDITORS:
Prof. Saulius Lukosevicius
Prof. Rymante Gleizniene
Prof. Ilona Kulakiene
Prof. Egle Monastyreckiene
Prof. Algirdas Edvardas Tamosiunas
Prof. Nomeda Valeviciene
Prof. Vincentas Veikutis
Prof. Elona Juozaityte
Prof. Arturas Inciura
Assoc. Prof. Jurate Dementaviciene
Assoc. Prof. Antanas Jankauskas
Med. Dr. Arturas Samuilis
Prof. Dr. Renaldas Raisutis
Prof. Dr. Minvydas Ragulskis
Prof. Renaldas Jurkevicius
Prof. Remigijus Zaliunas

ESTONIA:
Prof. Sergei Nazarenko
Prof. Ilvi Pilves

SWEDEN:
Assoc. Prof. Augustinas Sakinis
Assoc. Prof. Karolina Kublickiene

USA:
Prof. Jovitas Skucas
Assoc. Prof. Arunas Gasparaitis

UKRAINE:
Dr. Tetyana Yalynska
Prof. Olena Sharmazanova
Prof. Volodymyr Rogozhyn
Prof. Tetyana Kozarenko

CHINA:
Assoc. Prof. Guang-qing Lu

INTERNATIONAL EDITORS

LATVIA:
Prof. Gaida Krumina
Assist. Prof. Maija Radzina
Assoc. Prof. Karlis Kupcs
Assist. Prof. Peteris Prieditis

ADMINISTRATORS OF JOURNAL:
Julius Vidikas
Tomas Budrys
CONTENTS

Editorial board ................................................................................................................... 3

Intestinal pseudo-obstruction: adult Hirschsprung’s disease and Ogilvie’s syndrome. Clinical case report .......................................................................................................................... 6

Cephalometric comparison of sagittal lip position between patients with skeletal Class II divisions 1 and 2 using different reference lines ................................................................. 13

The diagnostic value of free intraperitoneal air amount while diagnosing gastrointestinal tract complications after intra-abdominal operations ................................................................. 21

Medullary thyroid carcinoma: evaluating the performance of diagnostic tests .......... 31

Treatment of uterine fibroids with A.Uterina embolisation in Latvia and Lithuania . 39

The role of computed tomography in the evaluation of the spread of ovarian cancer .... 47

Brain tumor in pregnancy: case report and literature overview ................................. 54

Advanced imaging in epilepsy: literature review and our experience ....................... 60

Patient preparation importance for diagnostic quality of PET-CT images .............. 68

Direct seventh-eighth cranial nerve involvement by brain stem glioma – a case report ... 75

Unilateral renal lymphangiectasia – the role of Ultrasound, CT and MRI. A case report ........................................................................................................................................ 81

Primary intraosseous menigioma of the calvarium presenting as a solitary osteoblastic lesion. A case report ................................................................................................................ 89

Ultrasound guided foam sclerotherapy: evaluation of complications and short-term effectiveness ................................................................................................................................. 95

Natural antiviral therapy (Cissampelos pareira mix) efficacy against dengue virus monitoring by PET CT as biomarker ........................................................................................................ 101
Intestinal pseudo-obstruction: adult Hirschsprung’s disease and Ogilvie’s syndrome. Clinical case report

Authors: Ernesta Utakienė¹, Vestina Strakšytė¹, Irina Gineikienė¹, Saulius Švagždys², Dainius Jančiauskas³, Gediminas Kiudelis¹, Algidas Basevičius¹, Mantas Vilčinskas⁵

¹ Department of Radiology, Hospital of Lithuanian University of Health Sciences Kauno klinikos, Eiveniu street 2, Kaunas, Lithuania.
² Department of Surgery, Hospital of Lithuanian University of Health Sciences Kauno klinikos, Eiveniu street 2, Kaunas, Lithuania.
³ Department of Pathology, Hospital of Lithuanian University of Health Sciences Kauno klinikos, Eiveniu street 2, Kaunas, Lithuania.
⁴ Department of Gastroenterology, Hospital of Lithuanian University of Health Sciences Kauno klinikos, Eiveniu street 2, Kaunas, Lithuania.
⁵ Hospital of Lithuanian University of Health Sciences Kauno klinikos, Eiveniu street 2, Kaunas, Lithuania.

ABSTRACT
Colonic pseudo-obstruction is a clinical and radiological syndrome of the large bowel dilatation without mechanical obstruction. We report two similar clinical cases of this syndrome with different origins – adult Hirschsprung’s disease and Ogilvie’s syndrome. Both conditions are rare and actual prevalence is unknown. Early recognition and management are extremely important because it can prevent occurrence of such complications as ischemia, volvulus or perforation and reduce morbidity with mortality.

Keywords: hypoganglionosis, computed tomography imaging, acute colonic pseudo-obstruction, megacolon, constipation.

INTRODUCTION
The term intestinal pseudo-obstruction denotes a syndrome characterized by a clinical picture suggestive of mechanical obstruction in the absence of any demonstrable intestinal lumen obstruction [1]. According to presentation, pseudo-obstruction syndrome can be subdivided into acute and chronic forms.

Acute colonic pseudo-obstruction (ACPO) also known as Ogilvie’s syndrome is characterized by massive colonic dilatation in the absence of mechanical obstruction [2]. ACPO is an important cause of morbidity and mortality. Ischemia and perforation are the threatening complications of ACPO. Spontaneous perforation has been reported in 3-15% of cases with a mortality rate estimated at 50% or higher when this occurs [3].

Chronic intestinal pseudo-obstruction (CIPO) is a syndrome defined by the presence of chronic intestinal dilatation and dysmotility due to various causes [4]. One of them is Hirschsprung’s disease (HD), which is considered a pediatric illness, as the vast majority of cases are diagnosed during the neonatal period [5]. Rare cases of Hirschsprung disease can be present in adulthood. The incidence of adult Hirschsprung’s disease is unknown, mainly because it is frequently overlooked in the adult population. The diagnosis of HD is usually much more difficult in adult than in infants, partly because of the rarity of the disease and the higher incidence of short or ultrashort segment aganglionosis in adults [6].

We should distinguish patients with ACPO from CIPO mainly because of treatment possibilities. However, despite the increasing awareness of these conditions its diagnosis remains difficult and is often delayed [2, 7]. We present two clinical cases of colonic pseudo-obstruction with different origins – Ogilvie’s syndrome and Hirschsprung’s disease.
CASE PRESENTATIONS

CASE 1

A 49-year-old man was admitted to the hospital with suspicious bowel obstruction. The anamnesis was poor because of patient’s speech and hearing disorders. Other serious underlying medical or surgical conditions were unknown. Physical examination findings were massive, rigid abdominal distension, diffuse lower abdominal pain, absence of peristalsis and no clinical signs of peritonitis. Digital rectal examination was negative (rectum empty). Routine laboratory blood test results were within the normal values.

Plain film of the abdomen showed marked diffuse dilatation of the colon (up to 11.2 cm diameter) without air-fluid levels and free air (Fig. 1). Abdominal ultrasound examination was uninformative because of gas filled bowel loops. A colonoscopy procedure failed due to retained stools in the rectum. A computed tomography (CT) scan confirmed persistent massive dilatation of the all large bowel (cecum diameter reaching 11.5 cm, rectum - 9.8 cm) filled with faeces and gas without evidence of mechanical obstruction (Fig. 2). The patient’s condition was improving and he was managed conservatively with intravenous fluids and enemas.

The diagnosis of Ogilvie’s syndrome was made based on the clinical and CT imaging findings.

CASE 2

A 27-years-old man was admitted to emergency department with severe abdominal pain followed by vomiting. He was unable to pass stool for two months and had a years history of obstipation. The patient had developmental disorders and epilepsy. Measurements of basic physiological parameters were within normal levels - respiratory rate 16 breaths per min, heart rate 60 beats per min, temperature 36.5°C, blood pressure 120/85 mmHg, oxygen saturations 98% on room air.

During a physical examination massive abdominal distention, diffuse abdominal pain, hyperactive bowel sounds, with no evidence of peritonitis were identified. Digital rectal examination demonstrated a hard mass of stool just above the anorectal ring. Routine and biochemical blood tests values were normal.

Whole abdomen did not fit in plain film of the abdomen (43 x 35 cm), because of the huge size (Fig. 3). Ultrasound examination was hard to interpretate because of distended bowel loops. A computed tomography (CT) scan was also performed and showed a massive dilatation of the rectosigmoid bowel, reaching 23 cm in diameter, with heterogeneous matter, other large bowel parts dislocated and dilatated 5 cm in diameter (Fig. 4).

Patient was treated conservatively as there was no evidence of perforation and no definite cause of mechanical obstruction. The Hirschsprung’s disease was not suspected. Despite management with intravenous fluids and enemas the patient’s condition became worse and the decision to perform a surgery was made. Sigmoid colon was resected and an intraoperative frozen sectional histological analysis has been performed (Fig. 5). Histopathological examination of the resected colon showed the absence of ganglion cells in the myenteric and submucosal plexus. Diagnosis of Hirschsprung’s disease was confirmed (Fig. 6). The patient’s postoperative course was uneventful, and the colostomy was closed 3 months after this operation. Thereafter, his defecation status became almost normal.

Fig. 1. Case 1. Plain film of the abdomen showing marked diffuse dilatation of the colon.
Fig. 2. Case 1. Computed tomography scan of the abdomen demonstrating persistent massive dilatation of the entire large bowel.

Fig. 3. Case 2. Plain film showing massive air fluid level and dilatation at the hepatic flexure (arrow). Small bowel loops are invisible, x-ray film can't contain diaphragm cupola and pelvis because of huge abdomen size.
Fig. 4. Case 2. Computed tomography scan of the abdomen showing a dilated colon packed with feces.

Fig. 5. Case 2. Operative findings showing a massively dilated (mega) sigma.

Fig. 6. Case 2. Histological appearance of distal resection line. No ganglion cells were observed (arrows). H and E staining, x24.
DISCUSSION

We presented two cases that were very similar radiologically but different in patients age, pathology, clinical manifestations and treatment. Both conditions are rare and actual prevalence is unknown. The Hirschsprung's disease occurs in approximately one in 5000 live births. Ninety-four percent of these cases are diagnosed before the patient is aged 5 years. In rare milder cases of these disorders, the patient may not receive a diagnosis until he or she reaches adulthood [8] probably because the proximal colon is often hypertrophied to compensate for the distal obstructed aganglionic rectum [6]. Do MY et al. hypothesized that adult-onset Hirschsprung disease manifests as a mild form of HD because this disease is associated with a lower degree of genetic abnormality (RET transmembrane receptor system and the endothelin receptor system) than childhood HD [9].

The exact incidence of adult HD is unknown because those cases are frequently misdiagnosed as chronic constipation or undiagnosed at all [6]. Grove and Ahlawat suggested the incidence of adult HD high as 2% of the population [7]. HD is characterized by aganglionosis (absence of ganglion cells) in the distal colon and rectum and is thought to either occur from a failure of neuroblasts in neural crest cells to migrate into bowel segments or degeneration of already migrated neuroblasts. It affects cells both in the myenteric and submucosal plexuses [10].

Ogilvie's syndrome is a rare but well recognized complication in the severely debilitated patient, after trauma, major surgery, or sepsis [11]. The pathophysiology of Ogilvie syndrome is not completely understood although it likely results from an alteration in the autonomic regulation of colonic motor function [12]. The vast majority of patients (>95%) with ACPO have the syndrome in association with one or multiple predisposing factors or clinical conditions. In a large retrospective series of 400 patients, the most common predisposing conditions were non-operative trauma (11%), infections (10%) and cardiac disease (10%) [13]. The mechanisms through which these different conditions temporarily suppress colonic motility and induce dilatation are unknown [14]. The exact prevalence of ACPO is unknown. In our case we don't know exact predisposing condition because of patient's speech and hearing disorders.

Clinical presentations of Ogilvie's syndrome and adult HD are different. Most often ACPO affects those in late middle age (mean age of 60 years), occurs in hospitalized or institutionalized patients with serious underlying medical and surgical conditions and associated with a wide spectrum of illnesses [15] or adult HD mean age 27.8 year [8]. Ogilvie's syndrome is characterized by abdominal distention, abdominal pain, nausea and/or vomiting, with a failure to pass flatus and stools documented in up to 60% of patients. Abdominal distention usually develops over 3-7 days but can occur as rapidly as 24 h [13]. In surgical patient, symptoms and signs develop at a mean of 5 days post-operatively. Massive colonic dilatation may cause ischemia and perforation, with the subsequent clinical finding of peritonism [15]. The approximate risk of spontaneous perforation is 3 percent, with an attendant mortality rate of 50 percent [8]. Physical examination in the uncomplicated situation typically reveals a tympanic, non-tender abdomen, with high-pitched “tinkling”, reduced or absent bowel sounds. Patients with complications present with marked abdominal tenderness and systemic features such as fever, tachycardia and leukocytosis [15].

A life-long history of refractory constipation is typical clinical manifestation of adult Hirschsprung's disease, like in our second case. Patients manage this condition by using cathartic agents, bulk formers, and enemas [8]. When functional decompensation of the colon occur, fecal impaction and megacolon may warrant urgent surgical intervention [16]. Rarely these patients may experience rapidly worsening subacute intestinal obstruction or even acute presentation with complications such as enterocolitis or volvulus [17].

Diagnosis relies on accurate clinical observation and plain abdominal radiography showing various degrees of colonic dilatation, mainly involving the proximal colon. Plain abdominal radiog-
Radiography can also give some indication of colonic diameter as well as detecting the presence of free air, suggesting perforation. CT should be performed to differentiate mechanical obstruction from pseudo-obstruction; CT with intravenous contrast has a sensitivity and specificity both of 91% [15].

The correct diagnosis of adult Hirschsprung’s disease is based on barium enema, anorectal manometry and, most important, the full-thickness rectal biopsy findings. Plain abdominal radiographs identify only nonspecific findings of massive distention of the colon, often with air-fluid levels in both conditions. A small narrowed distal segment in adult Hirschsprung’s disease may not be detected in approximately 20% of patients [8]. This finding may be due to a short, or more commonly, an ultrashort diseased segment [6]. Although CT is considered a common imaging modality for excluding other diseases such as colorectal cancer, which also causes chronic constipation in adults [8].

The HD diagnosis was confirmed after histological examination. Histologic examination of colorectal specimens for the presence of ganglion cells remains the standard method of evaluating patients with Hirschsprung’s disease and forms the basis for surgical treatment [18].

In both cases CT imaging was performed, and findings were very similar. In case 1, the diagnosis of Ogilvie’s syndrome was properly based on the grounds of massive bowel dilatation, absence of mechanical reason and patient clinical course. In case 2, HD was not suspected radiologically mainly because characteristic rectal narrowing was not identified on CT imaging.

Both conditions should be distinguished mainly because of treatment possibilities. It is extremely important to diagnose HD because surgical management is effective with satisfactory long-term functional results and significantly improves quality of life [19, 20]. The principles of pull-through surgery are firstly to remove all the hypoganglionic segments and secondly to achieve bowel continuity between the normally innervated bowel and the anal canal in order to provide bowel continence in the long term [20, 21]. The most common procedure performed is the Duhamel procedure [17]. This operation is associated with lower rate of major postoperative complications than the other procedures, and the higher rate of good long-term results [21].

In our case patients condition with HD was not properly assessed. Only after surgery and histological evaluation true diagnosis was made.

Treatment of Ogilvie’s syndrome depends on the severity of the clinical picture and the perceived risk of imminent ischemia and perforation [15]. Conservative treatment with nasogastric suction, enemas, and neostigmine is highly effective [19]. Colonoscopy is a safe and effective method for treatment of this syndrome when conservative treatment has failed. Surgical operation is indicated only for realized or imminent perforation, or in patients who have not responded to maximum non-surgical measures [15].

In both cases learning point is that massively dilated bowel loops and patients with anamnesis of obstipation may be representation of life threatening conditions such as Hirschsprung’s disease and Ogilvie’s syndrome.

CONCLUSIONS

Proper diagnostic and management techniques allows to avoid life-threatening conditions such as adult Hirschsprung’s disease and Ogilvie syndrome.

STATEMENT OF CONFLICTS OF INTEREST

The authors state no conflict of interest.
REFERENCES

Cephalometric comparison of sagittal lip position between patients with skeletal Class II divisions 1 and 2 using different reference lines

Arūnas Vasiliauskas¹, Greta Margelytė¹, Kristina Lopatienė¹, Antanas Šidlauskas¹, Rimas Adaškevičius²

¹Clinic of Orthodontics, Odontology Faculty, Medical Academy, Lithuanian University of Health Sciences.
²Department of Electric Power Systems, Faculty of Electrical and Electronics Engineering, Kaunas University of Technologies.

ABSTRACT

Objective: The objectives of this study were (1) to evaluate and compare sagittal lip position between skeletal Class II division 1 and 2 patients according to different cephalometric reference lines and (2) to evaluate the interrelation of the sagittal lip position and the inclination of the incisors.

Materials and Methods: A total of 100 patients with skeletal Class II (ANB>4°) and finished adolescent growth peak, evaluated with an improved version of the cervical vertebral maturation (CVM) method, were distributed into division 1 and 2, based on the inclination of the upper incisors. The inclination of upper and lower incisors was assessed by various methods. Sagittal lip position was evaluated using Burstone B, Ricketts E, Steiner S, and Holdaway H reference lines. For statistical analysis SPSS Statistics 17.0 software was used. Mann-Whitney U test and Student’s t-test were applied to evaluate the significance of the average difference between samples while LS least squares method assessed the dependence between the samples. Level of significance was set at \( p < 0.05 \).

Results: Division 1 patients showed statistically significant higher sagittal upper and lower lip position values than division 2 patients. According to the B line, the upper lip value was 4.79±1.81 mm in division 1 and 2.29±1.37 mm - in division 2, while the lower lip values were 3.23±3.01 mm and 0.76±1.78 mm, respectively. Due to the E line, the respective values were -1.07±2.38 mm and –4.40±1.78 mm in the upper lip and S line values were 1.46±2.01 mm and -1.56±1.49 mm, respectively. A statistically significant dependence was found between sagittal lip position and incisor inclination.

Conclusions: Skeletal Class II division 1 patients had more protrusive upper and lower lips, compared to division 2 patients. Sagittal lip position highly depended on the inclination of the incisors.

Keywords: cephalometry; orthodontics, Class II malocclusion

INTRODUCTION

Lateral cephalometric radiography, as a useful tool in orthodontics, was first presented by Broadbent [1] and has successfully been used ever since. Cephalometric analysis, which includes linear and angular measurements, is an effective diagnostic method that assists in the evaluation of facial morphology, the prediction of skeletal growth, the planning of orthodontic treatment, and the evaluation of treatment outcomes. [2] In today’s orthodontic treatment it is essential to estimate thoroughly not only skeletal and dental, but also soft tissues parameters. The cephalometric analysis is a simple, cheap, and sufficiently informative diagnostic technique, and the generated 2D images along with evaluation results are sufficiently reliable and may be an alternative to 3D imaging in the evaluation of soft tissue. Numerous studies have been conducted in order to evaluate the influence of orthodontic treatment on the soft tissue profile. Stamenković et al. [3] proved that when applying various treatment methods that affect skeletal and dental structures, the soft tissue profile may change as well. Kasai [4] in his study concluded that soft tissues do not necessarily equally follow the changing hard tissue profile during orthodontic treatment: some soft tissue structures are closely related to underlying hard tissues, while others are more influenced by such factors as function, thickness, and length. The authors agree that the patient’s final profile highly depends on soft tissues, especially those that vary in thickness.[5-7] Hence, failure to explore the soft tissue profile may prevent the most accurate prediction of
treatment outcomes. Many authors showed a great interest in exploring what impact altering the position of the incisors has on the soft tissue profile. A study by Meyer-Marcotty et al. [8] where skeletal Class II patients’ profiles were investigated before and after treatment with the Herbst appliance, revealed important changes, such as a reduction in the red margin of the upper lip, an increase in the lower lip height, mentolabial sulcus reduction, and a flatter facial profile. Significant lip changes were observed when premolar extraction treatment was applied. The results of a study by Verma et al. [9] showed that patients from the extraction treatment group had more retrusive both upper and lower lips. A study by Amirabadi et al. [10] where the patients’ lip parameters were evaluated before the extraction of the upper first premolars and after the extraction treatment, showed a significant reduction in the upper lip protrusion and a significant reduction in the lower lip protrusion and facial convexity when crowding was more than 4 mm. On the other hand, there are controversial data from a study conducted by Khan and Fida [11] who stated that even during the treatment, patients treated with premolar extractions showed more retruded upper and lower lips than did patients treated without extractions, while at the end of the treatment, their soft tissue profiles did not differ. Another recent study by Rathod et al. [12] which compared long-term soft tissue changes between patients treated with extraction and patients that had no treatment, also concluded that the soft tissue profile between the groups was similar at the endpoint.

As many studies have shown, orthodontic treatment may alter lip position by changing the inclination of the incisors, and therefore soft tissues, especially lips, have to be carefully evaluated before choosing the type of the treatment. There are studies assessing lip parameters in different malocclusions [13,14] and comparing different methods of the evaluation of the sagittal lip position [14]. However, these studies do not evaluate very important parameters, such as nose length and chin thickness, which usually are the reference points for sagittal lip position measurements. Neither do they evaluate lip thickness, which has a direct influence on sagittal lip position measurements. Moreover, none of these studies divide skeletal Class II patients into divisions, but rather investigate them as a single sample regardless of the evident differences in the anterior teeth between the divisions. As mentioned above, the incisor position may affect lip position, and therefore investigating Class II patients as a single unit might provide imprecise results. The objectives of this study were (1) to evaluate and compare sagittal lip position between skeletal Class II division 1 and 2 patients according to different reference lines and (2) to evaluate the dependence of the sagittal lip position on the inclination of the incisors.

MATERIAL AND METHODS

Sample
This retrospective study comprised of 100 randomly selected pre-orthodontic patients from the “Dolphin imaging 11” (Dolphin Imaging and Management Solution) database of the of the Clinic of Orthodontics of Lithuanian University of Health Sciences. The power of the research was 0.8, when the Type I error rate was 0.05. The inclusion criteria were the following: (1) skeletal Class II, which was established according to Steiner’s method, where ∠ANB was evaluated. [15] Patients with skeletal Angle Class II (ANB angle >4°) were included in the study. (2) Finished adolescent growth peak; its evaluation was based on an improved version of the cervical vertebral maturation (CVM) method. [16] According to this method, adolescent growth peak occur between vertebral development stages 2 and 3, and therefore patients with stages 3, 4, and 5 were included in this study. All the selected patients were divided into 2 groups according upper incisor inclination which was estimated with different methods: upper incisor inclination in relation to the cranial base, [17] in relation to the NA line, [15] in relation to the Frankfort horizontal,[17] and in relation to the palatal plane. [18] Patients with protruded incisors were considered as division 1 and patients with retruded incisors were marked as division 2. Every division had 50 patients: 36 girls and 14 boys. The study was conducted with the permission of the Kaunas Regional Biomedical Research Ethics Committee (February 9, 2015, No. BE-2-12).

Collection of cephalometric analysis data
The cephalograms were taken in centric occlusion under standard conditions using digital x-ray equipment. To minimize radiation dose digital cephalometric system Kodak 8000C was used and ALARA radiation safety principle was followed. For standardized positioning, a cepha-
lostat was used to maintain the subject's head in constant relationship to the sensor (sensor-focus distance - 1.50 m, object-sensor distance - 0.15 m). This in turn standardized the distance of the subject to the sensor, x-ray exposure, and magnification exposure. All subjects were asked to stand looking straight forward, with a lead apron on their chest. Ear rods were placed into the ear canals in a comfortable position, and the orbital pointer was accurately positioned.

Definitions of cephalometric landmarks used in this study are presented in Table 1. Planes and lines are presented in Table 2. Angular and linear measurements and their definitions are shown in Table 3. The inclination of the lower incisors was estimated using 3 methods: lower incisor inclination in relation to line NB,[15] in relation to the mandibular plane,[17] and in relation to the occlusal plane [17]. For the evaluation of the sagittal lip position, 4 different reference lines were used: Burstone B line,[19] Steiner S line,[15] Holdaway H line,[5] and Ricketts E line.[20] (Figure 1)

The sagittal lip position was assessed in millimeters by measuring the distance between the most prominent lip point to the reference line. Lip thickness was assessed by applying Arnett's method.[21] Upper lip thickness was measured from the upper lip vermillion point ULA to the upper lip inside, while lower lip thickness – from the lower lip vermillion point LLA to the lower lip inside. Nose depth was measured from point Sn to point Pr,[22] while chin thickness was evaluated by measuring the distance from point Pog to point Pog’ [21].

METHOD ERROR

The reliability of the method was tested by measuring 20 randomly selected lateral cephalograms. The intraclass correlation coefficient was used to estimate the difference of measurements between 2 observers [23]. There were no statistical differences found between cephalometric data in different time intervals.

STATISTICAL ANALYSIS

In order to conduct statistical analysis, SPSS Statistics 17.0 software was used. The significance of the average difference between independent samples was evaluated using the Mann-Whitney U test and Student's t-test. Correlation between the samples was determined by using Pearson's Correlation and Spearman's Correlation coefficient. To evaluate the dependence between the samples, the LS least squares method was applied. The difference in soft tissue thickness between female and male patients was measured according to the t-test for the equality of means. The level of significance for the analysis was set at p < 0.05.

RESULTS

The angle ANB value was 5.59±0.98° in division 1 patients and 5.54±0.88° - in division 2 patients. This difference between the divisions was not statistically significant (p = 0.76), meaning that those two samples had equal skeletal Class II.

In order to avoid possible sex-influenced soft tissue differences between boys and girls, which might affect the reference lines when evaluating sagittal lip position, such parameters as lip thickness, nose length, and chin thickness were compared between male and female patients in each division. No statistically significant differences were found between males and females in both divisions. The mean values of lip thickness, nose length, and chin thickness are demonstrated in Table 4.

Hence, no differences between the sexes were found, and further on, male and female patients were considered as a single sample.

A strong correlation was observed between all methods of the evaluation of upper and lower incisor inclination. The upper incisor inclination values were statistically significantly higher in division 1 patients according to all methods. All the applied methods also showed that division 1 patients had more protrusive lower incisors. This difference was statistically significant when assessed by the L1-NB and L1-Oc methods. The descriptive analysis of incisor inclination values is shown in Table 5.

A strong correlation was found between all methods of the evaluation of sagittal upper and lower lip position. The descriptive analysis of sagittal lip position is demonstrated in Table 6. All methods indicate that division 1 patients had statistically significantly higher upper and lower lip sagittal position values.

A statistically significant dependence was found between the sagittal upper lip position assessed by Steiner's and Burstone's methods and upper incisor inclination evaluated by all methods (p <0.001). When the sagittal upper lip position was evaluated by using the Ricketts method, it demonstrated a statistically significant depend-
ence on all the methods of the evaluation of upper incisor inclination (p < 0.001), except for the U1-Pal method, in which case the dependence was not statistically significant (p = 0.219).

Sagittal lower lip position, evaluated by all reference lines, demonstrated a statistically significant dependence on lower incisor inclination assessed by all methods. All values were p <0.05.

Both upper and lower lips were thicker in division 1 patients, but this difference was not statistically significant (upper lip p = 0.055, and lower lip p = 0.762). Mean upper lip thickness values were 12.05±2.31 mm in division 1 and 11.12±2.47 mm - in division 2, while lower lip thickness values were 8.90±2.95 mm and 8.53±1.77 mm, respectively. Nose length values were slightly higher in division 2 patients, but this difference was not statistically significant (p = 0.077). Mean values were 19.22±2.38 mm in division 1 and 20.02±2.51 mm - in division 2. There was no statistically significant difference in chin thickness between the divisions (p = 0.992). Mean values were 11.66±2.18 mm in division 1 and 11.74±1.68 mm - in division 2.

**Table 1** Definitions of landmarks used in this study

<table>
<thead>
<tr>
<th>Landmarks</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>S - Sella</td>
<td>The midpoint of sella turcica.</td>
</tr>
<tr>
<td>N - Nasion</td>
<td>The extreme anterior point of the frontonasal suture.</td>
</tr>
<tr>
<td>A – Point A</td>
<td>The deepest point in the curvature of the maxillary alveolar process.</td>
</tr>
<tr>
<td>B – Point B</td>
<td>The deepest point in the curvature of the mandibular alveolar process.</td>
</tr>
<tr>
<td>O - Orbitale</td>
<td>The most inferior point on the infraorbital rim.</td>
</tr>
<tr>
<td>Po - Porion</td>
<td>The most superior point of the external acoustic meatus.</td>
</tr>
<tr>
<td>ANS – Point ANS</td>
<td>The tip of the anterior nasal spine.</td>
</tr>
<tr>
<td>PNS – Point PNS</td>
<td>The tip of the posterior nasal spine.</td>
</tr>
<tr>
<td>Go - Gonion</td>
<td>The most convex point along the inferior border of the ramus.</td>
</tr>
<tr>
<td>Gn - Gnathion</td>
<td>The midpoint between Pogonion and Menton.</td>
</tr>
<tr>
<td>Me - Menton</td>
<td>The most inferior point of the chin.</td>
</tr>
<tr>
<td>Pog - Pogonion</td>
<td>The most anterior point of the chin.</td>
</tr>
<tr>
<td>Pr - Pronasale</td>
<td>The tip of the nose.</td>
</tr>
<tr>
<td>Cm – Point Columella</td>
<td>The most anterior point on the columella of the nose.</td>
</tr>
<tr>
<td>Sn - Subnasale</td>
<td>The point at which the nasal septum merges with the upper cutaneous lip in the mid-sagittal plane.</td>
</tr>
<tr>
<td>ULA – Point ULA</td>
<td>The most anterior point of the upper lip.</td>
</tr>
<tr>
<td>LLA - Point LLA</td>
<td>The most anterior point of the lower lip.</td>
</tr>
<tr>
<td>Pog' – soft tissue Pogonion</td>
<td>The most anterior point of the soft tissue chin.</td>
</tr>
</tbody>
</table>

**Table 2** Planes and lines used in this study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH – Frankfort Horizontal</td>
<td>The line connecting Orbitale and Porion.</td>
</tr>
<tr>
<td>Pal - Palatal</td>
<td>The line connecting ANS and PNS.</td>
</tr>
<tr>
<td>Occ - Occlusal</td>
<td>The line connecting overlapping cusps of first molars and incisal overbite.</td>
</tr>
<tr>
<td>SN – Cranial base</td>
<td>The line connecting Sella and Nasion.</td>
</tr>
<tr>
<td>NA</td>
<td>The line connecting Nasion and point A.</td>
</tr>
<tr>
<td>NB</td>
<td>The line connecting Nasion and point B.</td>
</tr>
<tr>
<td>Burstone B line</td>
<td>The line connecting Subnasale and soft tissue Pogonion.</td>
</tr>
<tr>
<td>Ricketts E line</td>
<td>The line connecting Pronasale and soft tissue Pogonion.</td>
</tr>
<tr>
<td>Steiner S line</td>
<td>The line connecting point Columella and soft tissue Pogonion.</td>
</tr>
<tr>
<td>Holdaway H line</td>
<td>The line connecting point ULA and soft tissue Pogonion.</td>
</tr>
</tbody>
</table>
### Table 3 Angular and linear measurements used in this study

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Variables</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angular</td>
<td>ANB</td>
<td>Angle determined by points A, N, and B.</td>
</tr>
<tr>
<td></td>
<td>U1-SN</td>
<td>Angle determined by the longitudinal axis of the upper incisors and the cranial base plane.</td>
</tr>
<tr>
<td></td>
<td>U1-NA</td>
<td>Angle determined by the longitudinal axis of the upper incisors and the line connecting points N and A.</td>
</tr>
<tr>
<td></td>
<td>U1-FH</td>
<td>Angle determined by the longitudinal axis of the upper incisors and the Frankfort horizontal plane.</td>
</tr>
<tr>
<td></td>
<td>U1-Pal</td>
<td>Angle determined by the longitudinal axis of the upper incisors and the Palatal plane.</td>
</tr>
<tr>
<td></td>
<td>L1-NB</td>
<td>Angle determined by the longitudinal axis of the lower incisors and the line connecting points Nasion and point B.</td>
</tr>
<tr>
<td></td>
<td>L1-GoGn</td>
<td>Angle determined by the longitudinal axis of the lower incisors and the line connecting points Gonion and Gnathion.</td>
</tr>
<tr>
<td></td>
<td>L1-Occ</td>
<td>Angle determined by the longitudinal axis of the lower incisors and the Occlusal plane.</td>
</tr>
<tr>
<td>Linear</td>
<td>ULA – B line</td>
<td>Distance between point ULA and B line in mm.</td>
</tr>
<tr>
<td></td>
<td>LLA – B line</td>
<td>Distance between point LLA and B line in mm.</td>
</tr>
<tr>
<td></td>
<td>ULA – E line</td>
<td>Distance between point ULA and E line in mm.</td>
</tr>
<tr>
<td></td>
<td>LLA – E line</td>
<td>Distance between point LLA and E line in mm.</td>
</tr>
<tr>
<td></td>
<td>ULA – S line</td>
<td>Distance between point ULA and S line in mm.</td>
</tr>
<tr>
<td></td>
<td>LLA – S line</td>
<td>Distance between point LLA and S line in mm.</td>
</tr>
<tr>
<td></td>
<td>LLA – H line</td>
<td>Distance between point LLA and H line in mm.</td>
</tr>
<tr>
<td></td>
<td>ULA – upper lip inside</td>
<td>Distance between point ULA and the upper lip inside in mm.</td>
</tr>
<tr>
<td></td>
<td>LLA – lower lip inside</td>
<td>Distance between point LLA and the lower lip inside in mm.</td>
</tr>
<tr>
<td></td>
<td>Sn-Pr</td>
<td>Distance between Subnasale and Pronasale.</td>
</tr>
<tr>
<td></td>
<td>Pog-Pog</td>
<td>Distance between Pogonion and soft tissue Pogonion.</td>
</tr>
</tbody>
</table>

### Table 4 Descriptive analysis of lip thickness, nose length, and chin thickness in female and male subjects.

<table>
<thead>
<tr>
<th>Division 1</th>
<th>Division 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (n=36)</td>
</tr>
<tr>
<td>Cephalometric variables</td>
<td>Mean</td>
</tr>
<tr>
<td>Upper lip thickness (mm)</td>
<td>11.86</td>
</tr>
<tr>
<td>Lower lip thickness (mm)</td>
<td>8.77</td>
</tr>
<tr>
<td>Nose length (mm)</td>
<td>18.98</td>
</tr>
<tr>
<td>Chin thickness (mm)</td>
<td>11.48</td>
</tr>
</tbody>
</table>

N.S. – not significant
Table 5 Descriptive analysis of the inclination of upper and lower incisors.

<table>
<thead>
<tr>
<th>Cephalometric variables</th>
<th>Division 1</th>
<th>Division 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>U1-SN (°)</td>
<td>113.40</td>
<td>4.90</td>
</tr>
<tr>
<td>U1-NA (°)</td>
<td>31.57</td>
<td>4.42</td>
</tr>
<tr>
<td>U1-FH (°)</td>
<td>121.32</td>
<td>6.44</td>
</tr>
<tr>
<td>U1-Pal (°)</td>
<td>120.10</td>
<td>4.85</td>
</tr>
<tr>
<td>L1-NB (°)</td>
<td>26.11</td>
<td>6.43</td>
</tr>
<tr>
<td>L1-GoGn (°)</td>
<td>97.99</td>
<td>7.0</td>
</tr>
<tr>
<td>L1-Occ (°)</td>
<td>62.45</td>
<td>6.34</td>
</tr>
</tbody>
</table>

* P < .05; N.S. – not significant

Table 6 Sagittal upper and lower lip position descriptive analysis.

<table>
<thead>
<tr>
<th>Upper lip</th>
<th>Lower lip</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Division 1</td>
</tr>
<tr>
<td>B line (mm)</td>
<td>4.79</td>
</tr>
<tr>
<td>E line (mm)</td>
<td>-1.07</td>
</tr>
<tr>
<td>S line (mm)</td>
<td>1.46</td>
</tr>
<tr>
<td>H line (mm)</td>
<td>-</td>
</tr>
</tbody>
</table>

* P < .05

Figure 1. Reference lines of the sagittal lip position: Burstone B line, Steiner S line, Holdaway H line and Ricketts E line.
DISCUSSION

Many investigators had interest in exploring the interrelation between skeletal class, soft tissue profile and surrounding soft tissues. The main disadvantage of this and similar studies is, that soft tissue parameters are evaluated in 2D view. The greatest accuracy may be achieved when analyzing 3D images, yet the disadvantage of this technique is high costs, and therefore cephalography is used as an alternative technique for the planning of orthodontic treatment.

Zhang et al.13 classified patients into 3 groups: Angle Class I, Angle Class II division 1, and Angle Class III. The aim of the study was to characterize the soft tissue profile (including sagittal lip position) specific to every group. The results showed that Angle Class II division 1 patients had more protrusive upper and lower lips, compared to Angle Class I patients. The upper lip was also found to be more protrusive than the lower lip. A study by Joshi et al.14 focused more on the sagittal lip position, and its aim was to evaluate differences in the sagittal lip position between different skeletal classes. The researchers reached the conclusion that the Sushner line was most suitable for the evaluation of the sagittal lip position in Chinese population with skeletal Class I and Class II patients, and the Burstone line was most suitable for Class III patients. The main shortcoming of these studies is that skeletal Class II patients were not divided into division 1 and division 2. As the present study revealed, the sagittal position of both upper and lower lips statistically significantly depended on incisor inclination. According to all reference lines, both upper and lower lips were statistically significantly more protruded in division 1 patients. In addition, previous studies did not take into account the parameters that may influence the sagittal lip position, such as lip thickness, nose length, and chin thickness. In the present study, these factors had no influence because neither lip or chin thickness nor nose length differed between the divisions. On the other hand, there are studies claiming that soft tissues adjust to the skeletal anomaly and camouflage it.[24-27] Usually, in this type of studies, skeletal classes are compared, but there also are studies where skeletal Class II divisions were investigated separately.[25,26] The results of the study where soft tissue profiles of patients with different skeletal classes (skeletal Class II division 1 and division 2, and skeletal Class III) were compared to the soft tissue profile of Class I patients showed that skeletal Class II division 1 patients had thinner upper lips and shallower upper lip sulci, while division 2 patients had thicker upper lips.[25] A study where only skeletal Class II division 1 and division 2 were evaluated showed that division 1 patients had thinner upper lips, shallower upper lip sulci, and thicker lower lips, compared to division 2 patients.[26] As mentioned above, in our study, lip thickness did not differ between the divisions, hence the hypothesis that soft tissues camouflage skeletal discrepancies was not confirmed.

The present study revealed, that sagittal lip position is highly affected by incisors inclination, therefore in future studies, these two groups should be investigated separately instead of one sample in order to get more precise results, evaluating different skeletal class soft tissue profile. According to all reference lines (Burstone B line, Ricketts E line, Steiner S line, and Holdaway H line), division 1 patients had more protruded upper and lower lips, compared to division 2 patients.

All the applied methods showed that the sagittal position of the upper lip statistically significantly depended on the inclination of the upper incisors, and the sagittal position of the lower lip – on the inclination of the lower incisors.
REFERENCES

The diagnostic value of free intraperitoneal air amount while diagnosing gastrointestinal tract complications after intra-abdominal operations

Mantas Vilčinskas¹, Irina Gineikienė², Saulius Švagždys³, Vestina Strakšytė²

¹ Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Lithuania.
² Department of Radiology, Lithuanian University of Health Sciences Kaunas, Lithuania.
³ Department of Surgery, Lithuanian University of Health Sciences Kaunas, Lithuania.

ABSTRACT

Background and aim. Pneumoperitoneum following a recent abdominal surgery is a diagnostic dilemma. The aim of the study was to determine the diagnostically significant amount of free air in the peritoneal cavity, evaluating probable complications that are associated with a break of gastrointestinal (GI) integrity and to identify clinical, laboratory and demographic impact on the results.

Materials and methods. 50 patients who underwent abdominal operations were examined, 30 had an uneventful post-operative period (the first group) and 20 developed complications (the second group). The abdominal radiographies (AXR) were performed on the fifth postoperative day as well as the complete blood count and C-reactive protein (CRP) tests. Pneumoperitoneum diagnosis was based on finding free air under the diaphragm.

Results. The average amount of free air in the first group was 6.59 mm, and in the second - 29.57 mm. Postoperative complications were correctly diagnosed in 70% of cases, and correctly denied in 60% of cases. Using a cutoff point of 9.65 mm, complications were diagnosed correctly in 70% of cases, and correctly denied in 83.33%. The amount of free air has a significant correlation with the body mass index (r = -0.620; <0.001) and CRP (r = 0.596; p = 0.006). No statistically significant difference of amount of free air between operated in an open manner and laparoscopically was observed.

Conclusions. AXR has limited specificity and sensitivity for diagnosing postoperative complications that are associated with a break of GI integrity; however, if the results are combined with CRP values, AXR remains a solid alternative to computed tomography scan.

Keywords: postoperative pneumoperitoneum, free air, radiography, perforation, anastomotic leak.

INTRODUCTION

Free air in the abdominal cavity following a recent abdominal surgery is a diagnostic dilemma. This can be a normal finding (physiological pneumoperitoneum) due to the passage of air during open operation, injected gas to improve visualization during laparoscopic surgery or postoperative drainage. However, this can also be a sign of anastomotic leakage or gastrointestinal (GI) perforation. In order to avoid unnecessary repetitive operations, it is essential to distinguish between physiological pneumoperitoneum and postoperative complications in which the patient needs urgent assistance [1, 2].

There is still no exact agreement on the amount of free air in the abdominal cavity and the duration of its observation, which would allow the differentiation of the postoperative physiological state from the pathological one. Early diagnosis of GI integrity disorders is also aggravated by the post-operative pain and the use of narcotic drugs, abdominal muscle tension, and paralytic ileus [3].

Computerized tomography (CT) and abdominal radiography (AXR) are commonly used to detect free air in the abdominal cavity. The CT study is superior to APR in detecting free air; however, the CT is not so easily accessible, its price is high, and CT is more harmful to the patient due to its higher exposure compared to the X-ray examination. As an alternative, X-rays are chosen, which are readily accessible, low-cost, and the ionizing radiation is about 11.42 times lower than in the CT scan [3, 4].
Based on the available data, this is one of the first studies in Lithuania that evaluates the role of X-rays in diagnosing free air in the abdominal cavity; however, there have been many studies in other countries that investigated the etiology of postoperative pneumoperitoneum, its size, duration and its correlation with clinical and laboratory data. Unfortunately, opinions about the role of abdominal radiographs in diagnosing pathological pneumoperitoneum remain controversial. A large part of the authors only analyse the duration of free-air in the abdominal cavity. The aim of this study is not only to evaluate the diagnostic significance of detecting the free air abdominal cavity, but also to establish the exact value for the free air that would differentiate the physiological pneumoperitoneum from the pathological state, and to ascertain the influence of clinical, laboratory and demographic indicators on the results.

MATERIAL AND METHODS

2.1 SOURCES OF DATA
The study was carried out in February, 2015 – April, 2016 at the Hospital of LUHS Kaunas Clinics, Departments of Surgery and Radiology, after it was approved by the local ethic committee. The object of the research was the free air in the abdominal cavity after intra-abdominal operations. The subject of the study was the patients who had undergone intra-abdominal operations. This is a quantitative case-control study. Patients were selected for the study in two stages: using targeted selection while performing retrospective analysis of medical records and with prospective patient research. A schematic diagram of the retrospective data collection is given in Figure 1.

Prospectively, patients over the age of 18 who had undergone surgery during which the gastro-intestinal tract was opened were included in the study. Exclusion criteria were: patient’s disagreement, age ≤18 years, current or suspected pregnancy. Abdominal radiographies as well as the complete blood count and C-reactive protein (CRP) tests were performed for all the patients who participated in the study on the 5th postoperative day, regardless of whether symptoms of possible postoperative complications were present. It was decided to perform ARX on 5th postoperative day, based on literature data, where it is said that free air of physiological origin in the abdominal cavity disappears in 97% of patients within 5 days [5], meanwhile in the case of postoperative complications, associated with the break of integrity of GI, the symptoms are most commonly reported later than the 5th postoperative day, when patients are critically ill [6]. Therefore, the 5th postoperative day was considered as an optimal time to differentiate between physiological and pathological pneumoperitoneum. Prospectively 33 patients were included in the study, of which 3 cases of anastomotic leakage occurred during the postoperative period and for the remaining 30 postoperative periods were uneventful. After compiling the information base from the retrospective and prospective sample data, two groups of study subjects were identified. First group (n = 20) – patients who had postoperative complications associated with gastrointestinal integrity violation (anastomotic leakage or perforation of the gastrointestinal tract) and second group (n = 30) - patients with an uneventful postoperative period.

2.2. ASSESSMENT
The diagnosis of pneumoperitoneum was based on the detection of free air under the diaphragm domes. The amount of free air was measured in millimeters, calculating the longest distance from the top to the bottom of the free air edge (Figure 2). In case of free air being under both of the diaphragm domes, the distances were summed up.

2.3. STATISTICAL ANALYSIS
Statistical data processing was performed using IBM SPSS Statistics for Windows, version 22.0 software package. The data is presented in the calculation of the mean and standard deviation (± SD). The Kolmogorov-Smirnov test was used to determine whether the variables corresponded to the normal distribution (p> 0.05). Student’s t-test was used for comparison of parametric quantitative values. The interdependence of qualitative attributes was evaluated using Fisher’s test. Pearson’s correlation coefficient was calculated to determine the linear dependence between the analyzed characteristics. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the sensitivity and specificity of free air on the 5th postoperative day for predicting postoperative complications that are associated with the violation of GI integrity (anastomotic leak or perforation). Logistic regression was used to determine the sensitivity and specificity of combination of two separate diagnostic tests.
RESULTS

The study population consisted of 50 patients. Demographic characteristics of full sample and characteristics of the complicated period group are presented in Tables 1, 2 respectively. Prevalence of pneumoperitoneum among the patients with uneventful and complicated postoperative periods is presented in Figure 3. Based on full sample data (n=50) the Fisher’s test showed that the postoperative course and the detection of free air were statistically significantly related (p = 0.048). Detection of free air on the 5th postoperative day in AXR has 70.00% sensitivity, 60.00% specificity for diagnosing postoperative complications such as gastrointestinal anastomotic leak or perforation. It was also found that the amount of free air was statistically significantly different depending on whether the postoperative course was uneventful or complicated (t = -3.061; p = 0.005). The average amount of free air in the uneventful postoperative course group was 6.59 mm (SN = 17.39) meanwhile in the group with postoperative complications it was 29.57 mm (SN = 30.07). Based on the ROC analysis (Area = 0.801; p <0.001) the limit value of the amount of free air which distinguishes physiological pneumoperitoneum from pathological was determined. In the selection of 9.65 mm as a limit value, sensitivity and specificity are 70.00% and 83.33% respectively (Figure 4). Analysis of data from patients with an uneventful postoperative period showed that there was no correlation between the amount of free air and demographic and clinical criteria other than BMI. The results are presented in Table 3. Also, there was no statistically significant difference in the amount of free air between men and women (t = 0.648; p = 0.522) and between patients who had open and laparoscopic surgery (t = 1.040; p = 0.307).

Analysis of the correlation between inflammatory laboratory parameters and the amount of free air showed no statistically significant association with WBC (r = -0.021; p = 0.930); however, a statistically significant positive correlation with CRP was observed (r = 0.596; p = 0.006) (Figure 5). Based on the ROC analysis (Area = 0.801; p <0.001), a CRP value that distinguishes an uneventful postoperative period from a complicated one (anastomotic leakage or perforation) was determined. In the selection of 110.85 mg/l as the limit value for CRP, sensitivity and specificity for identification of postoperative complications that are associated with the violation of GI integrity are 70.00% and 66.67% respectively (Figure 6).

After logistic regression, it was determined that the combination of detection of free air (9.65 mm) under the diaphragm domes and CRP 110.85 mg/l on the 5th postoperative day for identification of postoperative complications that are associated with the violation of GI integrity has sensitivity and specificity 70.00% and 83.33% respectively.

TABLES AND FIGURES

Figure 1. Retrospective data collection
Figure 2. Measurement of free air

Figure 3. Prevalence of pneumoperitoneum among the study groups

- **50 patients**
  - Complicated
    - Pneumoperitoneum
      - 14 (70%)
  - Postoperative period
  - Uneventful
    - Pneumoperitoneum
      - 12 (40%)
      - 18 (60%)
    - 30 (100%)
Figure 4. ROC curve for determining limit value of amount of free air on AXR on the 5th postoperative day in patients with GI integrity complications

Figure 5. Correlation between the amount of free air and CRP
Figure 6. ROC curve for determining limit value of amount of CRP on the 5th postoperative day in patients with GI integrity complications

Table 1. Demographic data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All subjects</th>
<th>Subjects with uneventful postoperative period</th>
<th>Subjects with postoperative complications</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>50</td>
<td>30</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>64,74 ± 15,04</td>
<td>60,66 ± 12,96</td>
<td>70,85 ± 15,49</td>
<td>0,017</td>
</tr>
<tr>
<td>BMI</td>
<td>23,18 ± 4,70</td>
<td>24,19 ± 3,94</td>
<td>21,66 ± 5,51</td>
<td>0,064</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>16</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>11</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Patients in whom postoperative complications were proved

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type of surgery</th>
<th>Amount of free air (mm)</th>
<th>WBC (x10^9/l)</th>
<th>CRP (mg/l)</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right hemicolecotomy</td>
<td>12,1</td>
<td>20,27</td>
<td>246</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>2</td>
<td>SBR</td>
<td>30</td>
<td>1,98</td>
<td>87,74</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>3</td>
<td>Hepaticojejunostomy</td>
<td>0</td>
<td>11,2</td>
<td>105</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>4</td>
<td>PDR</td>
<td>16,2</td>
<td>9,67</td>
<td>281,84</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>5</td>
<td>Sigmoidal resection</td>
<td>0</td>
<td>0,75</td>
<td>485</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>6</td>
<td>Hepaticojejunostomy</td>
<td>45,2</td>
<td>9,9</td>
<td>303</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>7</td>
<td>PDR</td>
<td>41</td>
<td>16,4</td>
<td>220</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>8</td>
<td>PDR</td>
<td>35,6</td>
<td>6,9</td>
<td>112</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>9</td>
<td>PDR</td>
<td>0</td>
<td>22,18</td>
<td>316</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>10</td>
<td>Rectal resection</td>
<td>57,6</td>
<td>4,5</td>
<td>96</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>11</td>
<td>Right hemicolecotomy</td>
<td>34,2</td>
<td>8,3</td>
<td>144</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>12</td>
<td>Sigmoidal resection</td>
<td>0</td>
<td>7,6</td>
<td>213</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>13</td>
<td>Sigmoidal resection</td>
<td>0</td>
<td>9,6</td>
<td>70,91</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>14</td>
<td>SBR</td>
<td>36</td>
<td>4,55</td>
<td>94,86</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>15</td>
<td>Subtotal colectomy</td>
<td>67,54</td>
<td>17,16</td>
<td>175,74</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>16</td>
<td>Sigmoidal resection</td>
<td>0</td>
<td>13,5</td>
<td>250</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>17</td>
<td>SBR</td>
<td>121,13</td>
<td>11,2</td>
<td>193,65</td>
<td>Perforation</td>
</tr>
<tr>
<td>18</td>
<td>Gastrectomy</td>
<td>21,1</td>
<td>2</td>
<td>45,59</td>
<td>Perforation</td>
</tr>
<tr>
<td>19</td>
<td>SBR</td>
<td>46,5</td>
<td>6,51</td>
<td>278</td>
<td>Perforation</td>
</tr>
<tr>
<td>20</td>
<td>SBR</td>
<td>27,3</td>
<td>13,5</td>
<td>148</td>
<td>Perforation</td>
</tr>
</tbody>
</table>

SBR – small bowel resection; PDR - pancreatoduodenal resection.

Table 3. Correlation between the amount of free air of physiological origin and the demographic and clinical criteria.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Correlation coefficient (r)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.133</td>
<td>0.482</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.620</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drain input</td>
<td>-0.161</td>
<td>0.397</td>
</tr>
</tbody>
</table>

DISCUSSION

The results of the study showing that only 60% of patients who had an uneventful postoperative period were not diagnosed with pneumoperitoneum on the 5th postoperative day do not coincide with the data provided by Nielsen and his colleagues stating that free air of physiological origin in the abdominal cavity disappears in 97% of patients in 5 days [5]. Some researchers point out that postoperative pneumoperitoneum can be diagnosed even up to 2 weeks after surgery [6-8]. Such a long period of time forces us to ask ourselves what influences these results. Based on literature data pneumoperitoneum is more commonly diagnosed in men, asthenic patients and patients with abdominal cavity drainage [9]. In this study we found that with increasing weight free air is less susceptible thus results are similar to those obtained by Gayer and his co-authors, but gender and age-related correlations have not been found – the same as with other authors who failed to do it [6, 7]. Results about the presence of abdominal free
air shows sensitivity and specificity for identification of postoperative complications that are associated with the break of GI integrity (anastomotic leakage or perforation) of 70.00% and 60.00% respectively are similar to those received by Milone et al. [3]. In order to maximize the diagnostic capabilities, with the use of ROC curve analysis, a limit value of free air of 9.65 mm was determined, which does not change the sensitivity but increases the specificity to 83.33%. Similar results are presented by Lee et al.: 11.7 mm limit value, 51.1% sensitivity and 83.7% specificity [7]. The diagnostic value of CRP for identifying postoperative complications associated with GI integrity violation was also studied separately. When choosing 110.85 mg/l as a limit value, the sensitivity and specificity are 70.00% and 66.67% respectively. The value obtained is nearest to the results of Ortega-Deballon and co-authors: limit CRP value on the 4th postoperative day 125 mg/L [10]. In contrast to other authors who studied the diagnostic value of CRP [10-15] in this research one of the aims was to find a connection between CRP and free air. By establishing a significant positive correlation between amount of free air and CRP, it can be said that if anastomotic leakage or perforation are suspected, these two diagnostic tests should be interpreted in parallel. After logistic regression, it was found that the combination of these two diagnostic tests (detection of free air (9.65 mm) under diaphragm domes and CRP 110.85 mg/l on the 5th post-operative day) show sensitivity and specificity for identification of postoperative complications associated with violation of GI integrity 70% and 83.33% respectively.

Although the CT scan is superior to AXR for diagnosing free air in the abdominal cavity it should not always be a first-choice test. AXR is done technically faster, cheaper and less harmful for the patient than the CT scan. Based on the results of this study and the data presented in the scientific literature [3,7], it could be said that in the postoperative period, when the patient develops an acute abdominal pain with elevated laboratory inflammatory parameters (CRB ≥ 110.85 mg/l) first of all it would be advisable to perform AXR. When ≥ 9.65 mm of free air is detected, a CT scan should be performed to specify the suspected perforation or anastomosis insufficiency. In the absence of free air in AXR, it is almost completely likely that GI violation can be ruled out thereby protecting patients from unnecessary CT scan whose exposure is significantly higher than AXR. However, it is important to emphasize that, even after denying the violation of GI integrity on AXR, one cannot forget about other possible causes of acute postoperative abdominal emergencies which cannot be excluded with AXR. Even in the absence of free air in the abdominal cavity on abdominal x-rays the patient should be closely monitored for possible complications such as intra-abdominal abscess, vascular thrombosis etc. [3]. The limitation of this study was that a part of the sample (retrospective patients’ data) was selected selectively - only patients with complicated postoperative period were included in the study, so this study does not reflect the real ratio of complicated and uncomplicated postoperative periods. This tactic was chosen in order to collect as much data as possible about patients who experienced postoperative complications associated with violation GI integrity and thus ensure significant results in a comparison between this and the control group (the uneventful postoperative period). In the future, research on this topic should abandon the collection of selective and retrospective data, accumulate information prospectively, randomly and for a longer period of time, thus collecting a larger sample and ensuring not only significant results in terms of comparison of the two groups but also reliable incidence rates of complications and pneumoperitoneum. The results and conclusions of this study should be interpreted and adapted responsibly in clinical practice, bearing in mind that the study was based on relatively small sample (50) of partly retrospective nature (17). There is still a need for further research in larger samples, distinguishing and analyzing different causes of free air in the abdominal cavity, in order to find the exact answer how to separate physiological pneumoperitoneum from the pathological one. However, the results of this study encourage to not underestimate the role of the abdominal X-ray.
CONCLUSIONS

Our study provides evidence that free air in the abdominal cavity on the 5th postoperative day is significantly more common in patients with the anastomotic leak or perforation. In addition, CRP values are increased in patients with higher amount of free air in the abdominal cavity. Our data suggests that AXR examinations are still necessary to rule out postoperative complications that are associated with the GI integrity disruption.
REFERENCES


Medullary thyroid carcinoma: evaluating the performance of diagnostic tests

Žygimantas Štaras, Ugnė Marcinkutė, Rasita Pavilonė, Valdas Šarauskas, Gintaras Kuprionis

1 Lithuanian University of Health Sciences, Kaunas, Lithuania

INTRODUCTION

Thyroid nodules are a frequent finding, with reported prevalence of 33–68% among adults [1,2]. These nodules can be malignant and fine-needle aspiration (FNA) is the most effective diagnostic test to determine malignancy or the need for surgery to reach such conclusion [3]. However, most of thyroid nodules are benign, with only a small percentage of thyroid nodules being malignant [4]. Therefore, it is not optimal to perform FNA in every case. Thyroid ultrasound (US) plays an important part in stratifying the risk of malignancy and deciding whether FNA is necessary or observation is sufficient.

When suspecting malignancy papillary thyroid carcinoma first comes to mind because it is the most common type of thyroid cancer [5]. Medullary thyroid carcinoma is more aggressive and more likely to metastasize [6,7]. However, it is also less common, ranking third in terms of frequency of thyroid cancer [8,9]. Treatment of medullary thyroid carcinoma is complex and prognosis is usually poor if the cancer has metastasized [10,11].

The aim of this study is to analyse sonographic, cytologic and histologic properties of medullary thyroid carcinoma.

LITERATURE REVIEW

Medullary thyroid cancer

Medullary thyroid carcinoma (MTC) originates from the parafollicular C cells of the thyroid gland. These C cells produce calcitonin. MTC accounts for 5–10% of all thyroid cancer cases, thus taking a third spot in terms of frequency. Most of the time MTC is sporadic, hereditary pattern is found in 20–30% of all MTC cases. Generally, in genetically determined cases MTC is a part of ‘multiple endocrine neoplasia type 2’ (MEN2 syndrome) with other components being pheochromocytoma and hyperparathyroidism in case of MEN2A or pheochromocytoma, multiple mucosal neuromas and marfanoid habitus in case of MEN2B. Familial MTC (FMTC) occurs when other neoplasia are absent [8,9,12].

Workup includes laboratory tests, imaging studies, fine-needle aspiration (FNA) procedure and histologic evaluation.

LABORATORY TESTS

Calcitonin – a 32-amino acid monomeric peptide which is processed from procalcitonin [13]. Serum calcitonin levels increase with MTC, therefore it is an important biochemical marker. Calcitonin levels are used for detection of MTC, staging, postoperative management and prognosis. Levels higher than 100 ng/l have been found to have 100% positive predictive value (PPV) of MTC [14,15]. Carcinoembryonic antigen (CEA) is another biomarker that can be used in the workup of MTC, but it is not specific. Elevated CEA serum levels are not useful for detecting MTC in early stages. However, it can be used to evaluate disease progression if MTC is already evident [14,16]. Missence mutation of RET proto-oncogene, located on chromosome 10q11.2, is present among people with MEN2 syndrome. This mutation can also occur in cases of sporadic MTC. Screening tests are based on locating mutation of RET proto-oncogene [14,17,18].

IMAGING STUDIES

Thyroid ultrasound (US) is the reason why thyroid nodules became such a frequent finding [1,2]. In 2017 American College of Radiology (ACR) revised their scoring system – Thy-
roid Imaging, Reporting and Data System (TI-RADS) which is used for identifying clinically significant malignancies. In TI-RADS solid or almost solid composition, hypoechoogenicity, taller-than-wide shape, lobulated or irregular margins, extra-thyroidal extension and punctate echogenic foci are considered features that suggest malignancy of thyroid nodules. Presence of these features require FNA as follow-up in most of the cases depending on the size of the nodule [19]. Although, these predictors of malignancy might be more aimed at papillary thyroid carcinoma they do not differ significantly in case of MTC [20]. Thyroid ultrasound has reported sensitivity of 85-96.6% in determining the risk of malignant nodules [21,22].

Fine-needle aspiration and histologic evaluation Whether FNA is required depends on thyroid US findings. Results of FNA are classified into 5 categories as suggested by American Association of Clinical Endocrinologists, American College of Endocrinology and Associazione Medici Endocrinologi (AAACE/ACE/AME) [23], American Thyroid Association (ATA) [39] and British Thyroid Association (BTA) [40]:
Category I – Non-diagnostic or unsatisfactory
Category II – Benign
Category III – Indeterminate
Category IV – Suspicious for Malignancy
Category V – Malignant
In case of non-diagnostic results FNA is repeated, usually one more procedure is sufficient [24]. FNA has reported sensitivity of 56.8-91.8% in detecting MTC [25-28]. Immunohistochemical staining for calcitonin increases the sensitivity of FNA [29]. If conclusion, whether a thyroid nodule is malignant, is not reached surgery may be required to provide a specimen for histological evaluation to reach a definitive diagnosis [3].

METHODS
A retrospective study was conducted, a total of 76 medullary thyroid cancer cases from 2004 to 2017 were analyzed in Hospital of Lithuanian University of Health Sciences Kaunas Clinics. In all of the cases diagnosis was verified by histological evaluation. Prior to the treatment, patients had a thyroid ultrasound examination and fine-needle aspiration was performed. Patients’ age, gender, presence of Type 2 Multiple Endocrine Neoplasia (MEN2 syndrome), sonographic features of thyroid nodules and results of cytologic and histologic evaluation were assessed.

During the thyroid ultrasound procedure patients were positioned lying face-up with a pillow placed under the shoulders to extend the area to be scanned. A linear transducer was used. In our study echogenicity (hyperechoic, isoechoic or hypoechoic) and US features suggesting malignancy (solid composition, irregular or lobulated margins, microcalcifications and taller-than-wide shape) of thyroid nodules was assessed [19]. Thyroid nodules were measured as well.

FNA procedure was performed under ultrasound guidance. Patients’ positioning did not differ from the one used during thyroid US procedure. Smaller gauge needles were used and 2-6 passes were performed for adequate sampling. Smears were prepared on unstained slides. All FNA procedures were performed adhering to principles of sterility. In our study we assessed the diagnostic value of FNA in detecting MTC.

Samples for histologic evaluation were provided after surgical treatment of patients with MTC. In our study diagnosis and size of MTC was assessed. Size measurements were compared with thyroid US findings.

Statistical analysis was performed with "IBM SPSS Statistics 17.0" and “MedCalc 18.2.1”. Descriptive statistics were given in form of means with standard deviation and minimum/maximum values of the variables. Student’s t-test was used to compare means of two variables at least on ordinal scale. Pearson correlation coefficient (r) was used to evaluate the correlation between two variables on the interval scale. Results were considered statistically significant with p values of 0.05 and lower.

RESULTS

Demographic and clinical characteristics Out of 76 cases that were analyzed, 51 patients
were female (67.1%) and 25 male (32.9%), with a male:female ratio of 2.04:1. Medullary thyroid carcinoma (MTC) was more prevalent among female patients (p < 0.001) compared to a study by Rich et al which shows a balanced male:female ratio of 1:0.96 [4]. Patients’ mean age was 53.36 ± 15.01 years, which is higher than the average age of 38 years mentioned in studies by Kebebew et al and Rich et al [30,31]. The lowest age value was 12, and the highest – 84 years. There was no significant age difference between male and female patients (p = 0.092).

Mutations of RET proto-oncogene were found in 9 of the MTC cases (11.8%) and Type 2 Multiple Endocrine Neoplasia (MEN2 syndrome) was diagnosed. In comparison, in a study by Maya et al prevalence of MEN2 syndrome was found to be 18.75-22.5% [26]. 3 other patients with MTC (3.95%) were suspected of having MEN2 syndrome but results of the genetic test were negative. Bilaterally located MTC (66.7%) was more common compared to localized only in the right or left lobe of the thyroid gland in patients with MEN2 syndrome (p < 0.001). MTC was found in the left lobe of thyroid gland in exactly half of the cases. In 13.2% of the cases MTC was bilateral. Distribution of MTC locations in the thyroid gland is shown in Fig 1. In 51 of the cases (67.1%) a solitary malignant nodule was found, 25 patients (32.9%) – had multiple nodules. Whether the number of nodules has any influence on the risk of malignancy or not is debatable. Some authors say that the risk of malignancy is higher in solitary nodules [32] and others say that there is no difference [33]. Our study supports the former.

Almost half (44.8%) of the patients were diagnosed with Stage I MTC. Similar results were provided in studies by Roman et al and Gilliland et al – 48% and 54.1% respectively. Also, these studies show that in 13% of the cases the MTC was diagnosed at Stage IV [10,34]. In our study only 3.9% of patients were diagnosed at Stage IV. Distribution of MTC stage at diagnosis is shown in Fig 2.

![Fig 1. Location of MTC in the thyroid gland](image1)

![Fig 2. MTC stage at diagnosis](image2)
SONOGRAPHIC FEATURES

Thyroid ultrasound (US) showed that 72.4% of malignant thyroid nodules were hypoechoic. In studies by Saller et al [35] and Kim et al [36] a bigger part of patients diagnosed with MTC had hypoechoic thyroid nodules – 100% and 95.3% respectively. In our study percentage of nodules that were isoechoic (7.9%) was similar to results shown in the study by Kim et al (4.8%). Distribution of echogenic appearance is shown in Fig 3.

Solid composition was the most common US feature with 85.5% of the MTC cases. In a study by Saller et al 90.5% of thyroid nodules were solid – a similar result [35]. Taller-than-wide shape and irregular or lobulated margins had a similar prevalence – 53.95% and 63.16% respectively. In their study Kim et al found that in 80.9% of the MTC cases malignant nodules had irregular or lobulated margins – a higher number compared to our study. However, in the same study the number of taller-than-wide shaped malignant nodules was very similar to our findings – 57.1% [20]. Compared to other US features suggesting malignancy, microcalcifications were more rare – they were found in 43.42% of the cases. This result was much lower compared to studies by Saller et al and Gorman et al where microcalcifications were much more common – found in 95% and 83.3% of the thyroid nodules respectively [35,36]. Distribution of ultrasound features is shown in Table 1.

Mean size of malignant thyroid nodules as seen during thyroid US was 2.75 ± 1.68 cm. The results of thyroid nodule measurements were dispersed widely – smallest nodule was 0.5 cm and biggest – 7.8 cm in diameter. In a study describing MTC US features by Zhou et al mean size of malignant nodules was almost two times smaller – 1.42 ± 0.75 cm [37].

Thyroid US was very sensitive in detecting malignant nodules with sensitivity value of 89.24%. Reported sensitivity of thyroid US varied from 85% to 96.6% [21,22]. Thus, the result found in our study falls right in the middle of that range. Specificity could not be calculated because all of the patients were diagnosed MTC.
Cytologic and histologic findings

In more than three-fourths of cases (68.42%) thyroid nodules were found to be suspicious after fine-needle aspiration (FNA) procedure and cytologic evaluation which required surgery to reach a definitive diagnosis. Only 9.21% of thyroid nodules were found to be malignant after FNA. In 4 of cases the FNA was non-diagnostic because of insufficient amount of cells obtained during the procedure. Results of FNA findings are shown in Table 2.

Table 2. Distribution of FNA findings

<table>
<thead>
<tr>
<th>Features</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taller-than-wide shape</td>
<td>41</td>
<td>53.95</td>
</tr>
<tr>
<td>Irregular or lobulated margins</td>
<td>48</td>
<td>63.16</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>33</td>
<td>43.42</td>
</tr>
<tr>
<td>Solid composition</td>
<td>65</td>
<td>85.53</td>
</tr>
</tbody>
</table>

FNA was sensitive in determining the risk of MTC. Sensitivity was 81.94%. According to some authors sensitivity of FNA can vary from 56.8% to 91.8% in detecting MTC depending on the method used – result found in our study is on the higher end of that range [25-28]. Specificity could not be calculated because all of the patients were diagnosed MTC.

In all cases surgical specimens were examined histologically. In 53.94% of cases only MTC was found and adjacent thyroid was normal. In 5.26% of cases another thyroid neoplasm was found. In a study by Desai et al the results were just a bit higher, albeit very similar – 57% and 7.9% respectively [38]. Results of histologic evaluation are shown in Table 3.

Table 3. Distribution of histopathologic findings

<table>
<thead>
<tr>
<th>Findings</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only MTC</td>
<td>41</td>
<td>53.94</td>
</tr>
<tr>
<td>MTC + hyperplastic nodules</td>
<td>10</td>
<td>13.16</td>
</tr>
<tr>
<td>MTC + autoimmune thyroiditis</td>
<td>9</td>
<td>11.84</td>
</tr>
<tr>
<td>MTC + toxic multinodular goiter</td>
<td>7</td>
<td>9.21</td>
</tr>
<tr>
<td>MTC + hyperplastic nodules and autoimmune thyroiditis</td>
<td>3</td>
<td>3.95</td>
</tr>
<tr>
<td>MTC + Graves’ disease</td>
<td>2</td>
<td>2.63</td>
</tr>
<tr>
<td>Mixed: MTC + Papillary thyroid carcinoma (PTC)</td>
<td>2</td>
<td>2.63</td>
</tr>
<tr>
<td>Mixed: MTC + Follicular thyroid carcinoma (FTC)</td>
<td>2</td>
<td>2.63</td>
</tr>
</tbody>
</table>

Mean size of malignant thyroid measured during histopathologic evaluation of surgical specimen was 2.63 ± 1.7 cm. The results of thyroid nodule measurements were dispersed widely – smallest nodule was 0.35 cm and biggest – 8.2 cm in diameter. There was so statistically significant difference in thyroid nodule size measures during thyroid US and histopathologic evaluation (p = 0.274). Also, a strong correlation was found between both size measurements (r = 0.87, p < 0.001). The correlation between thyroid nodule size measured during thyroid US and histopathologic evaluation is shown in Fig 4.
CONCLUSIONS

In our study we concluded that medullary thyroid carcinoma presented itself more often as a solitary nodule. In cases of MEN2 syndrome, medullary thyroid cancer located in both lobes of the thyroid gland was more common. Both thyroid ultrasound and fine-needle aspiration were sensitive in predicting malignancy of thyroid nodules. Thyroid nodule size measured during thyroid US correlated strongly with histological measurements.
REFERENCES


8. Ball DW, Medullary Thyroid Cancer: Monitoring and Therapy. Endocrinol Metab Clin North Am. 2007 Sep; 36(3): 823–VIII.


Treatment of uterine fibroids with A.Uterina embolisation in Latvia and Lithuania

Diana Uljanionok Zilovic1, Raimonda Bykovaite2, Karolina Eva Romeikienė2, Andrius Romeika2, Danguole Vildaite1, Audrius Sirvinskas1, Algimantas Simkaitis1, Andrius Pranculis3, Rytis Stasys Kaupas5, Inga Nalivaičio6, Mairija Kokare3, Karolis Kupčys6, Melita Lagzdina1, Sanita Ponamorjova5, Nellija Lietuvietė8, Lelde Kulmane9, Inga Vevere9

1 Vilnius University, faculty of Medicine
2 Lithuanian University of Health Sciences, faculty of Medicine
3 Republican Vilnius University hospital
4 Klaipeda University, Klaipeda University Hospital
5 Lithuanian University of Health Sciences Hospital Kaunas Clinics
6 Pauls Stradins Clinical University hospital
7 Latvia Children’s Clinical University hospital
8 Eastern Clinical University hospital
9 LiepAjas Regional Hospital

ABSTRACT
Aim: to evaluate the frequency and results of applying uterine artery embolization for uterine fibroids treating.

Research material and methods: The research retrospectively analyses the medical history of women (n=180), who were treated in 7 hospitals of Latvia and Lithuania. Uterine artery embolization (UAE) was applied for these women to treat symptomatic uterine fibroids. The diagnosis of uterine fibroids (TLK 10 D25.0, D25.1, D25.2, D25.9) was confirmed by ultrasound or magnetic resonance and gynaecologic exam. After the procedure, women were asked to fill out a questionnaire, which had to determine if they were content with the undertaken procedure and to evaluate the dynamics of the symptoms caused by uterine myomas.

Results: Main age of the patients was 43.5 ± 4.6 years, all of them had symptomatic uterine fibroids. For the majority of the patients UAE was the first treatment. According to the follow up results of the Latvian patients, the size of the uterine fibroids reduced 67.3 percent for the women versus Lithuanian - 100 percent. It takes 72.2 percent of the patient’s all together. None of the patients experienced early UAE complications. The average duration of hospitalization was 1.85±1.56 days. Three patients became pregnant after the UAE and delivered healthy babies.

Conclusions: UAE is minimally invasive, safe, efficacious, and cost-effective alternative to traditional surgical fibroids treatment. UAE helps to reduce symptoms of fibroids and is associated with rapid recovery with most women. It is suitable for women, who desire future childbearing. Appropriate patient evaluation and selection for a procedure are vital and critical for patient satisfaction.

Keywords: embolization, intervention.

INTRODUCTION

Uterine fibroids (myomas, leiomyomas) are one of the most common non-malignant uterine tumours. According to various literature, their frequency is up to 20–40% among fertile women age [1, 2]. Mostly uterine fibroids have no symptoms, but about 20% of women have symptomatic uterine myomas [3, 4]. The main symptoms are long and heavy menstrual bleeding, acyclic bleeding, pains of lower part of the stomach, painful intercourse [5]. Uterine myomas can be a reason of infertility among these women and it can impact their quality of life. Due to longer menstruation, women are prone to anaemia as well as fatigue, irritability and weakness [6].

To determine the best treatment strategy for women diagnosed with uterine myoma it is important to evaluate the most concerning complaints as well as the age of the patient, the size of the myomas, type and location. For a long time the standard treatment of uterine fibroids was
surgical – abdominal, vaginal or laparoscopic hysterectomy or myomectomy. However, more women request for an alternative to the surgical treatment [7, 8]. There are some other options for the uterine fibroids treatment: pharmaceutical treatment, magnetic resonance-guided high-intensity focused ultrasound (MRgFUS), transvaginal route for radiofrequency ablation, and uterine artery embolization (9). In 2015 pharmaceutical treatment of fibroids with ulipristal acetate (a selective modulator of the receptors of progesterone) began in Lithuania and in Latvia. Since 2017 this medication became compensated in Lithuania. Still, our treatment goals for uterine fibroids are long-term in reduction of fibroids size and numbers, which leads to reduction or elimination of fibroids symptoms. One of the alternatives is uterine artery embolization (UAE). It is the least invasive medical treatment which allows preserving the uterus. Also UAE effectively downsizes the uterine fibroids as well as their symptoms. According to literature overview, fibroids size decreases by 40-70% after UAE. In the course of one year, symptoms of fibroid disappear in 80-90% of women [9]. The main contraindications of UAE are pregnancy, infection of the genitourinary tract, malignant tumours and immunosuppression. Large myomas and submucosal location are not contraindications to not perform UAE.

For the first time UAE embolization for treating fibroids was applied in 1991 and in 1995 it was described for the first time by a French gynaecologist J. Ravina [11]. Uterine artery embolization is performed by interventional radiologists in X-Ray operating rooms. Premedication with analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are given prior the procedure. Usually, only local anaesthesia or mild sedation is applied. In the case of local anaesthesia, mostly the right common femoral artery is punctuated percutaneously. An introducer is inserted in the artery and through it along with a micro catheter, using an X-Ray, both uterine arteries are reached consecutively. The localisation of the catheter is approved by infusing radiocontrast medication. Usually, microspheres of 700 μm diameter or 500 μm particles are used for embolization, which are infused until the circulation slows down and the distal artery branches stop filling. It is necessary that embolization is performed on both sides. Later, the catheter and introducer are taken out and the artery puncture site is compressed and sealed. After the procedure, the patients must lay in bed up to 2 hours, to ease the post-embolization (PES) symptoms analgesics and anti-inflammatory medicine are prescribed. The following day, the physical activity of the patients is not limited and they undergo a treatment to decrease the symptoms of post-embolization syndrome.

During the UAE, a therapeutic tissue infarction is created. This procedure does not require a long period of hospitalization, the recovery after UAE is fast. A retrospective cohort research revealed that uterine artery embolization has less difficult side effects then hysterectomy (the chance ratio 0.25), however, the level of contentment is similar. After uterine artery embolization, 86% of the women would recommend the procedure to a friend [12, 13]. Possible UAE side effects are: PES (pain in the lower part of the stomach, nausea, vomiting, fever and moderately increased inflammatory indicators), infection, a hysterectomy or a second UAE might be necessary after the first procedure. In one year after UAE, the need for hysterectomy and/or second UAE can be up to 10% while in five years in can grow up to 20-25%. Another side effect of UAE might be early insufficiency of the ovary function which develops to 1-2% of the patients. It was noticed that the side effects of UAE are more frequent if the fibroids are submucosal or they are bigger than 10 centimetres [7].
Fig. 1 Patient with uterine fibroid visible on digital subtraction angiography (DSA) before uterine artery embolization and after. (IUD marked with arrow.)

Fig. 2 The view of uterine fibroid on DSA after contrast media injection pictures showing the vascularization of fibroid from both uterine arteries.
Fig.3 On picture there can see uterine fibroid sized approximately 8 cm on digital subtraction angiography (DSA) before uterine artery embolization and after it.

AIM

To evaluate the frequency of UAE applying for fibroids treatment and to assess results of this procedure.

METHODS

The research retrospectively analyses the medical history of women (n=180) treated in 3 hospitals of Latvia (Pauls Stradins Clinical University hospital, East Clinical University hospital and Liepajas Regional hospital) and 4 hospitals of Lithuania (Lithuanian University of Health Sciences hospital Kaunas Clinics, Klaipėda University hospital, Vilnius Republican hospital and Panevėžys hospital). Uterine artery embolization (UAE) was applied to these women when treating symptomatic uterine myomas from January of 2008 to December of 2016. The diagnosis of uterine fibroid (TLK 10 D25.0, D25.1, D25.2, D25.9) was confirmed by ultrasound or magnetic resonance, and gynaecologic exam. Exclusion criteria were: pregnancy, active inflammatory disease, pelvic malignancy. An original questionnaire was conducted aiming to evaluate if the women were content with the procedure and to evaluate the dynamics of the symptomatic uterine fibroids after the procedure. Our questionnaire comprised assessment of changes in fibroid-related symp-toms (general condition, heavy menstruation, pain, anaemia), satisfaction with the procedure, and recommendation to a friend. Changes in myoma-related symp-toms were clas-sified as follows: heavy menstrual bleeding became lighter, menstrual period became less painful, haemoglobin levels have reached the normal levels in patients with previous anaemia, pain in lower abdomen has decreased. Patient satisfaction with the procedure and its outcomes were classified as follows: were satisfied with the procedure, would recommend this procedure to a friend, were unsatisfied with the procedure.

The data was transferred into an Excel 2010 spread-sheet and analysed using the Statistical Package for the Social Sciences software (SPSS) version 17.0 for Windows. For the quantitative variables (age, uterine volume, number of fibroids, size of fibroids), data was expressed as means, medians, standard deviations, minimum, and maximum and percent's. Differences were analysed using Student’s t-test and were considered statistically significant when P < 0.05 and between groups, when P < 0.01.
RESULTS

180 women who underwent uterine artery embolization while treating uterine myomas, took part in the research. There were 155 patients from Latvia (Pauls Stradins Clinical University hospital, East Clinical university hospital and Liepajas Regional hospital) and 25 patients from Lithuania (Lithuanian University of Health Sciences hospital Kaunas Clinics, Klaipeda University hospital, Vilnius Republican hospital and Panevezys hospital). UAE procedure was technically successful on all patients and had no early post-procedural complications. The average age of the women was 43.5 ± 4.6 (27 to 52 years). 91.67 % of the patients chose UAE as their first procedure for uterine fibroid treatment. Only 6.1% of the patients (n=11) had the uterine fibroids removed surgically (myomectomy was performed) prior to uterine artery embolization, however, they experienced regrowth of the fibroids. The time period from myomectomy and UAE varies between 5 to 6 years mostly. For patients who underwent UAE twice (n=3, 1.67 %), the time period between two procedures was 1 month, 1 year and 3 years, respectively. One patient (0.56%) received abrasion of myoma.

For the majority of the patients UAE was the first treatment. None of the patients were taking any analogues of the gonadotropin-releasing hormone (GnRH) prior to the procedure. Before the procedure, most of the women had menorrhagia and painful menstruation (n=120, 66.7%). Some of the patients (n=17, 9.5%) had a feeling of pressure in the stomach area and neurological symptoms, such as: symptomatic of buttock nerve clenching or newly emerged urination disorders. 36.7% (n=66) of the women were diagnosed with anaemia before UAE. The diameter of the fibroids varied from 1.7 centimetres to 32 centimetres size (similarly to 24 weeks of pregnancy). The average amount of fibroids was 1.74 ± 1.29 (1 to 6 fibroids). The most frequent types of fibroids were intramural (n=118, 65.6%), also subserosal (n=48, 26.7%) and submucosal (n=12, 6.7%), in some cases type of the fibroids was unknown (n=2, 1.1%). Not every patient was followed-up, only 44.4% of all patients: 55 patients from Latvia and 15 patients from Lithuania. During the first month after UAE, size of the fibroids decreased by 3.72 cm (p<0.05) on average. For Latvian follow-up patients, uterine fibroids reduced in size for 67.3% (n=37) of patients. For Lithuanian patients the success rate was 100% (n=15) of the followed-up patients. It takes up 72.2% of the followed-up patients in total.

In Latvia, 10 patients underwent surgical treatment after the procedure: 6 of them had hysterectomy performed, 3 of them received myomectomy and another one had repeated uterine artery embolization procedure. The patient who received repeated UAE, was 46 years old at the moment of the first procedure. Because of minimal decrease in size of myoma and new myomas appearance 4 years later, second UAE was performed. 6 patients, who underwent hysterectomy after UAE, had their operation performed approximately 1 to 2 years after UAE, because there was no reduction in fibroids size or fibroids were even increasing in size. To sum up, 14.3 % (n=10) out of 70 patients underwent surgical procedure after the UAE.

The average duration of hospitalization was 1.85±1.56 days. The main duration of hospitalization was 3.68 days in Lithuania and 1.58 days in Latvia (P<0.001). All of the patients evaluated the procedure positively. None of the patients experienced early UAE complications. All patients experienced less painful and less heavy menstruation after the procedure, moreover, they did not experience such intense pressure in the stomach area anymore. Only 11 (6.1%) out of 180 women still had anaemia after UAE. Post procedural premature menopause occurred in 2.9% (n=5) of the patients.

Three patients became pregnant after the UAE. One patient who received UAE six months after this procedure there was also myomectomy performed. 5 years after the UAE procedure and myomectomy she delivered a healthy baby at the age of 32 years. Another 2 patients gave birth after 2-3 years after UAE procedure.
Tab. 1 Basic characteristic table

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>43.5 (27-57)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
</tr>
<tr>
<td>Heavy menstrual bleeding, n(%)</td>
<td>120 (67.2%)</td>
</tr>
<tr>
<td>Painful menstruations, n(%)</td>
<td>120 (67.2%)</td>
</tr>
<tr>
<td>Feeling of pressure in the stomach area and neurological symptoms</td>
<td>17 (9.5%)</td>
</tr>
<tr>
<td>Anemia, n(%)</td>
<td>66 (36.7%)</td>
</tr>
<tr>
<td>Number of fibroids</td>
<td></td>
</tr>
<tr>
<td>1, n(%)</td>
<td>88 (48.9%)</td>
</tr>
<tr>
<td>&gt;1, n(%)</td>
<td>92 (51.1%)</td>
</tr>
<tr>
<td>Dominant fibroid location</td>
<td></td>
</tr>
<tr>
<td>Intramural, n(%)</td>
<td>118 (65.6%)</td>
</tr>
<tr>
<td>Submucosal, n(%)</td>
<td>12 (6.7%)</td>
</tr>
<tr>
<td>Subserosal, n(%)</td>
<td>48 (26.7%)</td>
</tr>
<tr>
<td>Type of fibroid is unknown, n(%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Dominant fibroid maximum diameter (cm), median (range)</td>
<td>7.6 (1.7-32)</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
</tr>
<tr>
<td>Myomectomy, n(%)</td>
<td>11 (6.1%)</td>
</tr>
<tr>
<td>UAE, n(%)</td>
<td>3 (1.67%)</td>
</tr>
</tbody>
</table>

DISCUSSION

The main UAE indication is symptomatic uterine leiomyoma. The procedure is more suitable and safer for patients with prior pelvic surgery, including myomectomy and other interventions [10]. Key factors for performing UAE are: GnRH cannot be prescribed two months before UAE, the patient without a genital infection, the diagnosis of leiomyoma must be approved by a gynaecologist and an ultrasound and/or MRI. For leiomyomas diagnosing MRI sensitivity and its specificity is much better than ultrasound. Also, during imaging examination it is important to consider the type of the fibroid. That treatment tactic changes in 22% after applying MRI [17]. None of the patients from Latvia had MRI performed prior to UAE and only 2 patients from Lithuanian cohort which makes in general only 1.1%. This shows that it is still difficult for patients in Lithuania and Latvia to get an MRI despite its evident clinical benefit. Another group of women, for whom UAE might not be as effective, is infertile patients, who are wishing for pregnancy. UAE might increase miscarriages although there is not enough data to support this. There is not enough evidence based literature about how UAE and a combination of UAE and laparoscopic or laparotomy myomectomy treatment impacts fertility and the chances to get pregnant [16]. According to our research, 1 woman who was diagnosed with infertility, successfully conceived after UAE and gave birth to a healthy child, 2 more patients gave birth after the UAE procedure, but diagnosis of infertility was not confirmed, and that makes 4.3% of followed-up patients gave birth after the procedure. According to our findings it became evident that uterine artery embolization is not a common treatment for uterine fibroids, because as uterine fibroid is most common benign tumour, it should be treated only if symptomatic [21] but still during year 2008 and 2016 there were 180 uterine artery embolization performed in Latvia and Lithuania together. In our research most of women choose UAE as the first uterine fibroids treatment method and it accounted 91.67 % of patients and only 6.1% of the patients had surgical intervention prior to UAE (myomectomy was performed), however, they experienced regrowth.
of the fibroids. According to the literature, treating uterine fibroids with UAE is effective: there is a decrease in heavy menstruation and pain, the size of the fibroids decreases. [14, 15] We found out that before the procedure, most of the women had menorrhagia and painful menstruation (n=120, 66.7%), but after the procedure all patients experienced less painful and less heavy menstruation, as well as uterine fibroids reduced in size after the procedure in 74% of followed-up patients. The literature data of long-term observation (5 years) shows that there is a significantly smaller chance of complications after UAE than after a hysterectomy [14, 15]. Talking about complications of UAE procedure, they are classified as post embolization syndrome, early post procedural complications and late UAE complications. Post embolization syndrome occurs in up to 52% of patients and constitutes a general malaise with mild pyrexia and flu-like symptoms, which is self-limiting and usually lasts for 7 to 10 days [16]. Early complications are rare and may be described as prolonged pain episodes or liquefaction of the fibroid, which may cause a cramping pain by cervical dilation and passage of the tissue, by infection from ascending bacteria and infrequently heavy bleeding [19]. Rate of the lack of long term patency is high (28%–32%) because of re-intervention – including re-embolization, myomectomy, or hysterectomy – at 5 years post procedure [16, 17, 18, 20] and during 3 years follow up by 15% of re-intervention rate: 10% hysterectomy, 3% myomectomy and 2% repeated UAE [21]. In our study re-interventional rate was pretty similar as mentioned in the last source: 14.3% (n=10) in general from follow-up patients, 8.6% of them hysterectomies, 4.3% myomectomies and 1.4% repeated UAE. Late complication as early menopause after uterine artery embolization occurred in 2.9% (n=2) of followed-up patients. Induction of amenorrhea after UAE procedures is uncommon and most frequently seen among patients who are older than 45 years and/or perimenopausal [22].

CONCLUSIONS

UAE is a minimally invasive and a safe procedure with a rapid recovery time - women can return to daily activities without restrictions very soon after the procedure. Mostly women chose this procedure because of psychological aspects, wanting to preserve their uterus. Our study shows that this procedure is a good alternative to surgery – the uterine fibroids in most of the cases reduce in size after the uterine artery embolization, symptoms improve, nevertheless, the rate of post procedural re-intervention is rather high but complication rate is low. Also, for patients who have symptomatic uterine fibroids but want to have children after the treatment, this is the most suitable choice. Although the procedure is not that new anymore, further studies are still required about the selection of patients for uterine artery embolization and fertility after UAE. It is also important to note that it is necessary to pursue a pre and post procedural MRI in Lithuania and Latvia in order to obtain better results. This research is merely an overview of the current situation presenting the differences and similarities. The research shows that UAE is still not used as much as it should despite all the good outcomes which are known for a long time. The data obtained during the research is compared to other authors.
REFERENCES


The role of computed tomography in the evaluation of the spread of ovarian cancer

Greta Kaupaitė, Juozas Žilinskas, Stasys Žilinskas, Vaida Atstupėnaitė, Algidas Basevičius
Lithuanian University of Health Sciences, Kaunas Lithuania

ABSTRACT
The aim: To determine the role of CT in the evaluation of the spread of ovarian cancer.
Methods: The data of 64 female patients who underwent abdominal and pelvic CT examinations due to the suspicion of ovarian cancer during 2014–2015 in HLUHS CK were analyzed. All patients were operated and ovarian cancer was confirmed histologically.
Results: The average age of the patients was 60.06 ± 14.95 years. By the histological type, 37 (57.7%) cases of tumor were serous type. By the differentiation degree, 41 (63.5%) cases of tumor were G3. 27 (42.2%) of all the cases of ovarian cancer were diagnosed in the stage IIIC. CT sensitivity in the assessment of pathological lymph nodes was 41.9%, specificity – 81.8%, PPV – 68.4%, NPV – 60.0%, accuracy – 51.6%. CT sensitivity in the evaluation of peritoneal carcinomatosis was 62.5%, specificity – 81.3%, PPV – 90.9%, NPV – 41.9%, accuracy – 67.2%. The CT sensitivity to ascites was – 86.5%, specificity – 88.9%, PPV – 91.4%, NPV – 82.8%, accuracy – 87.5%.
Conclusions: 1. The symptoms of the ovarian cancer spread were determined more frequent in high-grade tumors. 2. Larger ovarian tumors typically were spread to the bladder and rectum. 3. The results of lymph nodes and peritoneal carcinomatosis showed that CT had moderate sensitivity, NPV, and accuracy, but it had high specificity. According to the pathological lymph nodes, PPV was average, but high according to peritoneal carcinomatosis. 4. The evaluation of ascites showed that CT sensitivity, specificity, PPV, NPV, and accuracy were high.

Keywords: ovarian cancer, spread, computed tomography.

INTRODUCTION
Ovarian cancer is one of the most common oncogynecological diseases diagnosed all over the world, which takes the fifth place amongst women malignant tumors. General morbidity of ovarian cancer in European Union (EU) countries is 13 per 100000 women, mortality – 7 per 100000 women. Around 400 new incidences of ovarian cancer are determined in Lithuania each year. Although there is similar morbidity in all EU, however there are most of all ovarian cancer death end cases calculated in our country. The reason is that an early stage of ovarian cancer has no characteristic symptoms; it is usually diagnosed already spread in third and fourth stages [1-3]. Early ovarian cancer diagnostics and detailed evaluation of tumor spread in later disease stages are relevant topics in oncogynecology. Timely diagnosis of the disease and evaluating its spread helps to choose optimal treatment tactics which are important for the prognosis of disease and the quality of life of the patients. Timely diagnostics also remains important for evaluation of the response to the treatment [1].

Ovarian cancer diagnosis can only be made based on conclusions of morphological examination. FIGO and TNM clinical classifications are used for the evaluation of ovarian cancer spread. The stage of the disease is mostly confirmed after surgical intervention. However, in some cases the staging of surgical disease cannot be done and the clinical stage of the disease then is confirmed based on morphological, objective and radiological research data only [1,4].
Various diagnostic tests are used to evaluate the spread of ovarian cancer, however CT remains the main test not only for ovarian cancer diag-
nosis and spread measurement but also for the evaluation of the possibility of optimal cytoreduction and response to the treatment [5]. Based on 2014–2015 years HLUHS Obstetrics and Gynaecology Clinics patients charts and the data of abdominal and pelvic CT tests, performed at Radiology clinics, retrospective analysis we aimed to determine the role of CT in the evaluation of the spread of ovarian cancer. By examining size, histological type, the degree of differentiation of malignant tumors, the age of the patients’ interrelation, also by evaluating values of diagnostic parameters, we aimed to analyze the possibilities of CT test.

METHODS

The data of 64 female patients, who underwent abdominal and pelvic CT examinations at the HLUHS CK Radiology Clinic in 2014–2015, surgical treatment at Obstetrics and Gynaecology Clinics, when ovarian cancer diagnosis was confirmed by histology for the first time, were analyzed retrospectively. Data about the age of the patients, histological test results and conclusions, confirmed stages of TNM and FIGO classifications and additional ovarian cancer surgical findings (ascites, peritoneal carcinomatosis, lymph nodes metastasis) were collected from patients’ charts.

Abdominal and pelvic CT images were also evaluated retrospectively. By analyzing CT images the size of primary tumor and additional findings (ascites (Fig. 1), pelvic and abdomen lymph nodes metastasis (Fig. 3), liver metastasis (Fig. 4), peritoneal carcinomatosis (Fig. 2, Fig. 3), tumor spread to bladder and rectum) which shows tumor spread, were evaluated. The results of CT scans were compared with histological tests and surgical findings Abdomen and pelvic CT were performed with "GE Light Speed VCT 64" or "Toshiba Aquilion One 320" multi-slice scanners with patient lying on the back and putting hands above his head. Native and contrast scans using non-ionic intravenous contrast were performed craniocaudally. 100–120 ml. contrast was injected with 3,0 ml/s speed automatic syringe. CT scans were performed in 30 and 55 seconds after contrast injection. Evaluation and measurements of CT scans were performed with images archiving, transferring and analyzing program "Cedara I–Reach 4.4". Microsoft Office Excel 2007 and SPSS 22.0 were used to systemize and analyze data. Significance level p<0,05 was chosen. For evaluation of CT method sensitivity, specificity, TPV, NPV and accuracy were calculated [7].
RESULTS

The study group consisted of (n=64) patients, who underwent abdominal and pelvic CT examinations at the HLUHS CK Radiology Clinic in 2014–2015, surgical treatment at Obstetrics and Gynecology Clinics, when ovarian cancer diagnosis was confirmed by histology for the first time. The age of patients in this group ranged from 29 to 86 years with an average age of 60,06±14,95 years. In most cases, ovarian cancer was diagnosed among patients, aged 40–60 (Fig. 5).

By the histological type, the highest number of serous tumors was detected - 37 (57,7%); the number of endometriotic tumors detected was 13 (20,3%). Relatively a little number of mucinous cells – 4 (6,3%), bright cells – 3 (4,7%), undifferentiated carcinomas – 2 (3,1%) and mixed – 2 (3,1%) ovarian cancer types were found; germ cells, genital mutilation, stroma and transitional epithelial tumors were detected only once (1,6%). During the study, the mean tumor size detected was 11,93 ± 5,0 cm. By the differentiation degree, a great number of G3 differentiation grade tumors was detected – 41 (64,1%) (Table 1). According to the FIGO stage, ovarian cancer was most commonly diagnosed in stage IIIC – 27 (42,2%), the cancer was detected just a few times in IVA–10 (15,6%), IA – 8 (12,5%) and IC – 7 (10,9%) stages.

Analyzing the possible relationship between ovarian cancer and the degree of differentiation of tumors, a statistically significant relationship was found between the signs of tumor spread (ascites, pathological lymph nodes, peritoneum carcinomatosis, urinary bladder and rectum) and differentiation degree. With increasing degree of tumor differentiation, these ovarian symptoms are more often diagnosed (p<0,05). However, there was no statistically significant relationship between degree of tumor differentiation and detectable metastases in the liver (p>0,05) (Table 2). By analyzing the relationship between ovarian cancer spread and tumor size, two groups of subjects were selected, based on the largest tumor size. The first group consisted of patients with tumors less, than 10 cm in length; the second group consisted of patients with tumors larger, than 10 cm. Data analysis revealed a statistically significant relationship only between tumor size and penetration in the bladder and rectum (p<0,05). Tumors of the most patients (83,3%), who had a tumor spread in the urinary bladder, was larger, than 10 cm. Tumors larger, than 10 cm were also detected among patients (62,2%) with signs of cancer, spreading to the rectum (Table 3).

To determine the effectiveness of the CT test method, its susceptibility, specificity, PPV, NPV and accuracy were estimated for evaluation of pathological lymph nodes. CT sensitivity was 41,9% in the assessment of pathological lymph nodes (95% confidence interval (CI) 2–53%), specificity – 81,8% (95% CI 72–93%), PPV – 68,4% (95% of CI 57–80%), NPV–60,0% (95% CI 48–72%), accuracy – 51,6% (95% of CI 39–64%).
To determine the effectiveness of the CT scan in evaluating peritoneal carcinomatosis, its susceptibility, specificity, PPV, NPV and accuracy were estimated. CT sensitivity in the evaluation of peritoneal carcinomatosis was 62.5% (95% confidence interval (CI) 51–74%), specificity – 81.3% (95% CI 72–91%), PPV – 90.9% (95% CI 84–98%), NPV – 41.9% (95% CI 30–54%), accuracy – 67.2% (95% CI 56–79%). To determine the effectiveness of the CT test method, its susceptibility, specificity, PPV, NPV and accuracy are estimated for ascites. The CT sensitivity to ascites was 86.5% (95% confidence interval (CI) 78–95%), specificity – 88.9% (95% of CI 81–97%), PPV – 91.4% (95% of CI 85–98%), NPV – 82.8% (95% CI 74–92%), accuracy – 87.5% (95% of CI 79–96%).

Fig. 5. Patients age groups distribution

Table 1. Tumors distribution by differentiation grade

<table>
<thead>
<tr>
<th>Tumors differentiation grade (G)</th>
<th>Cases count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>G1</td>
<td>16</td>
</tr>
<tr>
<td>G2</td>
<td>7</td>
</tr>
<tr>
<td>G3</td>
<td>41</td>
</tr>
<tr>
<td>Altogether</td>
<td>64</td>
</tr>
</tbody>
</table>

V = 60, 06 SNS = 14,95, n = 64
Table 2. Comparison between spread of ovarian cancer and tumor degree of differentiation

<table>
<thead>
<tr>
<th>Signs of the spread</th>
<th>Tumors differentiation grade (G)</th>
<th>Signs of tumor spread</th>
<th>( p^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ascites</td>
<td>G1</td>
<td>2</td>
<td>5,7</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>3</td>
<td>8,6</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>30</td>
<td>85,7</td>
</tr>
<tr>
<td>Pathological lymph nodes</td>
<td>G1</td>
<td>1</td>
<td>5,3</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>4</td>
<td>21,1</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>14</td>
<td>73,6</td>
</tr>
<tr>
<td>Peritoneum carcinomatosis</td>
<td>G1</td>
<td>3</td>
<td>9,1</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>5</td>
<td>15,2</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>25</td>
<td>75,7</td>
</tr>
<tr>
<td>Metastases in liver</td>
<td>G1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>8</td>
<td>100,0</td>
</tr>
<tr>
<td>Spread to bladder</td>
<td>G1</td>
<td>14</td>
<td>30,4</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>5</td>
<td>10,9</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>27</td>
<td>58,7</td>
</tr>
<tr>
<td>Spread to rectum</td>
<td>G1</td>
<td>2</td>
<td>9,5</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>19</td>
<td>90,5</td>
</tr>
</tbody>
</table>

Table 3. Comparison between spread of ovarian cancer and tumor size groups

<table>
<thead>
<tr>
<th>Signs of the spread</th>
<th>Tumors size group</th>
<th>Signs of tumor spread</th>
<th>( p^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ascites</td>
<td>&lt; 10 cm</td>
<td>5</td>
<td>14,3</td>
</tr>
<tr>
<td></td>
<td>≥ 10 cm</td>
<td>30</td>
<td>85,7</td>
</tr>
<tr>
<td>Pathological lymph nodes</td>
<td>&lt; 10 cm</td>
<td>6</td>
<td>31,6</td>
</tr>
<tr>
<td></td>
<td>≥ 10 cm</td>
<td>13</td>
<td>68,4</td>
</tr>
<tr>
<td>Peritoneum carcinomatosis</td>
<td>&lt; 10 cm</td>
<td>13</td>
<td>39,4</td>
</tr>
<tr>
<td></td>
<td>≥ 10 cm</td>
<td>20</td>
<td>60,6</td>
</tr>
<tr>
<td>Metastases in liver</td>
<td>&lt; 10 cm</td>
<td>4</td>
<td>57,1</td>
</tr>
<tr>
<td></td>
<td>≥ 10 cm</td>
<td>3</td>
<td>42,9</td>
</tr>
<tr>
<td>Spread to bladder</td>
<td>&lt; 10 cm</td>
<td>3</td>
<td>16,7</td>
</tr>
<tr>
<td></td>
<td>≥ 10 cm</td>
<td>15</td>
<td>83,3</td>
</tr>
<tr>
<td>Spread to rectum</td>
<td>&lt; 10 cm</td>
<td>8</td>
<td>42,1</td>
</tr>
<tr>
<td></td>
<td>≥ 10 cm</td>
<td>28</td>
<td>62,2</td>
</tr>
</tbody>
</table>
DISCUSSION

The study group consisted of 64 patients, who underwent abdominal and pelvic CT examinations at the HLUHS CK Radiology Clinic in 2014–2015, surgical treatment at Obstetrics and Gynecology Clinics, when ovarian cancer diagnosis was confirmed by histology for the first time. The age of patients in this group ranged from 29 to 86 years with an average age of 60,06 ± 14,95 years. Relatively, the similar average age of patients (63 years) is also indicated in literature sources [7–9]. In our study, ovarian cancer was predominantly diagnosed in patients, aged 40–60 years (n=29), although the literature suggests that this oncogynecological disease is most commonly diagnosed at a later age – in the seventh and eighth decades of life [7–9].

During the study, serous ovarian tumors were detected in the most cases, 37 (57,7%), of which 27 (65,9%) were of G3 differentiation degree. Similar results were obtained during the study, conducted by Pratt J., in which women with ovarian cancer of Spain participated. Comparing our results with the results of the Spanish study, it may be noted that early stage ovarian cancer usually does not have the characteristic symptoms of the disease, thus already advanced cancer is diagnosed – stages III and IV [4]. During our study, 30 patients (46,9%) had ovarian cancer, diagnosed in stage III, and 13 (20,1%) – in stage IV.

The study showed a statistically reliable relationship between CT scan of ovarian cancer (ascites, pathological lymph nodes, peritoneum carcinomatosis, urinary bladder and rectum) and tumor differentiation degree. Signs of ovarian cancer spread more frequently in tumors with higher differentiation degrees (p<0,05). References also indicate that there is a significant relationship between the FIGO stage and the tumor differentiation degree, the later stage of ovarian cancer is more often determined for tumors with higher differentiation degrees [10–14].

The study also showed a statistically significant relationship between tumor size and the spread of cancer to the bladder and rectum. In larger ovarian tumors, a higher incidence of urinary bladder and rectum (p<0,05) was observed. Similar results were obtained in a study, conducted in the United States of America, where it was found that the increase in tumors is characterized not only by the increased frequency of their spread to adjacent organs (bladder, rectum, uterus), but also by more frequent clinical signs of local tumor proliferation (urination, bowel obstruction, pain syndrome) [15].

During the study, we found that, in the evaluation of pathological lymph nodes, the CT sensitivity was 41,9%, specificity – 81,8%, PPV – 68,4%, NPV – 60,0%, accuracy – 51,6%. Relatively, similar results were obtained in a study, conducted by Aquilani L. and co–authors, where, in the evaluation of pathological lymph nodes, the CT sensitivity was 50%, specificity – 85,9%, PPV – 50%, NPV – 75,3 %, accuracy – 70,3 % [16]. During our study, in evaluating peritoneal carcinomatosis, CT sensitivity was 62,5%, specificity – 81,3%, PPV – 90,9%, NPV – 41,9%, precision – 67,2%, the CT sensitivity was 86,5%, specificity – 88,9%, PPV – 91,4%, NPV – 82,8%, accuracy – 87,5%. Similar data was obtained in a study, conducted by Aquilani L. and co–authors, where, in evaluating peritoneal carcinomatosis, the CT scan specificity was 47,6%, PPV – 86,2%, NPV – 48,7%, accuracy – 78,5%, in evaluating the ascites, the CT method specificity was 55,7%, PPV – 70,9%, NPV – 84,5%, accuracy – 75%. Relatively, Bezirgcioglu I. and co–authors in a study, conducted in Turkey to investigate ovarian cancer in women, comparing the CT scan sensitivity evaluation results. The authors state that, in evaluating peritoneal carcinomatosis and ascites, CT sensitivity is 57,4%. and 85,2 % accordingly [17].

Having reviewed the results of our and previous studies, as well as the literature data, we can observe that the ovarian cancer evaluation is relatively similar during CT, the differences are possible due to uneven research methods in various health care institutions.

CONCLUSIONS

1. The symptoms of the ovarian cancer spread were determined more frequent in high-grade tumors.
2. Larger ovarian tumors typically were spread
to the bladder and rectum.

3. The results of lymph nodes and peritoneal carcinomatosis showed that CT had moderate sensitivity, NPV, and accuracy, but it had high specificity. According to the pathological lymph nodes, PPV was average, but high according to peritoneal carcinomatosis.

4. The evaluation of ascites showed that CT sensitivity, specificity, PPV, NPV, and accuracy were high.

REFERENCES


Brain tumor in pregnancy: case report and literature overview

Diana Uljanionok Zilovic1, Jelena Volochovic1,2, Romoaldas Jursenas1,2, Jurate Dementaviciene3

1Vilnius University, Faculty of Medicine, Department of Obstetrics and Gynaecology, Vilnius, Lithuania
2Vilnius University Hospital Santaros klinikos Centre of Obstetrics and Gynaecology, Vilnius, Lithuania
3Vilnius University Hospital Santaros klinikos Centre of Radiology and Nuclear medicine, Vilnius, Lithuania

ABSTRACT

Introduction: The incidence of brain tumor in pregnant women is estimated to be 1 in 1000–2000 pregnancies and it is similar for pregnant and not pregnant women. Incidence of malignant brain tumors is 3.6 per 1 million live births. Treatment and diagnostic of malignant brain tumor during pregnancy has a lot of specificity and it is a challenge for neurosurgeons and obstetricians.

The aim: To report the case of brain tumor during pregnancy and summarize literature overview about brain tumor management and treatment during pregnancy. Case: A 34-years-old woman presented at 38th week of pregnancy complaining of headache, dizziness, nausea and fever. Patient was diagnosed with giant brain tumor after computed tomography (CT) was performed. Multi-disciplinary team decided that patient has to deliver by cesarean section and after neurosurgery have to be performed.

Conclusion: It is important to select proper diagnostic and treatment method to minimize maternal and fetal mortality and morbidity. Diagnosing of brain tumor during pregnancy may be difficult due to similar symptomatic such as hyperemesis gravidum, preeclampsia, eclampsia or normal pregnancy condition. Management of women with brain tumor during pregnancy has to be approached by multi-disciplinary team.

Keywords: brain tumor, pregnancy, glioma, astrocytoma.

CASE PRESENTATION

34-year-old female at 38 weeks of pregnancy (gravida 2, para 2) presented at Vilnius University Hospital Santaros Klinikos (VUHSK) with headache, dizziness, nausea and fever. During the last 6 months of pregnancy she had three episodes of headache and dizziness. Her obstetric history consisted of one labor without any complications. Patient had no history of cancer in her family. She was consulted by obstetrician gynecologist and there were no obstetric pathologies. After neurological counseling, a CT was performed which revealed brain tumor (Fig. 1, 2, 3). Multi-disciplinary team consisting of obstetrics and neurosurgery departments decided: vaginal delivery is contraindicated due to a giant tumor of the brain. Patient has to deliver by cesarean section (CS), brain surgery should be performed afterwards. Final treatment tactics should be considered after the magnetic resonance imaging (MRI), undertaken after CS. Diagnosis: Gravida 2, para 2, 38 weeks and 3 days. Cerebral tumor, unspecified.

At 38 weeks of gestation female newborn was delivered by cesarean section. According to Apgar scale she was evaluated by 9 points after 1 minute and by 10 points after 5 minutes. Patient was stable after CS, without focal neurological signs. MRI was performed after delivery (Fig. 3). Study was performed in T1, T2, FLAIR, T1+C sequences in sagittal, transverse, coronal planes with i/v Sol. Gadovist 7.5 ml contrast. MRI revealed huge lesion in the right hemisphere, well marginated, involving deep white matter of temporo-occipito-parietal and limbic lobes with expansion to the interhemispheric cortex T1 - hypointense, T2/FLAIR hyperintense, without diffusion restriction. Lesions cause significant transfalcine and uncal herniation with midbrain deforma-
tion, dislocation and deformation of ventricles with signs of asymmetric hydrocephalus and increased intracranial pressure. MRI results are suggesting low grade glial tumor. Multi-disciplinary team, including obstetricians, neurosurgeons, neurologists, decided to perform surgery. After CS, patient was treated in ICU for one day and two days in Obstetric department. Patient was treated with: adequate hydration, nonsteroidal analgesic and anti-inflammatory agents, anticoagulants, Sol Mannitol 15% 250 ml i/v 2 times per day, Sol. Dexamethason 8 mg 1 time per day, Tab Bromocriptin 2.5 mg 2 times per day. Three days after CS, patient and the newborn were released home (they both were in stable condition, without neurological deficit). No complications have been reported concerning the newborn during this period. There were several follow-up recommendations: continue taking Tab. Bromocriptin 2.5 mg 2 time per day for 14 day and Tab. Dexamethason 2.0 mg per day for 10 days.

Two weeks after delivery, second MRT was performed, which revealed no tumor progression (Fig. 4, 5). One month post-operatively, patient underwent operation: Craniotomia reg. P-O parasaggitale dex. extirpatio neoplasmatis. During operation extra biopsy was taken and histopathology results showed glioma. Operation was not radical, due to big mass of tumor. The pathology laboratory reported low grade diffuse glioma which can be further typed as diffuse grade II astrocytoma (World Health Organization). Immunohistochemistry of tumor cells revealed positive IDH-1 (30%) and GFAP (95%) expression. Few weeks after surgery patient showed complete neurological recovery and no adverse side effects. Further treatment will be prescribed after oncologist consultation.
Brain CT shows hypodense region in cerebral white matter with significant mass effect with subfalcial and transtentorial herniation. Lesion does not correspond to vascular supply regions and is suggestive of brain tumor.
Brain MR images: A) T1W image in axial plane, B) FLAIR (Fluid attenuated inversion recovery) image in axial plane, C) T2W image in coronal plane, D) DWI in axial plane. MRI reveals huge lesion in the right hemisphere, well marginated, involving deep white matter of temporo-occipito-parietal and limbic lobes with expansion to the interhemispheric cortex T1 - hypointense, T2/FLAIR hyperintense, without diffusion restriction. MRI with intravenous contrast injection showed central focuses of slight enhancement. Lesions caused significant transfalcine and uncal herniation with midbrain deformation, dislocation and deformation of ventricles with signs of asymmetric hydrocephalus and increased intracranial pressure. MRI results suggest low grade glial tumor.

DISCUSSION

Brain tumor diagnosis during pregnancy is rare. The incidence of brain cancer in pregnant women is estimated to be 1 in 1000–2000 pregnancies and it is similar for pregnant and not pregnant women [1]. Incidence of malignant brain tumors is 3.6 per 1 million live births. There is no accurate statistics for the prevalence of brain tumor during pregnancy in Lithuania. The most prevalent primary tumors according to literature are gliomas, followed by meningiomas, pituitary adenoma, choriocarcinomas and metastases of breast carcinomas [2, 3]. More frequently diagnosed cancers during pregnancy are breast cancer, cervical and hematological cancer. Anatomic and physiologic changes during pregnancy can increase risk for intracranial tumors in pregnant women. There are a lot of problems with diagnosis, and treatment of brain tumors during pregnancy. Maternal blood volume increases during pregnancy, which can lead to increased cerebral blood flow and may be a reason of edema surrounding the tumor. Symptoms of increased intracranial pressure, such as headache, nausea, vomiting, neurologic signs and seizures can simulate symptoms of early pregnancy, or pregnancy related hypertensive diseases, like eclampsia or preeclampsia. According to literature, 27–41% of pregnant women suffer from repeating seizures caused by the brain tumor. Symptoms of brain tumor are primarily caused by mass effect [4, 5]. Main symptoms of our patient were: headache, dizziness, nausea and fever. No status epilepticus was diagnosed in our case. Rarely, early tumor progression may occur without any symptoms. Brain tumor progression accelerates during pregnancy due to multiple factors: hemodynamic changes, hormonal changes, increased level of growth factors and angiogenic factors (vascular endothelial growth factor (VEGF) and placental growth factor) [6]. Meningiomas progression is the most frequent due to a strong relationship luteal phase hormones [7]. Pituitary tumors are hormone-secreting tumors and studies with mice have showed that pregnancy also promotes pituitary tumor growth. Brain-derived neurotrophic factor (BDNF) has a big impact on promoting tumor progression by increasing the rate of the cell cycle, which leads to growth of the pituitary tumor cells in vitro and in vivo [8,9]. It is very important to differentiate if symptoms are pregnancy related or are caused by neural infections, or brain tumor. To confirm brain tumors diagnosis, MRI or CT has to be performed. The choice of imaging method depends on specificity during different trimester of gestation. The American College of Gynecology and Obstetrics recommends reviewing every pregnant patient case basis to assess risk-benefit ratio for performing MRI or CT. CT study radiation dose is generally too low to cause teratogenic effects and the risk of radiation exposure during pregnancy is a common concern. Missed/delayed diagnosis may cause a greater threat for pregnant woman and her fetus than any hazard associated with ionizing radiation. CT uses iodinated contrast, which can cross the placenta and enter the fetal circulation, or pass directly into the amniotic fluid. Animal studies have reported no teratogenic or mutagenic effects from using it. Main advantage of MRI is the ability to image deep soft tissue structures. MRI has no known risk to the fetus during second/third trimester of pregnancy. During first trimester of pregnancy MRI should be performed only after consultation with radiology faculty. MRI with contrast gadolinium-based agents or super paramagnetic iron oxide particles can be used for pregnant patients, but only for absolutely essential clini-
cal indication. Intravenous gadolinium-based agents are teratogenic in animal studies only at high and repeated doses [10]. It is good practice to avoid performing MRI for pregnant patients, especially during the first trimester, but MRI remains to be preferable to any studies using ionizing radiation.

Mutation of isocitrate dehydrogenase (IDH) 1 and 2 were discovered in gliomas just recently. Mutation of IDH1/IDH2 is a good prognostic factor compared to gliomas with wild-type IDH. IDH mutation may predict response to radiation and/or alkylating chemotherapy. Nowadays, detection of these genes mutation is very important and can be done by immunohistochemistry and magnetic resonance spectroscopy [11].

Treatment of malignant brain tumors ever during pregnancy is possible. It usually depends on gestational age of the fetus, symptomatology and tumor location. Treatment has to be started at any gestational week, as soon as disease is diagnosed. Options of treatment during pregnancy (surgery, radiotherapy or chemotherapy) should be discussed by multidisciplinary counsel in order to individualize it. According to our clinical case brain tumor was diagnosed at 38th week of gestation. Treatment tactic was discussed by multi-disciplinary counsel and it was based on gestational age and symptoms. Due to large tumor size, vaginal delivery was contraindicated and it was decided to deliver by cesarean section. It should be noted that no matter what type of delivery is chosen for the patient, epidural anesthesia is a contraindicated, due to possible cerebral herniation (because of a wet tap).

If the patient is diagnosed with brain edema (neurologically stable) it is important to start with symptomatic treatment by using glucocorticoids to reduce cerebral edema and increased intracranial pressure, and accelerate fetal lung growth. Also we need to control seizures. Prolonged use of glucocorticoids during pregnancy can cause fetal adrenal suppression, but there are more benefits using this type of treatment. Hypoxia and fetal acidosis, caused by convulsion is more dangerous, than the possible side effect of treatment. If the patient presents stable neurological conditions, surgical treatment may be performed at the third trimester. The optimal timing of the treatment options should be chosen for each patient by multi-disciplinary consult. After 30 weeks of gestation, surgery is considered to be safer. Intensive care after surgical treatment should be carried out by monitoring the patient during recovery from anesthesia, adequate analgesia (systemic or spinal opioids), prophylaxis against venous thrombosis [2]. After surgery, birth can be given by vaginal delivery or cesarean section, depending exclusively on the obstetric criteria. If the patient is diagnosed with neurological deterioration during the fetal maturation period, craniotomy has to be performed immediately. Cesarean section can be performed before or after craniotomy [12].

If we suspect diagnose of malignant glioma and prognosis of maternal survival is poor, surgery should be performed as soon as possible, no matter of gestational age [5,13]. Adjuvant therapies, including chemotherapy and radiotherapy improve the outcome of glioma and quality of life. If chemotherapy is needed in the first trimester, risks of this type of treatment should be taken into account, because all chemotherapy drugs can cross placenta. Chemotherapy in the first trimester is teratogenic and associated with adverse fetal outcomes. Therapeutic abortion should be considered. In the second and third trimesters of pregnancy chemotherapy is associated with minimal risks [14].

**CONCLUSIONS**

We present a case of pregnant women in the third trimester with a large diffuse brain glioma. Diagnosing brain tumor during pregnancy may be difficult due to the overlapping symptoms and can be confused with hyperemesis gravidum, preeclampsia, eclampsia or normal pregnancy condition. Every aspect of care, treatment strategies, imaging, have their specificity during different trimester of gestation. Management of pregnant women with malignant brain tumor has to be approached by multi-disciplinary team. To minimize maternal and fetal mortality and morbidity it is important to select proper diagnostic and treatment strategy.
REFERENCES


Advanced imaging in epilepsy: literature review and our experience

Tomas Budrys¹, Greta Jurkeviciute¹, Laurynas Kucinskas¹, Rymante Gleizniene¹, Giedre Jurkeviciene¹, Algidas Basevicius¹

¹ Lithuanian University of Health Sciences, Kaunas, Lithuania

ABSTRACT

Background. The diagnosis of epilepsy is mostly based on clinical features of seizures and the results of electrophysiological and neuroimaging methods. Unluckily, there is no single imaging technique that can provide all the needed information: to confirm the etiology of seizures, to prognose the outcome of the disease and provide both structural and functional information that is required in pre-surgical evaluation of patients with drug-resistant epilepsy.

Aims and Objectives. 1. Systematic literature review of existing evidence. 2. To share our experience with epilepsy imaging.

Materials and methods. 1. A systemic search for relevant studies was performed from Medline (PubMed), Lippincott Williams & Wilkins, ScienceDirect, SpringerLink and Cochrane Library databases (these databases have been submitted on LSMUNI Library list of subscribed databases). 2. Thirty five patients with clinically proven refractory epilepsy were included into the study. All patients underwent a Fluorodeoxyglucose-18-PET/CT scan, MRI scan with epilepsy protocol used in our center, and an EEG at least 1 hour prior to a PET study and minimum 60 min in duration. The MRI was performed not earlier than 6 months before the PET/CT scan. All diagnostic tests were performed at Lithuanian University of Health Sciences hospital.

Results. We reviewed literature and characterized the complex correlation between imaging studies. Neuroimaging plays an important role in workup of patients with epilepsy. It helps to identify brain pathologies that require specific treatment. Identification of these lesions often helps in managing epilepsies more effectively.

In our experience most common localization of epileptogenic focus on all three imaging methods we chose were right temporal lobe. According to Wilcoxon signed ranks test results there is statistically significant difference in lesion amount between the different diagnostic methods.

Conclusions. This review compares available advanced imaging modalities, their specific role in patients with epilepsy, and practical applications of imaging data in the management of patients with epilepsy.

Keywords: epilepsy, MRI, FDG-PET, SPECT, spectroscopy, diffusion tensor imaging.

BACKGROUND

Epilepsy is a neurological disorder when activity in the brain becomes abnormal, causing seizures or periods of unusual behavior. As the disease itself the diagnosis is also very complex. The diagnosis is mostly based on clinical features of seizures and the results of electrophysiological and neuroimaging methods. Unluckily, there is no single imaging technique that can provide all the needed information: to confirm the etiology of seizures, to prognose the outcome of the disease and provide both structural and functional information that is required in pre-surgical evaluation of patients with drug-resistant epilepsy. While in most of the epilepsy cases magnetic resonance imaging (MRI) and computed tomography (CT) are the imaging tests of choice, the acquired information may not be enough when planning the outcome of surgical treatment [1]. There are other imaging tests and techniques that can be performed in this case like different MRI techniques: magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), functional MRI (fMRI) and nuclear imaging techniques: positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Although the value of these techniques are still sometimes controversial in everyday practice, the possibilities are almost endless.

MAGNETIC RESONANCE SPECTROSCOPY

MRS is a non-invasive diagnostic tool for
measuring biochemical changes in the brain. N-acetylaspartate (NAA) peak concentration is quantified and usually compared with creatine or choline peaks [1]. Due to the limited voxel coverage and long spectra acquisition time, MRS is mostly used for patients with focal epilepsies. Decreased NNA peaks strongly correlate with EEG and surgical results, thus MRS can be used for epileptogenic area lateralization and localization (changes are found in 70-80%), especially in MTLE patients with drug resistant epilepsy undergoing pre-surgical evaluation [1, 2, 3, 4]. Some studies suggest that NNA concentrations normalize after surgery, also NNA concentration appears to measure neuronal density, and in some cases NNA peak changes are bilateral in MTLE patients, therefore NNA changes should be interpreted with caution [1]. For properly selected patients MRS proves to be a valuable tool for pre-surgical evaluation and planning.

DIFFUSION TENSOR IMAGING

DTI is a subtype of diffusion weighted imaging (DWI) which measures the diffusion of water molecules within the white matter of the brain. This allows a non-invasive three-dimensional mapping of white matter tracts (tractography), including location, orientation and anisotropy [5, 6, 7]. DTI tractography has shown to be valuable in patients with drug-resistant temporal lobe epilepsy (TLE) undergoing anterior temporal lobe resection (ATLR) [8, 9]. Although, surgically treated patients have a high rate of seizure freedom (50-60% at 10 years) [10], 50-100% suffer postoperative visual field defect [9, 11, 12, 13]. DTI may be employed for presurgical planning and intraoperative navigation in order to avoid injury to the temporal loop of the optic radiation (Meyer’s loop), alongside conventional MRI imaging, DTI tractography has also proven helpful for evaluating post-operative damage to the Meyer’s loop [9, 14, 15, 16]. Another possible application of DTI is fractional anisotropy analysis for lateralizing epileptogenic area in temporal lobe epilepsy patients. Ahmadi, et al. Found that DTI correctly localized left vs right TLE in 90% of all cases [17]. It suggests possible DTI application for MRI negative epilepsy patients and might give some insights for further radiological investigation. Although, DTI is not well established in clinical practice, it shows promising results with possible clinical application.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

fMRI is a non-invasive imaging tool that can map functional areas in the brain by measuring changes in the cerebral blood flow. The most widely used fMRI technique employs blood oxygenation level - dependent (BOLD) effect. Due to different magnetic properties, changes in the ratio of oxyhemoglobin and deoxyhemoglobin concentrations can be measured, this allows to evaluate areas of altered neuronal activity. BOLD fMRI proved to be useful for functional area mapping related to specific tasks (i.e. language, memory, motor function) [3, 18, 19, 20, 21, 22]. Studies show evidence that task-based fMRI may be considered as an option to replace the invasive intra-carotid amobarbital procedure (IAP, also known as Wada test) which is the current standard for language and memory lateralization and outcome prediction prior to epilepsy surgery [23-25]. A study by Janecek et al. yielded promising results, showing 14% discordance rate between Wada and fMRI [26]. Another currently published practice guideline supports the idea, stating that fMRI could be used in place of IAP for lateralizing functional language and memory areas in the presurgical evaluation, and prediction of postoperative deficit [27]. However, there are no standardised protocols for fMRI tasks (a set of questions or commands), results vary between the institutions, technical IAP aspects also differ depending on the institution, this is the possible cause of notable concordance between the two techniques, thus leading to potential drawback of fMRI implementation in day-to-day clinical practice.

Another possible application of fMRI is simultaneous EEG-fMRI recording. While fMRI maps hemodynamic changes, EEG represents electri-
cal activity of the brain allowing to better understand epileptogenic regions, their extent and connection to other areas of the brain [3, 19-22]. In one study EEG-fMRI helped to identify epileptogenic regions in 55% of MRI-negative epilepsy patients, which was helpful for further search of subtle lesions or guidance for intracranial placement of EEG electrodes [28]. A number of studies have found that the change in fMRI BOLD signal correlates with recorded EEG electric discharges (ED) during the seizure. As mentioned, it not only helps to locate the area of the epileptogenic zone but also gives information about more remote structures that contribute to the ED. This could help for further investigation of epileptic networks, moreover to the better understanding of the pathophysiology of epilepsy [28-31]. In summary, although fMRI is still considered to be experimental, recent studies show potential applications for epilepsy diagnostics and surgery, that one day may become routinely used in clinical practice.

NEUROIMAGING IN NUCLEAR MEDICINE

Functional neuroimaging using PET or SPECT are well established techniques that help observe metabolic processes and can localize a focal abnormality in patients with drug-resistant epilepsy while planning surgical treatment (32, 33, 34). Functional neuroimaging is essential in pre-surgical evaluation of the epilepsy patient especially when other previous CT or MRI scans were negative. Physiologic ligand with a connected radioactive tracer is administered intravenously and attach to targeted areas. A scanner detects the emission of gamma rays and then might be transferred to structural images made with CT or MRI to provide both anatomic and metabolic information.

POSITRON EMISSION TOMOGRAPHY

Fluorodeoxyglucose (FDG) is the most common ligand used in PET scan to measure glucose metabolism in epilepsy patients. FDG-PET is usually performed between the seizures (inter-ictal FDG-PET). Epileptogenic zone in interictal FDG-PET appears as hypo metabolic. FDG-PET has the most value in determining the temporal lobe epilepsy with specificity of 80-84 % [32]. The found temporal hypo metabolic zone accurately coincides with EEG abnormalities even when a patient is MRI-negative (32, 35, 36, 37). However, FDG-PET is less valuable in extra temporal epilepsy. PET does not provide much information about the size or structure of lesion because the hypo metabolic region usually extends farther than the epileptogenic zone. Thus other imaging techniques like CT or MRI are performed together with FDG-PET. FDG-PET might also be valuable if there is more than one registered epileptogenic zone in EEG or if the symptoms and the findings in EEG do not correlate [3]. There are other experimental and less known and less widely used ligands that each assess different functions. They are mostly used in clinical trials, for example 11C- or 18F-flumazenil. 11C-FMZ binds to (GABA)-A benzodiazepine receptors. The number of benzodiazepine receptors is significantly decreased in epileptogenic zone. Therefore, the uptake of 11C-FMZ is also decreased in this zone and this change may help to identify the hypo metabolic epileptogenic zone. The found zone is usually smaller and better defined while comparing the epileptogenic zone found with FDG-PET and 11C-FMZ. Even though this could be very useful while planning the surgical treatment and help to perform the smallest resection possible, the use of 11C-FMZ is limited due to technical difficulties like very short half-life. So the role of 11C-FMZ – PET in pre-surgical workup is not very well established, although it suggests many ideas for the future. [3, 32].

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY

SPECT assess the cerebral blood flow using radiotracers like technetium-99m-hexamethylpropylene amine oxime (99mTc-HMPAO). The radiotracer is administered intravenously and the scan is performed after 30 to 60 s after the administration. The half-life of radiotracer is long
so the scan can be performed up to 4 hours after the intravenous administration [2]. Although the inter-ictal SPECT is usually performed to use the images for subtraction, but it can also be used to evaluate the decreased cerebral blood flow between the seizures [2]. Ictal (during the seizure) SPECT scan allows to identify the epileptogenic zone which appears as hyperperfusion. It is especially important when the patient is MRI-negative [3]. The radiotracer must be prepared in advance and administered as soon as the seizure starts. Then the scan is performed and compared with the inter-ictal scan of the same patient. The success of the scan highly depends on the speed of radiotracer administration. The faster the radiotracer administration and the scan is performed, the better the probability to identify the epileptogenic zone is. SPECT is not recommended if the usual seizure is less than 15 s in length [1]. SPECT subtraction is the image sum of both ictal and inter-ictal scans [32]. SPECT is even more valuable when the scan data is compared with the symptoms and EEG data as it might be important in planning the surgical treatment even when the patient is MRI-negative [2, 3, 32, 37]. SPECT shows better results in identifying the temporal epileptogenic zone [1]. SPECT scan can also be combined with MRI scan and it is then called SISCOM (subtraction ictal SPECT co-registered to MRI). With the additional step of data normalization and statistical analysis it is called STATISCOM (Statistical ictal SPECT co-registered with MRI). The importance of those tests is still debatable, although it is possible that they will be widely used in the future.

**OUR EXPERIENCE**

Patient characteristics (table 1)

Cases comprised 35 patients with clinically proven refractory epilepsy. Gender of the patients was distributed almost equally: there were 18 women and 17 men patients. Twenty seven patient were adults, 8 were children at the time of hospitalization for epilepsy imaging. Mean age of all patients was 28.31. Most of the cases (32) were with structural epilepsy. Other 3 had unknown etiology.

All patients had been admitted for a comprehensive assessment including EEG monitoring, MRI scan with epilepsy protocol and a Fluorodeoxyglucose-18-PET/CT scan.

### Descriptive Statistics (table 1)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Range</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient_age</td>
<td>35</td>
<td>61</td>
<td>2</td>
<td>63</td>
<td>28.31</td>
<td>2.550</td>
<td>15.088</td>
</tr>
<tr>
<td>Valid N (list-wise)</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### RESULTS

1. Most common localization for epileptogenic activity on EEG was right temporal lobe with 54.3% (table 2); most common lobe with structural changes on MRI was right temporal lobe with 42.9% (table 3); most common hypometabolism zone on PET/CT was in right temporal lobe with 45.7% (table 4).
### EEG Localization (Table 2)

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right_frontal</td>
<td>4</td>
<td>11.4</td>
<td>11.4</td>
<td>11.4</td>
</tr>
<tr>
<td>left_frontal</td>
<td>1</td>
<td>2.9</td>
<td>2.9</td>
<td>14.3</td>
</tr>
<tr>
<td>right_temporal</td>
<td>19</td>
<td>54.3</td>
<td>54.3</td>
<td>68.6</td>
</tr>
<tr>
<td>left_temporal</td>
<td>11</td>
<td>31.4</td>
<td>31.4</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100.0</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

---

### MRI Localization (Table 3)

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not_found</td>
<td>4</td>
<td>11.4</td>
<td>11.4</td>
<td>11.4</td>
</tr>
<tr>
<td>right_frontal</td>
<td>3</td>
<td>8.6</td>
<td>8.6</td>
<td>20.0</td>
</tr>
<tr>
<td>right_temporal</td>
<td>15</td>
<td>42.9</td>
<td>42.9</td>
<td>62.9</td>
</tr>
<tr>
<td>left_temporal</td>
<td>12</td>
<td>34.3</td>
<td>34.3</td>
<td>97.1</td>
</tr>
<tr>
<td>right_occipital</td>
<td>1</td>
<td>2.9</td>
<td>2.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100.0</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>
pet_localization (table 4)

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td>not found</td>
<td>7</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>right_frontal</td>
<td>2</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>left_frontal</td>
<td>1</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>right_temporal</td>
<td>16</td>
<td>45.7</td>
<td>45.7</td>
</tr>
<tr>
<td></td>
<td>left_temporal</td>
<td>9</td>
<td>25.7</td>
<td>25.7</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Wilcoxon Signed Ranks Test

Ranks (table 5)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean Rank</th>
<th>Sum of Ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td>eeg_lesion_amount - mri_lesion_amount</td>
<td>Negative Ranks</td>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.50</td>
</tr>
<tr>
<td></td>
<td>Positive Ranks</td>
<td>22&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.93</td>
</tr>
<tr>
<td></td>
<td>Ties</td>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>mri_lesion_amount - pet_lesion_amount</td>
<td>Negative Ranks</td>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8.25</td>
</tr>
<tr>
<td></td>
<td>Positive Ranks</td>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.00</td>
</tr>
<tr>
<td></td>
<td>Ties</td>
<td>21&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>pet_lesion_amount - eeg_lesion_amount</td>
<td>Negative Ranks</td>
<td>18&lt;sup&gt;g&lt;/sup&gt;</td>
<td>11.33</td>
</tr>
<tr>
<td></td>
<td>Positive Ranks</td>
<td>4&lt;sup&gt;h&lt;/sup&gt;</td>
<td>12.25</td>
</tr>
<tr>
<td></td>
<td>Ties</td>
<td>12&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

a. eeg_lesion_amount < mri_lesion_amount  
b. eeg_lesion_amount > mri_lesion_amount  
c. eeg_lesion_amount = mri_lesion_amount  
d. mri_lesion_amount < pet_lesion_amount  
e. mri_lesion_amount > pet_lesion_amount  
f. mri_lesion_amount = pet_lesion_amount  
g. pet_lesion_amount < eeg_lesion_amount  
h. pet_lesion_amount > eeg_lesion_amount  
i. pet_lesion_amount = eeg_lesion_amount
### Test Statistics (table 6)

<table>
<thead>
<tr>
<th></th>
<th>eeg_lesion_amount - mri_lesion_amount</th>
<th>mri_lesion_amount - pet_lesion_amount</th>
<th>pet_lesion_amount - eeg_lesion_amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>-3.443b</td>
<td>-1.460c</td>
<td>-2.665c</td>
</tr>
<tr>
<td>Asymp. Sig. (2-tailed)</td>
<td>.001</td>
<td>.144</td>
<td>.008</td>
</tr>
</tbody>
</table>

a. Wilcoxon Signed Ranks Test
b. Based on negative ranks.
c. Based on positive ranks.

Wilcoxon signed ranks test results (tables 5, 6):

#### Correlation of EEG violations with MRI abnormalities

First line in the Ranks table indicates number of cases (N=3) when number of epileptogenic foci found on EEG were lower than established on MRI. The sum of the rankings was 40.50; Average rank 13.50. Similar information was provided in 22 cases where number of epileptogenic foci detected by the EEG method was higher than established on MRI. The second table shows the Z-value (-3.443) and the p value (Asymp. Sig. (2-tailed) = 0.001). Since p <0.05 - there was a statistically significant difference between the number of epileptogenic focal points detected on EEG and MRI.

#### MRI correlation with PET / CT lesions

There were 8 cases where number of epileptogenic foci detected on MRI was lower than those which were found on PET/CT. These tests correspond to rank=66.00; average rank=8.25. In 5 cases epileptogenic foci number detected on MRI was higher than identified on PET/CT. Z-value was -1.460, p=0.144. Since p>0.05 - there was no statistically significant difference between the number of epileptogenic foci detected on MRI and PET/CT.

#### PET / CT correlation with EEG lesions

In 18 cases number of epileptogenic foci detected on PET/CT was lower than on EEG. Corresponding ranking=204.00; average rank=11.33). In 4 cases number of epileptogenic foci detected on MRI was higher than established on PET/CT. Z-value was -2.665, p = 0.008). As p<0.05 - there was a statistically significant difference between epileptogenic foci found on PET/CT and EEG.

### CONCLUSIONS

This review compares available advanced imaging modalities, their specific role in patients with epilepsy, and practical applications of imaging data in the management of patients with epilepsy. Conventional MRI is the common choice for imaging for now, mostly because of its ability to detect small lesions like mesial temporal sclerosis, cortical dysplasias and small tumors, that are not detected by CT, which is often needed only for the initial investigation and in acute situations. However, different MRI techniques, functional nuclear imaging methods like PET/CT is extremely useful imaging methods to assist in the localization of epileptogenic zones. Information that these neuroimaging methods provides is complementary to anatomical imaging of MRI and functional information of EEG and is a very important techniques in the process of sorting out patients in whom surgery may be indicated. According to our experience - there was a statistically significant difference in lesion amount between MRI, PET/CT and EEG diagnostic methods for epilepsy. Most common localization of epileptogenic focus on all three imaging methods we chose were right temporal lobe, which might be associated with fact that hippocampus is often involved in seizures, even if they are not generated there.
REFERENCES

Patient preparation importance for diagnostic quality of PET-CT images

Zilinskas Juozas¹, Kulakiene Ilona¹, Jurgelenas Tadas²

¹ Lithuanian University of Health Sciences, department of Radiology, Kaunas, Lithuania
² Lithuanian University of Health Sciences, department of Gastroenterology, Kaunas, Lithuania

ABSTRACT
Objective: to evaluate the importance of patient preparation for diagnostic quality of PET-CT images.

Methods: prospective study of 188 patients’ who underwent PET-CT examination at our Nuclear medicine department has been carried out. Patients were asked to fill in questionnaire about preparation for PET-CT. Then PET-CT images were analysed and attributed to one of the five quality categories, assigning score from 1 to 5. Additionally, average and maximum standardized uptake values (SUV) were calculated in the standard size (200cm³) region of interest (ROI) placed on the left ventricle of the heart. P<0.05 was considered statistically significant.

Results: diabetes was found in 14 (7.5%), obesity in 44 (23.4%) patients. Mean patients’ glycaemia prior 18F-FDG injection – 5.42±1.02 mmol/l. Most of the patients’ (n=186; 98.9%; p<0.001) had their last meal more than 6 hours before PET-CT. One hundred sixteen (61.7%; p<0.001) patients consumed 3-4 glasses (0.75-1 litre) of water during last 6 hours. Patients have followed low carbohydrates low fat containing products diet (n=97; 51.6%), low carbohydrates diet – 32 (17.0%), high proteins diet – 15 (8.0%), high fat diet – 2 (1.1%). SUVmax – 2.78±1.36, SUVav – 1.63±0.79. Most of the PET-CT images were considered as high quality (p<0.05): 82 (43.6 %) images were assigned for 4 points, 48 (25.5%) - 5 points. PET-CT images of diabetic patients’ were significantly lower quality compared with non-diabetic patients (p<0.001) and in obese patients compared with non-obese (p<0.001). Mean quality of PET-CT images was associated with glycaemia (r=-0.29; p<0.001), SUVav (r=-0.38; p<0.001). SUVmax (r=0.2; p=0.006) and SUVav (r=0.19; p=0.01) were associated with glycaemia.

Conclusions: Eighty percent of the patients’ have followed the instructions of preparation for PET-CT examination. Quality of PET-CT images was lower in patients’ with diabetes, obesity and higher pre-test glycaemia. Higher glycaemia levels were associated with higher SUVmax and SUVav in the left ventricle of the heart.

Keywords: patient’s preparation, positron emission tomography – computed tomography, quality of images.

INTRODUCTION
In clinical practice, 18F-FDG PET-CT is commonly used in the evaluation and management of many types of cancer, including tumour diagnosis, staging, restaging, treatment monitoring, and radiation therapy planning [1]. 18F-FDG is glucose analogue, therefore, accumulation of this radiopharmaceutical is detected in these locations of organism where use of glucose is increased. Due to high activity of hexocinase and higher amount of GLUT-1 transporters activated, cancerous cells use more glucose for their metabolism, which manifests in increased accumulation of 18F-FDG during PET-CT examination [2]. Therefore, accumulation of 18F-FDG can be detected in normal tissues, particularly in brain and heart, which complicates evaluation of images and can lead to false positives results [3]. Thus, appropriate patient preparation and comprehensive clinical and anamnestic data are important to reduce risk of inaccurate interpretation of PET-CT images. Appropriate preparation include restrictions in diet and physical activity, management of blood glucose levels in diabetic patients, as well as an awareness of the effect of medications and environmental conditions [1]. While patients are usually instructed to avoid any meal and insulin injection for 4-6 hours before their study, it is not uncommon to encounter...
diabetic patients who are not following instructions. This can result in increased diffuse cardiac and/or skeletal muscle uptake [4]. By analysing patients’ questionnaires and PET-CT images, we aim to evaluate the importance of patient preparation for diagnostic quality of PET-CT images.

METHODS

Prospective study of patients’ who underwent PET-CT examination at Nuclear medicine department of our hospital from 2017 September to 2017 November has been carried out. Permission number: BEC – LSMU (R)-28 received from our Bioethical institution. One hundred eighty eight patients were investigated. Of these 108 (57.4%) were men and 80 (42.6%) were women. Oldest patient was 87 years old, youngest – 15 years. Mean patients’ age (± standard deviation) 57.1±16.7 y. In order to find out how patients followed the recommendations of preparation for PET-CT examination, they had to fill in questionnaire (appendix 1).

Additional patients’ data collected from nuclear medicine department: gender, metabolic disorder (diabetes, obesity), other conditions that can affect quality of images (infection, fever, use of antibiotics, interventional procedure, smoking). All patients were measured (height, weight) and glycaemia results were acquired prior 18F-FDG injection. Patients were divided into two groups according their glycaemia levels prior 18-FDG injection: first group - glycaemia up to 4.5 mmol/l (n=37; 19.7%) and second group - glycaemia >4.5 mmol/l (n=151; 80.3%).

A whole-body PET-CT from skull to mid-thigh was performed with GE Discovery VCL device 60 minutes after 18F-FDG injection. Patients’ PET-CT images were analysed and assigned to one of the five categories of quality (1-5): inappropriate for evaluation, insufficient, average with some restrictions, good, perfect quality.

Statistical analysis was done using „IBM SPSS Statistics 23“ and „Microsoft Excel 2013“ software. Statistical averages of quantitative variables were evaluated using Student’s (t) test. Categorical variables interrelations evaluated using Pearson’s χ² and Fisher’s exact. Cramér’s V test was used to measure association between two nominal variables. P<0.05 was considered statistically significant.

RESULTS

One hundred eighty eight patients’ body mass index (BMI) was calculated. Patients with BMI more than 29.9 were considered obese (n=44; 23.4%). Fourteen (7.5%) patients were diabetic, 8 (4.3%) of these had obesity too. All patients except one used metformin for treatment of diabetes. Mean patients’ glycemia prior 18-FDG injection – 5.42±1.02 mmol/l, highest - 8.50 mmol/l, lowest - 2.80 mmol/l.

Questionnaire analysis showed that most of the patients’ (n=186; 98.9%) had their last meal more than 6 hours before PET-CT. Also four (2.1 %) patients had tea or coffee with sugar less than 6 hour before examination. The majority of patients’ consumed enough water during last 6 hours: 0.75-1 litre - 116 (61.7%), up to 2 litres – 15 (8.0%), more than 2 litres – 1 (0.5%). Unfortunately, 53 (28.2%) patients had insufficient amount of water consumed (less than 0.5 l) and 3 (1.6%) hadn’t any water. Statistically significant relationship between consumed amount of water and quality of PET-CT images wasn’t found (p>0.05).

All patients were advised to follow diet prior PET-CT examination. Patients had followed low carbohydrates and low fat containing products diet (n=97; 51.6%), low carbohydrates diet only – 32 (17.0%), high proteins diet – 15 (8.0%), high fat diet – 2 (1.1%), low carbohydrates and high proteins diet – 8 (4.3%), low carbohydrates, low fat and high proteins containing diet – 13 (6.9%). Twenty one (11.2%) patients hadn’t followed any diet. There wasn’t statistically significant relationship between diet and quality of PET-CT images (p>0.05)

In our questionnaire we provided the list of
products which shouldn’t be used before PET-CT examination. Patients were asked to select products from the list which they used during last 24 hours. Eighty seven patients (46.3%) had chosen at least one product from the list, while 101 (53.7%) hadn’t chosen any. The next question was if the patients had used any of the listed products during last 6 h. Most of the patients (n=162; 86.2%) hadn’t used any products during last 6 hours, while twenty six (13.8%) consumed at least something. Due to discordance of answers to the last question, this question considered unreliable and was excluded from the final analysis.

PET-CT images analysis showed that SUV-max values of left ventricle of the heart varied between patients’ from 1.4 to 11.0 (SUVmax – 2.78±1.36). SUVav values - from 0.9 to 7.0 (SUVav –1.63±0.79).

Most of the PET-CT images were considered as high quality (p<0.05): 82 (43.6 %) images were assigned for 4 points, 48 (25.5%) - 5 points. Forty eight (25.5%) images were evaluated as average with some restrictions (3 points) and ten (5.3%) - insufficient quality (2 points). There were no inappropriate quality images. For more accurate statistical analysis, mean score of PET-CT quality of images (3.89±0.85) was calculated. Statistically significant relationship between diabetes and diagnostic quality of PET-CT images (p<0.001) was found. PET-CT images of diabetic patients’ were significantly lower quality compared with non-diabetic patients (Picture 1).

Picture 1: diabetes and quality of PET-CT images interrelation.

Statistically significant relationship between obesity and quality of PET-CT images was found (p<0.001). PET-CT images of non-obese patients’ were significantly higher quality than obese group (Picture 2). Average glycaemia was significantly higher (p<0.001) in obese patients’ group (6.03±0.85 mmol/l) than non-obese group (5.23±0.99 mmol/l).
Our analysis showed that PET-CT images were significantly higher quality (p=0.17; CI 0.07-0.67) in patients with glycaemia below 4.5 (4.19±0.81) when compared with glycaemia levels over 4.5mmol.l (3.82±0.84). Mean quality of PET-CT images was associated with glycaemia (r=-0.29; p<0.001).

We calculated SUVav and SUVmax in the ROI placed on the left ventricle of the heart and found negative linear correlation between SUVav and quality of PET-CT images. As SUVav increases, quality of PET-CT images decreases (r =-0.38; p<0.001). Negative linear correlation between SUVmax and quality of PET-CT images was also found (r=-0.42; p<0.001). As glycaemia increase, SUVmax (r=0.2; p=0.006) and SUVav values (r=0.19; p=0.01) increases.

Appendix 1: questionnaire about preparation for PET-CT
**Questionnaire about preparation for PET-CT**

(underline appropriate answers)

**Date..............................................**

When was your last meal?

1. Less than hour ago.
2. 1-3 hours ago.
3. 3-6 hours ago.
4. More than 6 hours ago.

Have you consumed any of the listed drinks during last 6 hours?

1. Water.
2. Tea or coffee with sugar.
3. Sweet beverages.
4. Other.

How much water you consumed during last 6 hours?

1. Didn't drink at all.
2. 1-2 glasses (0.5 liter).
3. 3-4 glasses (1 liter).
4. Up to 2 liters.
5. More than 2 liters.

Have you followed any specific diet during last 24 hours?

1. Low carbohydrates (sugars) diet.
2. High protein diet.
3. High fat diet.
4. Low carbohydrates and low fat diet.
5. Haven't followed any diet.

Underline the products which you used during last 24 hours:

Bread, donuts, pasta, potatoes, rice, cookies, sandwich, toast, crackers, muffins, peanut butter, jam, yogurt, curd, peanuts, juice, candies, chewing gum, cough drops, beans.

Which of these products listed above you used during last 6 hours?

**DISCUSSION**

In our hospital patients are invited to nuclear medicine department and instructed orally how to prepare for PET-CT, all the questions about the procedure are answered and written information forms are given to patients by nuclear medicine technologist. Low carbohydrate and low fat diet is recommended for 24 h before scanning. To minimize dietary glucose–related competitive inhibition of 18F-FDG uptake and reduce serum insulin to near basal levels, complete fasting for a minimum of 6 h before the scan is recommended. Similar recommendations with subtle differences are found in the various clinical societies guidelines [5-9]. Our results showed that most of the patients’ had followed these instructions.

Only six patients (3.2%) used any kind of carbohydrates intake less than 6 h before scan and a fifth of all patients hadn’t followed dietary recommendations, in spite of very detailed oral and written instructions. Statistically significant relationship between diabetes and diagnostic quality of PET-CT images was found. PET-CT images of diabetic patients’ were significantly lower quality compared with non-diabetic patients. Most of the patients’ were using metformin for treatment of diabetes. Gontier et.al prospective study showed that metformin significantly increases 18F-FDG uptake in colon and to a lesser extent in small intestine. This increase is typically intense, diffuse and continuous along the bowel, strongly predominant in colon in both digestive wall and lumen. It cannot
be confused with malignant focal bowel uptake, but it can mask an actual neoplastic bowel disease and can induce false-negative results [10]. Statistically significant relationship between obesity and quality of PET-CT images was found. Obese patients' quality of PET-CT images was significantly lower than of non-obese group. Zasadny and Wahl found out that in fasting woman, the normal SUV's of blood, liver and spleen are strongly correlated with body weight in similar way [11]. As 18F-FDG reaches tumour via the bloodstream, tumour SUV may correlate with body weight [11]. Because of body weight impact on diagnostic quality of PET-CT images, some investigators describe a SUV normalization procedure based on lean body mass or the body surface area to be a more reliable parameter to estimate glucose metabolism [12].

Our results showed negative linear correlation between glycaemia prior 18F-FDG injection and quality of PET-CT images. The biodistribution of 18F-FDG is affected by blood glucose levels. The main problem with increased levels of serum glucose is the associated increase in insulin levels. Increased insulin levels result in increased muscle uptake of 18F-FDG, decreasing the quality of the images [13]. That is why it is very important to follow up dietary instructions to prevent high glucose levels in the blood. Further studies should be performed in order to find out most common mistakes of preparation for PET-CT.

CONCLUSIONS

Eighty percent of patients' have followed instructions of preparation for PET-CT examination. Quality of PET-CT images was lower in patients with diabetes, obesity and higher pre-test glycaemia levels. Higher glycaemia levels were associated with higher SUVmax and SUVav in the left ventricle of the heart.
REFERENCES


Direct seventh-eighth cranial nerve involvement by brain stem glioma – a case report

Sanjay M. Khaladkar, Aarushi Gupta, Arijit Ghosh, Poorvi Sharma, Pooja Karanjule
Department of Radiodiagnosis, Dr.D.Y. Patil Medical College and Research Center, India

ABSTRACT
Brainstem gliomas constitute 10-20% of all pediatric CNS tumors. Brain stem astrocytomas are usually fibrillary. Based on their appearance they can be focal, exophytic, cervico-medullary and focal tectal gliomas. Malignant gliomas are characterized by the infiltrative growth of malignant cells and they grow along the white matter tracts. Rarely, an extension of a tumor may be seen along the cranial nerve, simulating a nerve sheath tumor. We report a case of a brainstem glioma in a 5-year old female patient, extending along left seventh-eighth cranial nerves into the left internal auditory canal.

Keywords: Brainstem, Glioma, Cerebello-pontine angle, seventh–eighth nerve complex.

INTRODUCTION
Brainstem gliomas (BSG) constitute 10-20% of all pediatric CNS tumors. They generally occur in childhood with the average age of diagnosis in 7-9 years with no gender predisposition [1, 2]. Prior to the era of modern imaging, all brainstem gliomas were regarded as a single pathological entity and their prognosis was considered poor. In 1969 MATSON summarized that BSG must be considered as a malignant tumour regardless of specific histology as their location renders them inoperable [3]. A classification system was later introduced to identify tumors that benefitted from surgery. With the advent of MRI, morphological patterns of brainstem gliomas evolved. These help in predicting tumor behavior and in the management protocol.

A CASE REPORT
A 5-year old female patient presented with the loss of balance, headache, deviation of mouth to the right side, double vision for the past 2 months, and vomiting, neck pain for the past 8 days. MRI of the brain was performed with contrast. It showed a large diffuse lesion involving pons and medulla, causing pontine expansion. It was heterogeneously hypointense on T1WI (Figures 1, 7), heterogeneously hyperintense on T2WI and FLAIR (Figures 2, 3, 4). Extension of the lesion was noted in the left cerebellopontine (CP) angle cistern and along the left seventh and eight nerve complex into the left auditory canal (Figures 2 d, 4 b, 6). Posteriorly, it was extending into the floor of the fourth ventricle (Figures 1, 2, 3). No proximal obstructive hydrocephalus was noted. The dorsal portion of the mass was extending along the fourth ventricle and in the left CP angle cistern, and showed a mild restricted diffusion with low ADC values (Figure 5). The contrast study showed a heterogeneous enhancement in the dorsal and cisternal portions of the mass (Figure 8). The remaining portion of the mass showed no significant enhancement. MR spectroscopy revealed elevated choline relative to the NAA signal (Figure 9). Radiotherapy was suggested, which was refused by parents. The patient eventually died after two months.
Figure 1: Sagittal T1WI – showing a diffuse hypointense lesion in the medulla and pons with cervicomedullary kinking.

Figure 2: Axial T2WI – showing a diffuse hyperintense lesion in the medulla and pons with extension in the left paramedullary, parapontine and left cerebellopontine cisterns, and with extension along the left seventh-eight nerve complex into the left internal auditory canal.
Figure 3: Axial FLAIR – showing a diffuse hyperintense lesion in the medulla and pons with extension in the left paramedullary, parapontine and left cerebellopontine cisterns.

Figure 4: Coronal T2WI – showing a diffuse hyperintense lesion in the medulla and pons with extension in the left paramedullary, parapontine and left cerebellopontine cisterns, and with extension along the left seventh-eight nerve complex into the left internal auditory canal.

Figure 5: Axial DWI and ADC – showing a subtle restricted diffusion in the left lateral portion of the mass with low ADC values.

Figure 6: Axial CISS – showing a diffuse hyperintense lesion in the medulla and pons with extension in the left paramedullary, parapontine and left cerebellopontine cisterns, and with extension along the left seventh-eight nerve complex into the left internal auditory canal.

Figure 7: Axial T1WI fat saturated (Pre-contrast) – showing a diffuse hypointense lesion in the medulla and pons extending into the left paramedullary cistern.
Figure 8: Post-contrast Axial T1WI fat saturated (a), Coronal FLAIR (b) – showing a diffuse enhancement in the lateral portion of the mass extending to the left parapontine and left cerebello-pontine cisterns.

Figure 9 – MR Spectroscopy in the enhancing portion of the mass shows raised choline and reduced NAA, with increased choline creatinine ratio.
DISCUSSION

Brain stem astrocytomas are usually fibrillary in contrast to cerebellar astrocytomas, which are usually pilocytic. MRI is useful in detecting the epicenter of a tumor, expansion of involved portion of the brainstem, predicting its biological behavior. Depending on the appearance, they can be focal, exophytic, cervicomedullary and focal tectal gliomas.

Diffuse brainstem gliomas are generally more than 2 cm in size during the time of presentation, and are characterized by a diffuse infiltration and swelling/ hypertrophy of the brainstem. The epicenter of a lesion is usually in the pons. Rostral or caudal tumor extension may be seen. Focal tumors are defined as a demarcated lesion in the midbrain, pons or medulla, either solid or cystic, and have well defined margins in the MRI. They are usually histologically benign (Grade I or II), rarely anaplastic gangliogliomas and PNET have been reported. There is a lack of infiltration and edema. Exophytic tumors (dorsally exophytic brainstem gliomas) arise from subependymal glial tissue. The bulk of tumor resides in the fourth ventricle. Hence, there is a relatively late onset of symptoms [4-6].

Malignant gliomas are characterized by infiltrative growth of malignant cells and they grow along the white matter tracts [7]. The cranial nerve nuclei are within the brain parenchyma and have glial cells, which extend into the root entry zone and proximal cisternal segments with the gradual replacement of Schwann Cells of more than 1-9 mm [7, 8]. Hence, infiltrating growth is seen along the white matter tracts. The extension of a tumor may be seen along the cranial nerve, simulating a nerve sheath tumor, intracranial perineural spread of head and neck tumor, and leptomeningeal spread of tumor [7].

Before 2014, 11 unique cases of gliomas directly infiltrating cranial nerves have been reported in the literature with 8 cases detected in imaging [8-10]. 8 additional cases of pathologically confirmed gliomas with imaging findings indicating direct involvement of cranial nerves have been identified by M.C.Mabray [7]. The imaging technique in identifying the intra-axial origin of a disease is the involvement of the pons and medulla, deep to the root entry zone of the cranial nerves by a lesion contiguous and matching the cranial nerve involvement in signal characteristics, and enhancement patterns, and expansion of the brainstem.

Expansion of the adjacent pons or midbrain, thickening of the root entry zone and the cisternal segment of the cranial nerve having similar signal characteristics and enhancement patterns on MRI are the key features in differentiating intra-axial origin of a tumor with the involvement of cranial nerves from the nerve sheath tumors, diffuse neoplastic, infectious or inflammatory leptomeningeal diseases.

Cranial nerves, which can be involved, are the oculomotor nerve and the trigeminal nerve apart from the vestibulocochlear nerve and the facial nerve.

Intrinsic tumors of the brainstem are astrocytoma (the most common), PNET, lymphoma, ganglioglioma and oligodendroglioma [11]. Non-neoplastic lesions arising from the brainstem are tuberculomas, cavernous malformations, haemangioblastomas and epidermoids.

CONCLUSION

Brainstem gliomas directly infiltrating cranial nerves is a rare but known condition. This entity should be known in order to differentiate it from the nerve sheath tumor, intracranial perineural spread of head and neck tumor, and leptomeningeal spread of a tumor. These tumors can cause cranial neuropathy. Identification of intraparenchymal, intraaxial origin of a cranial nerve involvement by glioma is the key to its correct diagnosis.
REFERENCES

Unilateral renal lymphangiectasia – the role of Ultrasound, CT and MRI. Case report

Sanjay M. Khaladkar, S. G. Gandage, Dr. Dwaram Jyoti Reddy, Aarushi Gupta
Department of Radio-diagnosis, Dr. D.Y. Patil Medical College and Research Centre, India

ABSTRACT
Renal lymphangiectasia is a rare disorder characterized by ectasia of perirenal, peripelvic and intrarenal lymphatic vessels. A disturbance in the drainage of renal sinus lymphatics results in ectasia of peripelvic, intrarenal and perirenal lymphatics, and leads to the formation of renal lymphangiectasia. Multiple cysts with various sizes are seen in the perinephric space, renal parenchyma and in the renal sinus. The presence of fluid, density lesions in the retroperitoneum and around the great vessels, crossing the midline at the level of the origin of renal vessels are the diagnostic criteria. We report a case of a 27-year old female with multiple tiny cysts in the perinephric space and renal cortex, and a large cyst in the fat of the renal sinus, discovered with sonography, confirmed with CT Urography and MRI.

Keywords: renal lymphangiectasia, peripelvic cyst, renal lymphangioma, intrarenal and perinephric cyst.

CASE REPORT
A 27-year old female patient presented with vague pain in the right lumbar region for the past 2-3 months. There was no h/o fever/burning micturition/hematuria. No previous h/o Hypertension/Diabetes mellitus/Surgery/Renal calculus. Urine sample, renal function tests were within normal limits.

Ultrasonography of abdomen (Figure 1) showed multiple anechoic cystic lesions in various sizes (0.5-3.1 cm) in the fat of the renal sinus, not communicating with each other and with the pelvicalyceal system. Multiple small anechoic cystic lesions (3-5 mm) were seen in the renal cortex and perinephric space adjacent to the upper and lower pole and regions. The left kidney and the urinary bladder were normal. Ascites or retroperitoneal lymphadenopathy were not seen.

CT Urography was performed by obtaining arterial phase, corticomedullary phase, nephrographic phase and excretory phase after plain study (Figures 2-5). The size of the left kidney was 9.3x4.4 cm and appeared normal. The right kidney was 10.5x5.3 cm. CT showed a large cystic lesion, the size of approx. 3.7x3.2x4.5 cm in the fat of the right renal sinus, causing extrinsic compression on adjoining renal pelvis. The cystic lesion was extending to adjoining renal parenchyma alongside of infundibula and calyces in the upper, interpolar and lower pole calyces, which were effaced. Tiny hypodense cysts, the size of approx. 2-3 mm were noted in the renal cortex. Multiple small cysts, the size of 2-6 mm were noted in the perinephric space, more along its lower pole. No extensions of calyceal contrast were noted in these cystic lesions. The right kidney showed normal function. The right ureter appeared normal. These cystic lesions appeared to be displacing the intrarenal arteries.

MRI of the abdomen was performed for kidneys by obtaining T1WI, T2WI and T2 fat saturated sequences in axial, coronal and sagittal planes (Figures 6, 7). Multiple cystic lesions were noted in the right kidney – in the peripelvic region, extending into renal parenchyma, involving cortex. These appeared hypointense on T1WI and hyperintense on T2WI. Multiple cystic lesions were also seen in the perinephric space. Cystic lesions were extending along the right upper ureter and in adjoining retroperitoneum posteriorly, right lateral and anterior aspects of IVC, extending to interaortocaval region. Thin hyperintense fluid
was also noted in the retroperitoneum, on right side, and in the right anterior pararenal space. MRI has an advantage of detecting the location and the content of cysts, extensions of the disease and associated involvement of retroperitoneal lymphatics and thoracic duct. The diagnosis of renal lymphangiectasia/lymphangioma/lymphangiomatosis was made. Histopathology report of USG Guided aspirated fluid showed lymphocytes, occasional eosinophils, macrophages, mesothelial cells and few degenerated cells in the background of proteinaceous fluid. No signs of malignancy were seen in the specimen.

Figure 1. USG of the Right Kidney in transverse (A), and longitudinal (B-D) showing multiple anechoic cystic lesions in the fat of the renal sinus, extending around the pelvicalyceal system, small cysts in the renal parenchyma and in the perinephric space (C).
Figure 2. CT of the ABDOMEN – Axial Plain CT (A), Axial corticomedullary phase (B-D) showing hypodense fluid cyst in the fat of the right renal sinus, extending to the renal parenchyma, small cortical cysts in the lower pole (C), small cysts in the perinephric space adjacent to the lower pole (C), hypodense fluid collection in the retroperitoneum extending anteriorly to the aorta and IVC (D).

Figure 3. CT of the ABDOMEN Axial arterial phase (A-D), showing hypodense fluid cyst in the fat of the right renal sinus, extending in the renal parenchyma, displacing the intrarenal arteries, small cortical cysts in the lower pole (C), small cysts in the perinephric space adjacent to the lower pole (C), hypodense fluid collection in the retroperitoneum, extending anteriorly to the aorta and IVC (D).
Figure 4. CT of the ABDOMEN Axial excretory phase (A-D), showing hypodense fluid cyst in the fat of the right renal sinus, extending in the renal parenchyma alongside of the infundibula and calyces in the upper, interpolar and lower pole calyces, which were effaced, small cortical cysts in the lower pole and in the perinephric space, adjacent to the lower pole (D).

Figure 5. CT of the ABDOMEN Coronal (A), Sagittal (B-D), excretory phase showing hypodense fluid cyst in the fat of the right renal sinus, extending in the renal parenchyma alongside of the infundibula and calyces in the upper, interpolar and lower pole calyces, which were effaced, small cortical cysts in the lower pole and in the perinephric space, adjacent to the lower pole.
Figure 6. MRI of the ABDOMEN Axial T2 fat sat. (A-F) showing cysts in the fat of the right renal sinus, extending in the renal parenchyma in the upper, interpolar and lower pole regions (A-C), small cortical cysts in the lower pole and in the perinephric space, adjacent to the lower pole (C-D), hyperintense fluid collection in adjoining retroperitoneum, extending anteriorly to the IVC and in the interaortocaval region (D-F), pole appearing hyperintense on T2WI.

Figure 7. MRI of the ABDOMEN – Coronal T2WI (A), Sagittal T2WI (B), Coronal T1WI (C) - showing cysts in the fat of the right renal sinus, extending to the renal parenchyma in the upper, interpolar and lower pole region, small cortical cysts in the lower pole and in the perinephric space, adjacent to the lower pole, appearing hyperintense on T2WI and hypointense on T1WI.
INTRODUCTION

Renal lymphangiectasia is characterized by the ectasia of perirenal, peripelvic and intrarenal lymphatic vessels. Renal lymphangiectasia is a more appropriate term than other terms used, as renal lymphangioma. It is usually bilateral, but can be unilateral and may be asymptomatic or present with flank pain, hematuria, abdominal distension, and proteinuria. Neck (75%) and axilla (20%) are common sites for lymphangioma. 5% of cases occur in the retroperitoneum, mediastinum, mesentery, omentum, pelvis and colon. Retroperitoneal lymphangiectasia accounts for 1% of all lymphangiectasias (1). Renal lymphangiectasia is rare. Unilateral lymphangiectasia is extremely rare with only 3 out of 21 reported cases of renal lymphangiectasia in a literature review, done in the last decade (2).

DISCUSSION

The lymphatics of the renal capsule and renal parenchyma drain into the renal sinus lymphatics, which empty into the paracaval, paraortic and interaortocaval lymph nodes. Though pathophysiology of renal lymphangiectasia is unclear, both congenital and acquired obstructive inflammatory processes are suggested, and etiological factors. A disturbance in the drainage of renal sinus lymphatics results in the ectasia of peripelvic, intrarenal and perirenal lymphatics leading to the formation of renal lymphangiectasia. Hypertension is seen in about 50% of unilateral cases and 15% of bilateral cases, and usually occurs due to compressions, caused by parapelvic, intrarenal and perirenal cysts in the intrarenal arterial circulation, which leads to the renin dependent hypertension. The natural history of renal lymphangiectasia is unclear. It can appear suddenly, grow rapidly, squeeze or regress spontaneously (3).

It can exacerbate in pregnancy. The dilated lymphatic ducts can decompress the urinary tract leading to chyluria. Hemorrhages, ruptures, ascites and hypertension are the most common complications secondary to perirenal fluid collection. Venous thrombosis is a less reported complication (1). It is usually seen in children and less frequently occur in adults. Microscopically, they can be capillary or cavernous depending on size of the lymphatic spaces. Abnormal lymphatic channels can be unilocular or multilocular. Usually it occurs due to obstruction of the lymphatic ducts through the renal pedicle (4).

Renal lymphangiomatosis, renal lymphangioma, peripelvic lymphangiectasia, renal peripelvic multicystic lymphangiectasia are the other terms used for renal lymphangiectasia. Renal lymphangiectasia is a preferred name and has replaced the others, as there is the ectasia of perirenal, intrarenal and peripelvic lymphatics, renal polycystic disease, renal hygroma (5,6). Two different patterns of cystic lesions are observed in the renal sinus. The first pattern is called peripelvic - characterized by multiple small confluent cysts in the renal sinus, which are benign, usually bilateral and intraparenchymal. These usually occur due to lymphatic duct obstruction with resultant renal sinus lymphangiectasis. These mimic hydronephrosis, but do not fill with excreted contrast and usually cause extrinsic compression and displacement of the collecting system. The second pattern is called parapelvic cyst and correspond to a large single cyst in the renal sinus, which originate from the medial renal parenchyma encroaching into the renal sinus. These appear like the renal cortical cyst. They may cause hydronephrosis due to compression of the renal collecting system. In the absence of radiological and pathological data, the term cystic lesions of the renal sinus can be used. Multiple small cystic lesions are seen in the perinephric space surrounding the kidney, the view represents capsular lymphatic dilative perirenal lymphangiectasia. Sometimes perinephric fluid accumulation occurs in renal lymphangiectasia and is not surrounded by a wall. This occurs due to continuous secretion of fluid by the perirenal lymphatics, associated with altered retroperitoneal lymphatic pressure balance, that prevents reabsorption of the fluid. Multiple dilated tortuous cystic lesions are seen in the retroperitoneum, around the great vessels, and represents the ectasia of the lymphatic channels (6). Renal lymphatic aspirate is not chylous or milky
intrarenal and peripelvic regions. Extension of cysts can be seen in adjoining retroperitoneum. The signal intensity of cysts may vary, if there is high in protein content or hemorrhage within the cyst (3).

The treatment is not required in asymptomatic cases, especially those, which are detected incidentally. In symptomatic cases, percutaneous cyst aspiration is the first line treatment. However, high relapse rates are known in larger lesions, as they are multiseptated. Aspiration and sclerosis of the cystic lesions of the renal sinus is also useful. Sclerotherapy is contraindicated for peripelvic cysts due to the risks of leading to stenosis. Due to the leakage of sclerosing agent (6).

Symptomatic management includes antihypertensives for arterial Hypertension and diuretics for ascites. In severe cases, laparoscopic ablation and nephrectomy can be performed. Differential Diagnosis includes polycystic kidney disease, nephroblastomatosis, multilocular cystic nephroma, lymphoma and urinoma, polycystic renal disease (9).

CONCLUSION

Unilateral renal-lymphangiectasis is rare. It should be suspected if cystic lesions are seen in the perinephric space, within the renal parenchyma and in the renal sinus. The presence of fluid density lesions in adjoining retroperitoneum around the great vessels and crossing the midline at the level of origin of the renal vessels represents dilated renal lymphatics, draining into the larger retroperitoneal lymphatics, and is a typical sign of renal lymphangiectasia (7). Renal lymphangiectasia may show certain genetic mutations like Trisomy 7Q, monosomy X chromosome and mutations in VHL gene (Von-hippel Lindau gene) (8).

On MRI, the cyst appears hypointense on T1WI and hyperintense on T2WI, and shows septations. These cysts can be seen in the perinephric, like, the thoracic lymphatic duct as well as renal lymphatics are outside the pathway of mesenteric drainage. They contain lymphocytes and small amounts of fat and protein material.

Imaging is based on Ultrasonography, the involved kidney may be normal or enlarged in size. Renal cortical echotexture may be normal or increased. Corticomedullary differentiation can be normal or lost. Multiseptated thin walled anechoic cystic lesions can be seen in the renal parenchyma, the fat of the renal sinus, in the peripelvic region and perinephric space. It can present as a solid mass, when small intrarenal lymphatics are obstructed. Retroperitoneal cystic lesions may be seen adjacent to the aorta and Inferior vena cava along with ascites. In the CT scan, they are seen as multiple well defined hypodense fluid lesions, the CT value (0-20HU), in the perinephric region. These can be unicocellular or multilocular, high density fluid represents intracystic hemorrhage. Intervening renal parenchyma shows normal enhancement with normal excretion of contrast, mass effect can be seen in adjoining pelvicalyceal system.

The presence of fluid density lesions in adjoining retroperitoneum around the great vessels and crossing the midline at the level of origin of the renal vessels represents dilated renal lymphatics, draining into the larger retroperitoneal lymphatics, and is a typical sign of renal lymphangiectasia (7). Renal lymphangiectasia may show certain genetic mutations like Trisomy 7Q, monosomy X chromosome and mutations in VHL gene (Von-hippel Lindau gene) (8).
REFERENCES


9) Al-Dofri SA. Renal lymphangiectasia presented by pleural ef
Primary intraosseous meningioma of the calvarium presenting as a solitary osteoblastic lesion. Case report

Sanjay M. Khaladkar, Shikha Bhadoriya, Rajesh Kuber, Poorvi Sharma
Department of Radio-diagnosis. Dr.D.Y.Patil medical college and research center, India

ABSTRACT
Background: Intraosseous meningiomas are extradural meningiomas, which are rare lesions arising in the skull. They are likely to originate from intraosseous entrapment of arachnoid cells. They are often asymptomatic, but may cause symptoms depending on the location and size. Surgical resection is usually used to treat patients. Radiation therapy and chemotherapy may be needed as an adjuvant therapy in tumors, which cannot be completely resected.

Clinical case - We report a case of a 42–year old male patient presenting with painless, gradually progressing swelling over the right frontoparietal region for 4 years. CT scan of the brain with contrast revealed an expansive osteoblastic lesion with lobulated outlines involving right frontoparietal bone, with obliteration of diploic space, and with associated enhancing diffuse extra-cranial soft tissue component, also with a thin extra-axial soft tissue component suggestive of an osteoblastic intraosseous meningioma. Surgical resection was performed. Biopsy was confirmatory.

Conclusion - Intraosseous meningiomas are osteoblastic or osteolytic. Osteoblastic lesions mimic fibrous dysplasia. They are extradural meningiomas, which are rare lesions arising in the skull. They are extradural meningiomas, which are rare lesions arising in the skull.

Keywords: Meningioma, intraosseous, extradural, osteoblastic, calvarial.

INTRODUCTION
Meningiomas can be intradural or extradural. Usually, meningiomas are the primary intradural lesions and are located in the subdural space. Extradural meningiomas, arising in locations other than the dura mater, constitute 1-2 % of all meningiomas [1]. Primary intraosseous meningioma (PIOM) is a subset of extradural meningiomas that arise from bone with no neural attachment [2]. Majority of intraosseous meningiomas arise from cranial bones with few cases arising from mandibles. Extradural meningiomas are also named as ectopic, secondary, extra-calvarial, cutaneous, primary extraneuraxial meningiomas. Extradural meningiomas arising in the skull are named as calvarial, intradiploic and intraosseous [3]. Another nomenclature used is primary extradural meningiomas, which differentiates this tumor from those originating in the dura with extracranial extension, and from extracranial meningiomas, that are distinct metastases from primary intradural meningiomas.

CASE REPORT
A 42-year old male patient presented with painless gradually progressive swelling over the right frontoparietal region for the last 4 years. Computed tomography (CT) of the brain was performed without (Figure 1) and with contrast (Figures 2), showed an expansive osteoblastic/sclerotic lesion with lobulated outlines involving right frontoparietal bone, with obliteration of diploic space, and with associated enhancing diffuse extra-cranial soft tissue component, also with a thin extra-axial soft tissue component suggestive of an osteoblastic intraosseous meningioma. Surgical resection was performed. Biopsy was confirmatory.

Rest of the cranial vault appeared normal. A
diagnosis of Type III intraosseous meningioma was made. CT brain angiography showed mild hypertrophy of the right superficial temporal artery, which appeared more tortuous as compared to its counterpart. It was stretched and draped over the bony mass, however it was not supplying the mass. No arterial supply to the mass from any intracranial arteries was noted. The anterior third of the superior sagittal sinus was in close contact with the mass. Histopathology showed a tumor with cells in a nested and whorled pattern. Syncytial cell pattern was present. Focal sheets of cells showed an infiltration into surrounding soft tissue. Underlying bone was involved by the tumor. Tumor cells were positive for vimentin and focally positive for EMA. Cytokeratin was negative. MIB labeling index was 2-3%. Diagnosis was meningothelial meningioma (Grade I).

Image 1 - Plain axial brain CT showing expansive osteoblastic lesion in the right frontoparietal region with slightly hyperdense intracranial and extracranial soft tissue components.

Image 2 - CECT Brain axial (a-c), coronal (d) showing an expansile osteoblastic lesion in the right frontoparietal region with an enhancing intracranial and extracranial soft tissue component.
Image 3 – axial CT brain bone window (a-d) showing an expansile osteoblastic lesion in the right frontoparietal bone with obliteration of diploic space.

![Image 3](image3.jpg)

Image 4 – Coronal (a), Sagittal (b) CT of the brain bone windows showing an expansile osteoblastic lesion in the right frontoparietal bone with obliteration of diploic space.

![Image 4](image4.jpg)
DISCUSSION

Meningioma constitutes about 20% of primary intracranial tumors. Winkler in 1904, first described a meningioma in extradural locations [4]. Different hypothesis exists regarding the intraosseous and primary extradural meningioma. They usually arise from arachnoid cap cells or ectopic meningiocytes, trapped in the cranial sutures during moulding of the head at birth [5]. Calvarial meningiomas are prone to develop malignant changes (11%) compared with intracranial meningiomas (2%) [1].

Lang and colleagues have classified primary extradural meningiomas as type- I Purely extracalvarial tumors, Type II – Purely calvarial tumors and Type III – calvarial tumors with extracalvarial extension. Each category is further divided into two subsets, depending on anatomical location: C – convexity, and B – Skull base. Hence, intraosseous meningioma is Type II and III primary extradural meningioma [2].

Common locations of intraosseous meningiomas are frontoparietal and periorbital regions [6]. They are usually firm and painless with intact overlying skin, and are usually detected incidentally. Neurological symptoms and signs are usually absent. But it may present with headache, vague sensations in the head, seizures, vomiting, dizziness and tinnitus, which may precede months to year prior to the diagnosis. Though, skull base intraosseous meningioma is painless and slow growing, may present with cranial nerve deficient like ophthalmoplegia or visual field defects, proptosis, deformity, atrophy of the optic nerve. Lesions involving paranasal sinuses or nasal cavity may present with nasal obstruction or epistaxis.

Intraosseous meningiomas can be osteoblastic or osteolytic. The majority is osteoblastic. X-ray of the skull often shows hyperostosis, irregular calcific foci and atypical vascular markings. CT scan with bone window shows focally thickened hyperdense lesion causing an expansion of calvarium. It is usually hyperdense on plain CT with CT value +65-+85 HU and shows dense enhancement on contrast study as intradural meningiomas. Due to bone expansion and ground glass appearance of intraosseous meningiomas, it mimics fibrous dysplasia. Entities, which mimic osteoblastic intraosseous meningiomas, are osteoma, fibrous dysplasia, Paget's...
disease, meningioma en plaque, osteosarcoma. Fibrous dysplasia usually stops its growth after puberty, while intraosseous meningioma appears after puberty and continues to grow slowly. Fibrous dysplasia lacks tumors blush on angiography, which is seen in meningiomas. Serum Alkaline phosphatase levels are raised in Paget's disease [3, 6].

Osteolytic intraosseous meningiomas are rare and are seen as lytic lesions on skull X-ray. On CT scan, they show expansion, thinning and interruption of the inner and outer cortex. They are hyperdense with respect to the brain in plain CT, and show homogeneous enhancement in contrast view. Differential diagnosis for osteolytic meningiomas are hemangiomas, dermoid, epidermoid, Brown tumor, Giant cell tumor, Aneurysmal bone cyst, eosinophilic granuloma, plasmacytoma and metastases [3, 6]. MRI findings in both osteolytic and osteoblastic subtypes of intraosseous meningiomas are as seen in intradural meningiomas i.e., hypointense on T1WI, hyperintense on T2WI with marked homogeneous enhancement on contrast study. Though dural tail is not observed, gadolinium enhancement of the underlying dura may be seen due to dural irritation or tumor invasion [6].

On histopathology, the most common lesion is meningotheliomatous meningioma. Other histological types are psammomatous, transitional, microcystic, choroidal, fibroblastic, atypical and malignant [6].

The diagnostic criteria of an intraosseous meningioma are lack of involvement of the brain, arachnoid and dura; location should be epidural and intraosseous; and presence of histopathological features of a meningioma [7, 8].

Ectopic meningiomas can arise from the calvarium, perineural sheath of cranial nerves, paranasal sinuses, orbit, salivary glands. Primary intraosseous meningioma is a subset of extradural meningioma, arising in the bone and constituent 2/3rd of all extradural meningiomas. These are usually observed at or near suture lines, usually coronal or pterion sutures, or at previous fracture sites. The age ranges from 7 months to 82 years with male to female ratio 1:1.1[7].

They are usually treated with a wide surgical excision. Adjuvant therapy like radiation therapy, chemotherapy, Gamma knife surgery and biphosphate therapy is considered in unresectable tumors causing neurological deficit or demonstrating malignant changes. Wide surgical resection is followed by the placement of high density polyethylene for cranial reconstruction; it is the treatment of choice [3, 7].

CONCLUSION

Intraosseous meningiomas are extradural meningiomas, which are rare lesions arising in the skull. Majority of them are osteoblastic, mimicking fibrous dysplasia. Osteolytic lesions are rare. Though usually asymptomatic, neurological symptoms may occur depending on the location and size. It should be considered as differential diagnosis in radiography of the skull with osteoblastic or osteolytic lesions. Tumor resection and cranioplasty is curative. Adjuvant therapy like radiotherapy and chemotherapy is needed in tumors, which cannot be completely resected.
REFERENCES


PMID: 27012383


Ultrasound guided foam sclerotherapy: evaluation of complications and short-term effectiveness

Nita Hubert, Kevin Varghese, Athira Dinesh, Sara Ammu Chacko
Department of Radiodiagnosis, Dr. Somervel Memorial C.S.I. Medical College, India

ABSTRACT
Objectives: To describe the complications following ultrasound guided foam sclerotherapy, and outcomes at 2 and 6 months following treatment.
Methods: Patients with primary or secondary varicose veins and treated with UGFS were followed up at 1 week and 2 months by Duplex Doppler Ultrasound to assess the effectiveness of the procedure and to document the complications.
Results: 117 patients, from the median age group of 47 years (ranging from 18–74 years) were treated; of which 79 were males and 38 were females. 91 of these were cases of primary varicose veins and 26 were of secondary or recurrent varicose veins (post-surgery recurrence in 24 and post-sclerotherapy recurrence in 2).
The complications noted in this study included severe pain at the time of injection (10), vasovagal syncope (1), focal perforator thrombosis (5), local skin ulceration (3), hyperpigmentation (3), ipsilateral inguinal lymphadenopathy (1) and an exacerbation of chicken pox vesicles in the injected leg 3 weeks after injection (1).
During the 2 month follow up 79 legs showed complete thrombosis and 20 had partial thrombosis. Pre-procedure CEAP grading ranged between 1 & 6 with a mean value of 4. Post-procedure CEAP grading ranged between 0 & 6 with a mean value of 3.3. This decrease in mean CEAP was found to be statistically significant (p<0.01). 6 month follow up in 35 legs with complete thrombosis, showed good thrombosis in 31 legs and early recanalization in 4 legs.
Conclusion: UGFS is a simple, cost effective procedure, which leads to significant improvements in clinical symptoms and decreasing morbidity, associated with chronic venous disease.

Keywords: Varicose veins, Ultrasound, Duplex Doppler, Foam sclerotherapy, Sodium Tetra Decyl Sulphate (STDS), Saphenous veins


INTRODUCTION
Ultrasound guided foam sclerotherapy (UGFS) has played a significant role in the treatment of varicose veins, since its usage was reported in 1989 [1]. It is a minimally invasive method, which is cost-effective and significantly improves the quality of life. UGFS as a first line treatment for varicose veins has been reported in 2006 [2]. While endoluminal thermal and laser ablation is used in the treatment of truncal incompetence, sclerosant can be used for both truncal incompetence and varicosities involving the tributaries [2]. The earliest report at sclerotherapy was in 1680s with a large series of modern sclerotherapy being reported in 1939 by McCausland [3]. Foam sclerotherapy uses a foam sclerosant, i.e. sclerosant mixed with air or other physiological gases. Foam displaces blood from the vein and the contact between the foam and the endothelium causes vasoconstriction and occlusion. Sclerosant causes chemical damage to the endothelium, which initiates thrombogenesis. Progressively, the vein becomes a fibrotic cord [4]. According to Jia et al though foam sclerotherapy is not as effective as surgery, it is more effective than liquid sclerotherapy [5]. Sclerosants are classified into three categories
Osmotic agents, detergents and irritant / corrosives. Hypertonic saline is an osmotic agent; polidocanol, sodium tetradecyl sulphate, sodium morrhuate, and ethanalamine oleate are detergent sclerosants. Irritant /corrosive agents include ethanol, phenol, polyiodinated iodine, chromated glycerine and glycerine / lidocaine / epinephrine [3].

Contraindications to sclerotherapy includes the history of allergy to the sclerosant, pregnancy, infection, deep vein thrombosis (DVT) and severe arterial disease[3].

The most common side effects of sclerotherapy are superficial thrombophlebitis and skin pigmentation. Other immediate complications include pain, vasovagal syncope and anaphylaxis. Persistent swelling, matting and staining, transient migraines scotomata, transient thrombus in common femoral vein / DVT, pulmonary embolism, nerve damage, arterial injection, hyperrichosis, sepsis, stroke and fatality are also mentioned [1].

CEAP classification (Table 1) is a simple and easy descriptive system in chronic venous disorders to base decisions for appropriate treatment. However, venous severity scoring and quality of life scores are essential to assess outcomes [6].

OBJECTIVES

The aim of this retrospective study was to evaluate the immediate complications, the short term efficacy of the procedure at 2 months, and the improvement in CEAP scores.

MATERIALS AND METHODS

A retrospective analysis of the records was made. 117 patients who underwent UGFS in the Department of Radiodiagnosis between October 2009 and December 2013 were analysed.

All patients were symptomatic (CEAP 2-6) with primary or secondary varicose veins referred for UGFS. They had undergone a pre-procedure Doppler evaluation for the assessment of deep vein thrombosis (DVT), Sapheno femoral junction & Sapheno-popliteal junction incompetence and perforator incompetence. Pre-UGFS CEAP score was also documented. All patients were above 18 years of age. Pregnant or lactating patients, children, patients with deep vein thrombosis, history of allergy to sclerosant, infection and severe peripheral vascular disease were excluded.

PROCEDURE

UGFS was done in the Department of Radiodiagnostic, with the patient in supine position. Based on the involvement of the GSV or SSV system, the vein to be injected was marked after USG screening. Pulse and oxygen saturation of the patient was monitored during the procedure by a pulse oximeter. The vein was viewed in the longitudinal plane and a 23G needle or intravenous cannula was positioned within the lumen. Foam sclerosant was injected under visualisation and followed up to the Saphenofemoral (SFJ) or saphenopopliteal junction (SPJ) as applicable. After elevation of the lower limb to about 45 degrees, compression of the SFJ or SPJ was done up to about 5 minutes following the injection. Compression bandage was applied from the foot up to the thigh following the procedure. Large perforators adjacent the injection site were also occluded by finger compression.

The sclerosant used was Sodium TetraDecyl Sulphate 3% (STDS) as a foam, mixing it with air by Tessari method [3]. The ratio of foam:air during the period of study was 1:4.

All patients were issued post-procedure instructions regarding being ambulant and were kept under observation for about 2 hours following the procedure, and sent home the same day. They were instructed to wear compression bandage continuously for 2 weeks. Follow up Doppler was done after 1 week to assess complications and to document the extent of venous thrombosis. Further follow up Doppler was done at 2, 6, 12 months, and yearly after that.

Efficacy was defined as a complete thrombosis of the great and small saphenous veins or its tributaries. Non-compressible superficial veins with or without visible intraluminal thrombus and no colour uptake was termed thrombosed.

Complete thrombosis indicated that the dilated superficial veins and the GSV / SSV up to the junction were thrombosed.
It was considered partial thrombosis, when either the GSV / SSV was not thrombosed up to the SFJ or few of the superficial veins in the system were partially thrombosed or patent. Lack of thrombosis of the GSV / SSV and the superficial veins was considered as no thrombosis.

ETHICS

All the procedures followed were in accordance with the ethical standards of this institution.

RESULTS

Records of UGFS done in 117 limbs, 79 of whom were men and 38 of whom were women were analysed. They ranged in age from 18 to 74 years (median age was 47 years). 91 (77%) were primary and 26 (23%) secondary or recurrent varicose veins. The CEAP scores of the patients prior to UGFS were as follows:

Table/Fig 1: Distribution in the patients according to CEAP clinical grade

<table>
<thead>
<tr>
<th>CEAP GRADE</th>
<th>DESCRIPTION</th>
<th>DISTRIBUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0</td>
<td>No visible or palpable signs of venous insufficiency</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>C1</td>
<td>Telangiectasis and/or reticular varicosities</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>C2</td>
<td>Varicose veins</td>
<td>28 (24%)</td>
</tr>
<tr>
<td>C3</td>
<td>Varicose veins with edema</td>
<td>25 (21%)</td>
</tr>
<tr>
<td>C4</td>
<td>Venous eczema, pigmentation, lipodermatosclerosis, atrophie blanche</td>
<td>23 (19%)</td>
</tr>
<tr>
<td>C5</td>
<td>Healed varicose ulcers</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>C6</td>
<td>Active venous ulceration</td>
<td>10 (8%)</td>
</tr>
</tbody>
</table>

Table/Fig 2. Percentage distribution of the sample according to the outcome at 2 months following UGFS

- SUCCESS 80 %
- FAILURE 20 %

*Success is defined as a complete occlusion
+Failure is defined as partial/no occlusion
Table/Fig 3 Comparison of CEAP before UGFS and after UGFS (2 months follow-up)

<table>
<thead>
<tr>
<th></th>
<th>PRE CEAP</th>
<th>POST CEAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>4.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Median</td>
<td>4.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Minimum</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>6.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*Wilcoxon signed Rank test = 8.8, p<0.01

Table/Fig 4. Percentage distribution of the sample according to post procedural complication at 1 week

<table>
<thead>
<tr>
<th>Follow up at 1 week complication</th>
<th>Count (out of 114)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No complications</td>
<td>89</td>
<td>78</td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Perforator thrombosis</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Edema</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Ulcer</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Vasovagal syncope</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Inguinal lymphadenopathy</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

DISCUSSION

UGFS was performed in 117 patients who were referred from the Department of General Surgery for the treatment of lower limb varicose veins. Prior to the procedure, all patients were examined clinically to evaluate the severity of the venous disease using CEAP scoring system and Duplex Doppler to determine the site of reflux and the involvement of great saphenous or short saphenous system, or both.

The patients were followed up at an interval of 1 week initially to look for the procedure related complications, and later at 2 months to assess the efficacy of the procedure.

The patients included in this study were in the age group ranging from 18 to 74 years.

Of the sample patients, 91 (77%) had primary varicosity, 26 (23%) had secondary / recurrence of varicose veins. Studies have shown that primary and secondary varicosities can be effectively closed with UGFS, with high levels of patient satisfaction [7, 8]. In our study also, there were high levels of success in patients with primary and secondary varicosities.

Out of the 99 patients (18 defaulters at 2 months follow up), 79 (80%) patients were found to have a successful outcome following UGFS. Success of UGFS was defined as a 2 month Duplex Doppler showed complete occlusion / thrombosis of the superficial veins. 20 patients (20%) with partial occlusion at 2 months follow up were considered to have a failed outcome. 6 month follow up in 35 legs with complete thrombosis, showed good thrombosis in 31 legs and early recanalization in 4 legs.

Figueiredo et al, reported that GSV treated with UGFS showed a success rate of 80% [9]. This is similar to the result obtained in our study.

Prior to the procedure, the severity of the venous disease was assessed using the CEAP scoring system. Out of the 117 sample patients, 18 patients were defaulters at 2 months follow up. Out of the 99 patients, 89 (90%) showed an improvement
in the CEAP classification and the rest (10%) remained static. The mean CEAP score before the procedure was 4.3 and after the procedure at 2 months follow up was 3.3. This difference in mean CEAP following UGFS at 2 months follow up was found to be statistically significant. A study by Gamal et al showed an improvement in CEAP classification in 80% of the patients at one year follow up, following UGFS [10]. This improvement is similar to our study.

Procedure related complications were assessed immediately after the procedure and after 1 week following UGFS; 3 patients showed discoloration at the injection site, 10 complained of pain at the injection site, 3 were found to have edema, 5 had perforator thrombosis, 3 developed injection site ulceration, 1 developed inguinal lymphadenopathy and 1 had vasovagal syncope. A patient had exacerbation of chicken pox vesicles in the injected leg 3 weeks after injection. Accordingly to the study done by Guex et al, UGFS for the treatment of CVD is associated with a low rate of major complications [11]. Other studies have also shown major complications like stroke, anaphylaxis and pulmonary embolism to be very rare [12-15]. In our study also, there were no major complications like stroke, anaphylaxis and pulmonary embolism.

Thomas et al, detected skin staining in (28%), pain in (14%), DVT in (1%), skin blistering in (1%), an allergic reaction in (1%) [8].

LIMITATIONS

1. Clinical grading using the recent tools (Revised Venous Clinical Severity Score - VCSS) were not done prior to and after the procedure to better assess the improvement in the quality of life. However, CEAP grading as documented was used.
2. Since this was a retrospective study, patients in whom the recorded data of follow up was unclear were excluded.
3. Patient compliance, regarding wearing of the compression bandage, was also not documented.
REFERENCES

Natural antiviral therapy (Cissampelos pareira mix) efficacy against dengue virus monitoring by PET CT as biomarker

Ameen MD, Vetriraj MD, Girish Venkat MD, Andrew John MD, Samson BAMS
Annaii medical college, India

ABSTRACT
Background: Dengue mosquito borne viral infection consisting of four serotypes has been increasing morbidity and mortality to steady rise in India for more than decade. Lack of specific treatment caused significant challenges to the health system in the management of fatal cases. The clinical spectrum of dengue, caused by any of the four serotypes of DENV, ranges from mild self-limiting dengue fever to severe forms of dengue such as hemorrhagic fever (DHF) and dengue shock syndrome (DSS).
Objective: To study and analyze natural anti-viral therapy (Cissampelos pareira mix) efficacy against dengue virus using PET CT as biomarker for the treatment efficacy. Methodology: 31 patients sample size; 18 patients serologically positive for dengue were analyzed prospectively. 3 patients with negative serology test were excluded from the study; 10 patients were assigned to control group. All positive serotype patients were analyzed using the NS1 antigen test; serotype grouping was also performed for all 18 patients. Before and after 2 weeks of use of natural antiviral (CP mix) therapy, followed up by PET CT. Ultrasound (n=18) and CXR (n=18) were performed as standard screening protocol for all 18 patients to rule out radiological abnormality. Other Radiological investigations were also used for screening (CT ABD n=2, MR Brain=3 & CT chest n=4) for a few patients that had more severe symptoms after USG & CXR as an additional test before PET CT to avoid false positive results. Hematology study (n=8) was also performed in a few patients that had more severe symptoms.
Results: data descriptive statistics frequency analysis was applied for analysis of PET CT of 18 patients. Percentage analysis was Chi- Square test was applied to test the significance of the categorical data. Patients were grouped into primary (n=8) and secondary (n=10) groups based on the clinical manifestation.
Conclusion: compared to the current extensive use of PET CT in oncological imaging, infection monitoring and treatment efficacy, it will be a big breakthrough challenge, future prospects for infection imaging and treatment efficacy monitoring.

Keywords: 18F-FDG PET/CT; dengue DENV SEROTYPES: Antiviral (Cissampelos pareira CP mix) therapy, vaccines, future prospects.

INTRODUCTION & BACKGROUND
According to the statistics, dengue endemic in India (Figure 1) prevalence rate and morbidity and mortality ratio has been increasing for more than decade.
There are four known serotypes of dengue, but severe form of dengue fever is caused by infection by more than one serotype.
Dengue virus is a single-stranded RNA virus of Flaviviridae family. There are four distinct yet closely related serotypes of dengue virus – DEN1, DEN2, DEN3, and DEN4. Recovery from infection ensures lifelong immunity from the particular serotype. However, cross immunity to other serotypes is partial and temporary. The virus serotypes are closely related but antigenically distinct [11,12,14,15].
Dengue is one disease entity with different clinical presentations that often has unpredictable clinical evolution and outcome [6]. Two types of infections are caused by DENV, namely, primary infection and secondary infection. Primary infection causes acute febrile illness known as dengue fever. Secondary infection is more severe and results in hemorrhagic fever (DHF) or den-
gueshock syndrome (DSS)[7]. Both DHF and DSS can be fatal and can lead to death of the pa-
tients [8].

**WHO classification for dengue manifestations:**
- Undifferentiated fever
- Dengue fever (DF)
- Dengue hemorrhagic fever (DHF)
- 4 severity grades
- Grades III and IV: dengue shock syndrome (DSS)

Radiological manifestation of dengue are de-
scribed extensively in the reviews of literature,
however, the findings are non-specific.

The radiotracer 18F-fluorodeoxyglucose (18F-FDG) is widely used in clinical medicine
for non-invasive imaging, staging, and moni-
toring treatment responses of neoplastic disea-

eses [23]. 18F-FDG has also been used to inspect
the non-specifically image sites of viral infec-
tion or inflammation; the findings may be pro-
portional to the glycolytic activity of the cells
that trap [17, 18].

After intravenous application, 18F-FDG is pref-

erably stored in tissues with high glucose con-
sumption. The tracer is filtered in the kidney glo-

eruli, and only a small amount is reabsorbed
by the renal tubular cells. Rapid clearance of
18F-FDG from the intravasal compartment re-

sults in a high target-to-background ratio within
a short time, and imaging. Bio distribution of the
18F-FDG active transport by a Na1-dependent

glucose transporter (GLUT), is important in kid-

ney epithelial cells as well as the digestive tract.

A high accumulation of 18F-FDG is regularly
observed in the brain, especially in the cortex
and the basal ganglia. Cardiac uptake is infre-
fently noted and often patchy. Accumulation
of 18F-FDG activity in the urine is common.

Circumscribed or diffuse gastrointestinal uptake
may be caused by smooth muscle peristalsis. Up-
take of 18F-FDG in the reticuloendothelial sys-
tem, especially in the bone marrow, varies.

To confirm the pathological accumulation, tai-
lored follow up PET CT is essential, according
to the disease pattern, and also 18F-FDG could
not be used to stand alone due to false positive
results. If other radiology imaging is additional-
ly applied as screening protocol, the pathologic
18F-FDG accumulations can significantly re-
duce false-positive findings.

In case of infection, abdominal and pelvic ab-
scesses, active tuberculosis, bacterial colitis, di-
verticulitis, and infected vascular grafts can be
accurately identified by 18F-FDG PET, sensitivi-
ty generally exceeding 90% [4,5].

18F-FDG PET appears to be a reliable, non-in-
vasive method of monitoring disease activity and
response to therapy. In a prospective series of
GCA patients, 18F-FDG PET was more reliable
than MRI in monitoring disease activity during
immunosuppressive therapy. Normalization of
18F-FDG uptake during follow-up clearly cor-
related with clinical improvement and normali-

zation of laboratory findings, whereas MRI per-
formed at similar intervals on the same patients
showed improvement in only a minority of the
vascular regions that had initially shown vessel
wall thickening. Enlarged lymph nodes in the
infection conditions are of higher sensitivity, it
is a must to avoid nodal biopsy in the future and
diagnosis efficacy has to be replaced by PET CT.

As there is no cross-protection between the four
dengue serotypes, and because of the possibility
of the immune enhancement by monotypic anti-
body leading to DHF with subsequent natural
infections, worsening cross infections and Anti-
body mediated enhancement are possible.

Indian scientists at the International Centre
for Genetic Engineering and Biotechnology
(ICGEB), New Delhi have developed a DENV-2
E protein based non-infectious virus-like parti-

cle (VLP) using the yeast Pitchia pastoris as the
expression system. The DENV-2 E VLP was able
to induce high titre of neutralizing antibodies in
murine models, however, the research is still at
initial stage.

Live attenuated dengue virus vaccines should be
tetravalent formulations producing a balanced
neutralizing immune response that acts protec-
tively against all four serotypes. Currently Sanofi
Pasteur’s vaccine has overgone phase III trials in
India, however, it was not approved, as the age
group < 9 years was not included, extensive se-
rotype immunity analysis was not done in India.
& dengue vaccine induced infection cases also proved. Although there are vaccines available for other flaviviruses, development of a dengue vaccine is complicated by the phenomenon known as antibody-dependent enhancement (ADE)[5]. Hypothesis of another study, RNAI against DENV, states that RNAI exciting field of the functional genomics can silence viral genes. However, this study has not performed trials in either humans or definitive animal models. The prevalence of mosquito vector, circulation of all four dengue viruses, that are endemic in India, drug or vaccine for dengue needs are increasing. According to our knowledge, few human trials has only done with anti-viral drugs, but none efficacy was followed by PET CT significance.

Cissampelos Pariera (CP mix) with Triphala has been used extensively in India for menstrual irregularity for a century in Ayurvedic medicine. This herbs also grows and is largely cultivated in India; It is easily available in market. As of now, no side effects have been proved. Cissampelos Pariera natural antiviral efficacy study was performed by Ruchi Sood et al, stating that this therapy is effective against all four serotypes. However, trials in humans were not performed and only microbiological investigation was applied as treatment monitoring biomarkers. No additional investigation was performed.

AIM

The main purpose of our study was to achieve significance of Cissampelos Pariera (CP Mix) against all four serotypes of dengue and to be proved by PET CT as biomarker.

METHODOLOGY

Sample size - 31 patients, 18 patients serologically positive for dengue were prospectively analysed. 3 patients with negative serology were excluded from the study; control group consisted of 10 patients.

Serologically positive patients should have non-structural protein-1 (NS-1) Ag test, therefore, dengue immunoglobulin G/immunoglobulin M tests were performed to confirm the diagnosis. NS-1 undergoes least antigenic variation and is a glycoprotein present in high concentration in the serum of dengue infected patients. 18 patients that were serologically positive and grouped according to the serotypes grouped were included in this prospective study. 10 patients were assigned to the control group, separately subjected to PET CT to rule out false positive results. Haematological study was also performed, patients with haemorrhagic or suspicious shock symptoms (platelets, haematocrit concentration and leucocytes) were included in study.

As illustrated in figure 3, flow chart design for patient selection mentioned. Hematological investigation carried out in (n=8) patients where clinical suspicion of dengue hemorrhagic and shock manifestation. Radiological procedures (abdomen US and CXR) uses as baseline in all 18 serological proved cases. Radiological (CT & MRI) and tailored according to clinical suspicion and to avoid false positive results in PET CT acquired data. CT (CT chest or abdomen, n=2) & MRI brain (n=3) scans were included in the study as according to clinical manifestations.

Figure 4, based on radiological / hematological and clinical manifestations was classified into two groups (Primary and Secondary group). Primary group is presented with mild fever or asymptomatic at the time of the study, yet serologically proved (n=5) and three patients (n=3) with fever.

Secondary group is symptomatic and have undergone all the above-mentioned investigations, as for the primary group, only baseline modality investigations were done (n=15).

Ultrasound (n=18) and CXR (n=18) were also performed as a part of standard screening protocol for all 18 patients to rule out radiological abnormality. Other radiological investigations were also used for screening (CT ABD n=2, MR Brain=3 & CT chest n=4) in a few patients that had more severe symptoms as additional test.
Moreover, a hematology study was also performed in a few patients (n=8) that had more severe symptoms (platelet count and hematocrit level tests were only performed for a few patients that had more severe symptoms).

Plant Cissampelos pareira. After filtered, dried and concentrated at low pressure, capsules were prepared from plant powder extract.

Cissampelos mix was given to patients as 500 mg dose along with Triphala (Amla Indian gooseberry extract) 150 mg dose. Triphala extract was added to immune system in dengue infected patients. The volume of the oral dose was standardized as 650 mg, given twice daily and all our patients tolerated Ayurvedic substance well, with no side effects during therapy and after general 3 months follow up. No drug related side effects were documented.

After initial PET CT performed in 18 patients, 650 mg Cissampelos mixed anti-viral introduced in two divided dose for continuous 14 days after meals as designed by our herbalist. After 14 days follow up of each patient, second PET CT study is reviewed. All patients successfully completed follow up PET CT after post therapy course.

**STATISTICAL ANALYSIS**

The collected data was analyzed with IBM SPSS statistics software 23.0. To describe data we used descriptive analysis. Percentage, analysis were used. Chi-Square test was used to test significance in categorical data. In the above statistical tool the probability value .05 is considered as a significant.

**ETHICAL CLEARANCE**

Written informed consent was obtained from all 18 patients, and legally registered. Ethical clearance was also formally obtained from institutional board from ANNAI and TAGORE teaching hospital.

**PET CT IMAGING PROTOCOL AND IMAGE ANALYSIS**

All patients involved in the study underwent whole body 18F-FDG PET/CT. An appointed PET/CT scanner (Biograph 16 HR, by GE DVCT) was used. The PET component is a high resolution scanner with a spatial resolution of 4.7 mm and has no septa, thus allowing 3-dimensional-only acquisitions. Together with the PET system, the CT scanner is used both for attenuation correction of PET data and for the localization of 18F-FDG uptake in PET images. All patients were advised to fast for at least 4 hours before the integrated PET/CT examination. Each patient’s blood glucose level was tested prior to the tracer injection. The threshold of blood glucose level for FDG injection was below 180 mg/dL. After injection of about 3 MBq of 18F-FDG per kilogram of body weight, followed by saline push. The procedure is followed by a standard CT contrast study (Omnipaque with maximum of 60 ml, body weight calculated protocol). All patients rested for a period of about 60 min in a comfortable position. Emission images ranging from the proximal femur to the base of the skull were acquired for 2-3 min per bed position. Acquired images were reconstructed using the attenuation weighted - ordered subset expectation maximization (OSEM) iterative reconstruction, with 2 iterations and 8 subsets. The Gaussian filter was applied to the image after reconstruction along the axial and trans axial directions. The data were reconstructed over a 128 × 128 matrix with 5.25-mm pixel size and 2-mm slice thickness. Processed images (3 sections PET CT) were displayed in coronal, transverse, and sagittal planes.

**IMAGE ANALYSIS AND INTERPRETATION**

Persistent avid PET CT uptake was observed in all three phases up to 2 hours taken as positive PET CT scan. PET/CT images were also assessed quantitatively using the maximum standardized uptake value (SUV max). All PET/CT scans were performed by a nuclear medicine specialist who interpreted all images. Radiological imaging (CXR, ABDOMEN US) and tailored modality of choice were done by one of the senior radiologists.
RESULTS

Table 2 and Figure 7 showing incidence of DENV serotypes in our study group (before and after anti-viral CP mix) efficacy monitoring results from PET CT. In our study, CP mix is effective against DENV TYPE 1 & TYPE 2 in more than 60% significant correlation, as compared to DENV TYPE 2 & TYPE 4 50% significant correlation. Table 3, showing percentage of Serotypes before and after PET CT by CP mix efficacy by percentage calculation in another methodology. Serotype DENV 1, showing 83% before CP mix proved to be reduced to 16% after therapy. Likewise all serotype showing percentage of reduction as mentioned in table 3.

In above mentioned table-4, showing chi square test and like hood ratio for Anti-Viral therapy before and after PET CT is above 0.789 and hence proved to be statistically significant. Table 1, 5 (a and b) also showing before and after CP mix therapy, in primary & secondary group in our study results.

Radiological/clinical and haematological interpretation before and after CP mix therapy reduction rate and efficacy is in moderate nature.

---

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical</th>
<th>Hematology</th>
<th>CXR</th>
<th>USG</th>
<th>CT Chest</th>
<th>MR Brain</th>
<th>CT ABD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total %</td>
<td>94.4</td>
<td>44.4</td>
<td>33.3</td>
<td>66.7</td>
<td>22.2</td>
<td>16.7</td>
<td>11.1</td>
</tr>
<tr>
<td>Primary</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Secondary</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
Figure : 3

FLOW CHART OF PATIENT SELECTION

TOTAL CASES
N=21

SEROLOGICAL PROVED
(NS - 1) AG TEST or
IGM/IgG Ratio
N=18

SEROLOGICAL
STUDY NOT DONE
IN 2 PATIENTS
(Mortality High)
N=03

PRIMARY GROUP INFECTION
N = 08

SECONDARY GROUP INFECTION
N = 10

BASE LINE

USG ABDOMEN
PR-CXR
N = 08

PET CT
BEFORE ANTI VIRAL RX
N = 18

AFTER ANTI VIRAL RX

MR BRAIN

CT CHEST

CT ABD

CHTNL MANIFESTATION
N = 03

ABDOMINAL CLINICAL MANIFESTATION
N = 02

DENGUE HEMORRHAGIC SHOCK CLINICAL MANIFESTATION
N = 08

Figure : 4

SHOWING INFECTION GROUP & CORRESPONDING
CLINICAL / RADIOLOGICAL FINDINGS

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Hematological Values</th>
<th>CXR</th>
<th>USG</th>
<th>CT Chest</th>
<th>MR Brain</th>
<th>CT ABD</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>94.4</td>
<td>0</td>
<td>8</td>
<td>4</td>
<td>22.2</td>
<td>11.1</td>
</tr>
<tr>
<td>90</td>
<td>44.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>80</td>
<td>33.3</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>70</td>
<td>66.7</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>22.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>16.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>11.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total % Primary Secondary
Fig 5(A-D):
(A). Showing avid hyper metabolic activity in bilateral axillary node.
(B). Showing axial PET CT sections bilateral activity before anti viral therapy.
(C). Showing after 2 weeks follow up decreased activity with CT persistent nodes.
(D). Showing biopsy confirmation of infected tissue during course of treatment.
Fig 6(A-D):
(A). Showing increased avid hyper metabolic activity in right side terminal ileum.
(B). Sagittal MIP sections showing persistent activity in small bowel after 2 hours.
(C). Axial fusion sections showing persistent nodule before antiviral therapy.
(D). Coronal MIP sections after 2 weeks anti viral therapy follow up showing decreased nodule size.
DISCUSSION

The validity of 18F-FDG mapping of 18F-FDG tissue uptake by terminal bio distribution studies showed a consistent and prominent tissue-specific uptake pattern in the spleen, small intestine and large intestine, for both nonlethal primary and secondary seen in all serotypes.

Radiological and haematological manifestations were not correlating with PET CT changes in our study. Results are equivocal in our study. Likewise study mentioned viremia load and clinical manifestation in dengue not correlating (12, 13). Radiological and haematological investigations used in our study do not reap any significance overall. Main objectives for using radiological and other investigations in our study was to avoid false positive or to analyse sensitivity of Before PET CT in picking up hyper-metabolic activity in cross modality positive cases. Results are mixed in our study. All four serotypes, CP mix do not yield better results in post PET CT follow up. DENV 1 & 2 serotypes have moderate results as compared to DENV 3 & 4.

In 3 cases, nodal avid uptake positive in PET CT. Subsequent lymph node biopsy also revealed atypical nodal infection before CP mix therapy. After therapy, significant changes in hypermetabolic activity were seen in 3 of our cases. Persistent increased activity seen in intestines, lymph nodes, spleen and after drug reduced in few patients. Although 18F-FDG PET is a state-of-the-art procedure for the assessment of multiple malignancies, it is still not used as a routine procedure in the work-up of FUO/infection. 18F-FDG uptake was sufficiently sensitive as a biomarker to distinguish between primary dengue virus alone and lethal antibody-enhanced infection ADE infection [11,12]. The 18F-FDG PET/CT scan confirmed inflammation of several joints and lymph nodes infection. But 18F-FDG been suggested for infection-associated inflammation biomarker, cannot standalone due to low specificity [6-9].

There are no biomarkers that can sensitively distinguish viral load reduction due to innate cellular antiviral response from the viral load reduction or due to antiviral drug-mediated mechanisms [27-29]. Increased cytokine production is one of the hallmarks of dengue infection. The “cytokine storm” with its accompany-
ing inflammation and vasculopathy, is thought to play a critical role in disease severity [31,32]. Cissampelos pariera Linn (Cipa extract) was a potent inhibitor of all four DENVs in cell based assays, assessed in terms of viral NS1 antigen secretion using ELISA, as well as viral replication, based on plaque assays (1). Virus yield reduction assays showed that Cipa extract could decrease viral titers by an order of magnitude. The extract conferred statistically (1). However, this study lacks human trials as done in Wister rats, moreover study efficacy done exclusively in microbiology based, no PET CT study included to monitor metabolic activity.

Cipa extract targets effect on secretion of inflammatory cytokines as mentioned in previous study. In our small series study, the method was successful in analyzing metabolic activity decreased in previous infected regions like lymph nodes, spleen, intestine, following Cissamepelos mix in more than 50 % sensitivity. However, limitation of study is small volume but still successful attempts in monitoring treatment efficacy.

Dengue is a major threat due to DSS, especially in tropical countries like India

CONCLUSION

Ayurveda science based Cissampelos Mix against dengue virus by PET CT evaluation for monitoring efficacy, manifests potent antiviral activity against at least two DNEV viruses more than 50% accuracy and moderate improvement. However, outcome of this drugs in large series has to be studied and yet it is a future challenge in the clinical use.

CONFLICT OF INTEREST

Authors declares there is no conflict of interest.
REFERENCES


2. Johannes mellar, carslen Oliver Sahlmann et al. 18f –FDG PET and PET CT in fever of unknown origin. J nuclear medicine 2007; 48:35-45


5. Ann Marre Chacko, Satorus Watznabe et al. 18F-FDG as an inflammation biomarker for imaging dengue virus infection and treatment response. JCL.insight 2017;2;93-107

6. Jinal Hu, fiixin et al. CT findings of severe dengue fever in chest and abdomen.Journal of Radiology and infectious diseases 2015; 2;77-80


