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Nonapoptotic cell death induced by *Hypericum* species on cancer cells

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ABSTRACT

Objectives. There are approximately 400 *Hypericum* species that grow naturally in different geographic origins of the world. Those species have been used in different folk medicines and screened for their biological activity including cancer. Our country is an important place for *Hypericum* species which are known as "kantaron, binbirdelik otu, kan otu, kılıç otu, yaraotu, kuzukıran". We therefore evaluated the possible cytotoxic/apoptotic activities, total phenolic content and antioxidant capacity of the crude methanol extracts *Hypericum adenotrichum* Spach. and *Hypericum olympicum* L. which are still used in Turkish folk medicine. ***Methods.*** The total phenolic content and antioxidant capacity were determined by Folin-Ciocalteu and ABTS methods. Anti-growth effects were screened in human hepatoma (Hep3B) and rat glioma (C6) cell lines by the MTT and ATP viability assays. The cell death mode (apoptosis/necrosis) was investigated by fluorescence imaging and the level of caspase-cleaved cytokeratin 18 (M30), active caspase-3 and cleaved PARP (poly (ADP-ribose) polymerase). ***Results.*** The results indicate that the crude methanol extracts of *Hypericum olympicum* L. and *Hypericum adenotrichum* have both anti-growth/cytotoxic activities on these cells in a dose dependent manner. ***Conclusion.*** These extracts clearly induced non-apoptotic cell death in human hepatoma (Hep3B) and rat glioma (C6) cell lines.

Eur Res J 2017;3(1):1-10

Keywords: *Hypericum olympicum, Hypericum adenotrichum*, cell death, necrosis

Introduction

Cancer is one of serious public health problem worldwide and second cause of death in developed countries. Despite current treatment regimens used clinically, survival rate is far from satisfactory [1]. Resistance to chemotherapy and other targeted therapies is a main problem for cancer research. In this context, there is an inevitable need to newly improved treatment options [2].

Medical plants have wide range usage worldwide and some of them are becoming an important part of clinical practice following screening for anticancer activity [3]. Hence, novel anticancer drugs from

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medicinal plants continue to play a crucial role in human health of the world's population [4].

Hypericum (Guttiferae or Hypericacea) is a large genus of herb with approximately 400 species that grows widely at temperate region of the world and has been used as traditional medicinal plant for hundreds of years. There are 89 *Hypericum* species in our flora of which 43 are endemic [5-7]. Anti-inflammatory, anti-viral, anti-microbial, anti-fungal, anti-depressant, anti-oxidant and cytotoxic activity of different species of *Hypericum* genus have been already identified [8-12]. Moreover, recent studies have reported their antitumor and apoptosis-inducing activity in addition to inhibition of tumor invasion and metastasis [13-18]. The present study was focused on the cytotoxic/apoptotic effect of crude methanol extracts from *Hypericum olympicum* and *Hypericum adenotrichum* (endemic) against on human hepatoma (Hep3B) and rat glioma (C6) cell lines. In addition, we investigated that the total phenolic content and antioxidant capacity of *Hypericum adenotrichum* and *Hypericum olympicum* extracts. This study reports the first time that both *Hypericum olympicum* and *Hypericum adenotrichum* have cytotoxic activity on these cells and trigger cell death in a non-apoptotic manner.

Methods

Plant Materials

Collection, authentication and extraction of *Hypericum olympicum* and *Hypericum adenotrichum* were described previously [19]. The crude extracts of *Hypericum adenotrichum* and *Hypericum olympicum* were dissolved in DMSO as a stock solution (100 mg/ml) and stored at -20ºC. The content of *Hypericum adenotrichum* extract (HAE) and *Hypericum olympicum* extract (HOE) were determined by GCXGC-TOF/MS method in York University, England. The content of *Hypericum olympicum* (unpublished data) and *Hypericum adenotrichum* has been published by Sarimahmut *et al.* [20].

Determination of Total Phenolic Content and Antioxidant Capacity

The HAE and HOE were prepared with mixed of methanol/water (50:50, v/v%) for determination of total phenolic content and antioxidant capacity. The Folin-Ciocalteu assay was used for the quantification of total phenolic content of HAE and HOE [21]. Absorbance at 750 nm was read using a Varian Cary 50, Australia spectrophotometer after incubating the reaction mixtures (Lowry A: 2% aqueous Na_2CO_3 in 0.1 M NaOH; Lowry B: 0.5% CuSO4 aqueous solution in 1% $NaKC_4H_4O_6$ solution; Lowry C: prepared freshly as mixture 50 ml Lowry A and 1 ml Lowry B). Folin-Ciocalteu reagent was diluted with H_2O at a volume ratio 1:3 prior to use. The extracts (0.1 ml), 1.9 ml of H_2O and 2.5 ml of Lowry C solution were mixed and the mixture was let to stand for 10 min. At the end of this period, 0.25 ml of Folin reagent was added at room temperature for 30 min for stabilization of the blue color. The assay was done in duplicate. Results were expressed as mg of gallic acid equivalent (GAE) per g of lyophilized extract.

The total antioxidant capacity HAE and HOE were determined with ABTS method, as described by Sahin *et al.* [22]. The working solution was prepared by mixing two stock solutions of 20 mM ABTS and 2.45 mM potassium persulfate solution and allowed to react for 12–16 h at room temperature in the dark before use. The procedure for HAE and HOE were performed by adding 0.10 ml extract, 3.90 ml of ethanol and 1 ml of the $ABTS^+$ radical cation solution, which was diluted with ethanol at a ratio of 1:10, and the absorbance at 734 nm was recorded against blank after 6 min. The results were expressed as milligram Trolox equivalent (TE) per gram of lyophilized extract.

Cell Culture and Treatments

Human hepatoma (Hep3B) and rat glioma (C6) cell lines were cultured in RPMI 1640 supplemented with L-glutamine, 10% fetal bovine serum, penicillin G (100 U/ml) and streptomycin (100 µg/ml) at 37ºC in a humidified atmosphere containing 5 %CO_2. Further dilutions of extracts dissolved in DMSO were made in culture medium to obtain the various concentrations ranging from 1.56 to 100 µg/ml. The highest concentration of DMSO did not exceed 0.1% (v/v) in the cell culture and the untreated/control cells received vehicle only (0.1% DMSO).

The MTT Viability Assay

The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay was used to determine drug sensitivity of cells based on the linearly correlation between the number of viable cells and mitochondrial activity [23]. Hep3B and C6 cells were seeded in a 96-well plate at a density of $1x10^4$ cells/per well and subsequently treated with HAE and

HOE at the range of 1.56-100 µg/ml for 72 h. Each experiment was conducted twice in triplicates. At the end of the treatment period, 1:10 volume of MTT solution (5 mg/ml) was added to each well and allowed to formation of soluable formazan crystals by the living cells at 37ºC for an additional 4 h. 100 µl of solubilizing buffer (10% sodium dodecyl sulfate dissolved in 0.01 N HCl) was added to dissolve all crystals. After overnight incubation, the absorbance (Abs) was read by a spectrophotometer (FLASH Scan S12, Analytik Jena, Germany) at 570 nm and cell viability was determined by using the following formula: Cell viability (%) = [100 x (Sample Abs)/(Control Abs)].

ATP Viability Assay

The ATP assay was used to determine the level of cellular ATP as an indirect marker in the assessment of cell viability and to verify the MTT results because of its sensitivity [24]. The seeding of cells, treatment conditions and the calculation of viability were all performed same as the MTT assay (see above). At the end of the treatment period, the ATP content of metabolically active cells was determined through the extraction of ATP from the cells following addition the luciferin-luciferase solution for luminometric measurement by using the ATP Bioluminescent Somatic Cell Assay Kit (Sigma, St. Louis, MO, USA) according to the manufacturer's recommendations. The luminescence signal was measured at luminometer (Bio-Tek, USA).

Determination of Cell Death Mode

Caspase-Cleaved Cytokeratin 18 (M30) Detection

The level of the apoptosis-specific epithelial cell-derived caspase-cleaved cytokeratin 18 (ccK18, M30) was determined by using M30 Cytodeath ELISA kit (Peviva, Bromma, Sweden) according to the manufacturer's instructions. Hep3B cells were seeded at a density of $1x10^4$ per well of 96-well plate in triplicate and treated with 100 µg/ml of HAE and HOE for 72 h to obtain maximum cell death. C6 rat glioma cell line was excluded in this assay because M30 assay detects only human-origin antigens. Paclitaxel (3.12 µM) was used as a positive control for apoptosis.

Measurement of Active Caspase-3 and Cleaved PARP Levels

The levels of the active caspase-3 and cleaved PARP (poly(ADP-ribose) polymerase) associated with the apoptotic process were determined using human caspase-3 (active) ELISA kit (Invitrogen Corporation, Camarillo, CA) and PARP Cleaved [214/215] ELISA kit (Invitrogen, CA) according to the protocols described in the manufacturers' instructions. $1x10^6$ Hep3B cells were seeded in 25 cm^2 flasks and subsequently treated with 100 µg/ml of the HAE and HOE for 72 h. Each experiment carried out in twice and results were given as fold change.

Fluorescence Imaging of Nucleus and Annexin V-FITC Staining

Phosphatidylserine translocation to the outside of the plasma membrane as an early apoptotic event was analyzed using the Annexin-V-Fluos kit (Roche, Mannheim, Germany). Propidium iodide (PI, 1 µg/ml) was used for the assessment of cells with damaged membranes due to primary necrosis or late apoptosis (secondary necrosis). Hoechst dye 33342 (5 µg/ml) was also added to the staining solution to evaluate apoptosis based on the nuclear morphology as described previously [25]. Hep3B and C6 cells were seeded at a density of $1x10^4$ cells per well of 96-well plate and treated with HAE and HOE (50 and 100 µg/ml) for 48 h. Cells were visualized under fluorescence microscope after staining and considered as following:

-*Viable cells:* Annexin-V (-) and PI (-) as well as without nuclear pyknosis and/or chromatin condensation.

-*Early apoptotic cells:* Annexin-V (+) and PI (-) as well as with nuclear pyknosis and/or chromatin condensation.

-*Late apoptotic cells:* Annexin-V (+) and PI (+) as well as with nuclear pyknosis and/or chromatin condensation.

-*Non-apoptotic cells:* Annexin-V (-) and PI (+) as well as without nuclear pyknosis and/or chromatin condensation.

Statistical Analysis

All statistical analyses were performed using the SPSS 20.0 statistical software package for Windows. Significance was calculated using one-way analysis of variance (ANOVA). A value of $p<0.05$ was considered statistically significant. The results are expressed as the mean ±SD (Standard deviation).

Results

Total Phenolic Content and Antioxidant Capacity of

Hypericum olympicum and Hypericum adenotrichum Extracts

Total phenolic content of HAE and HOE were determined spectrometrically according to the Folin-Ciocalteu method and calculated as gallic acid equivalents (GAE). Total phenolic content was found 235±12 mg GAE/g for HAE and 333±13 mg GAE/g for HOE. Total phenol content was also determined in comparison with standard tannic acid. The potential antioxidant capacity of the extract was determined as milligrams TE/g lyophilized extract by ABTS method. Antioxidant capacity was found 303±5 mg TE/g for HAE and 725±2 mg TE/g for HOE. We showed that the total phenolic content and antioxidant capacity of HOE was considerably higher in HOE than HAE.

Anti-Growth Activities of Hypericum olympicum and Hypericum adenotrichum Extracts

Anti-growth activities of HAE and HOE against Hep3B and C6 cells were displayed in Figure 1,2 and

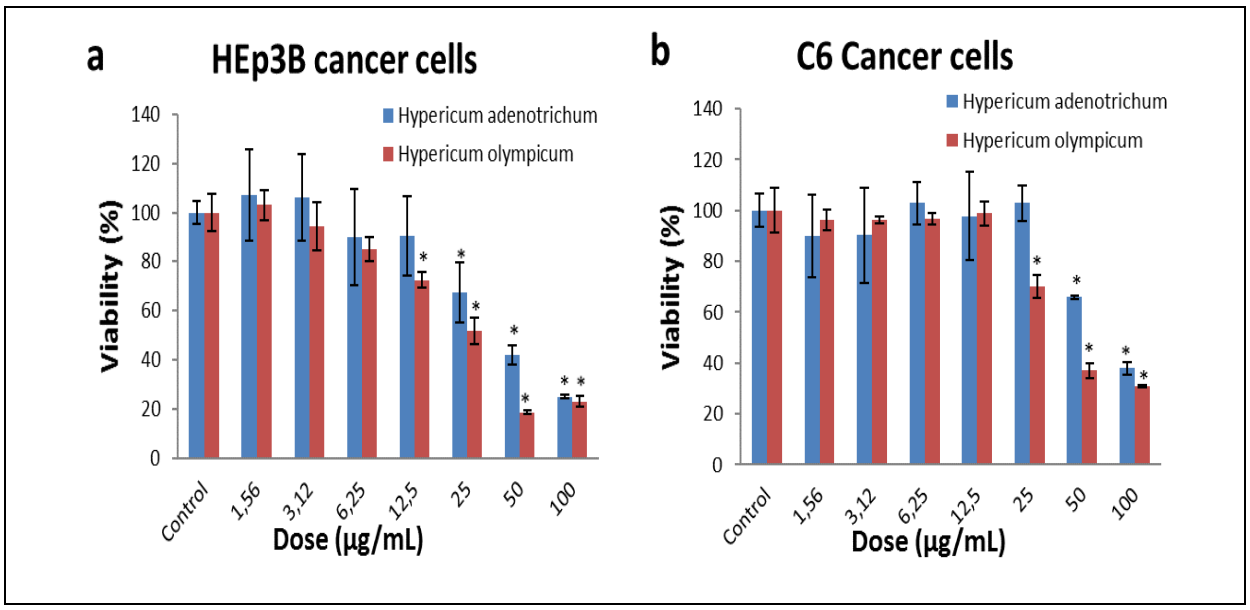

Figure 1. The anti-growth effects after the treatment with varying doses of *Hypericum adenotrichum* extract and *Hypericum olympicum* extract for 72 h against Hep3B (a) and C6 (b) cancer cell lines by the MTT assay. *Denotes statistically significant differences in comparison with control (p<0.05).

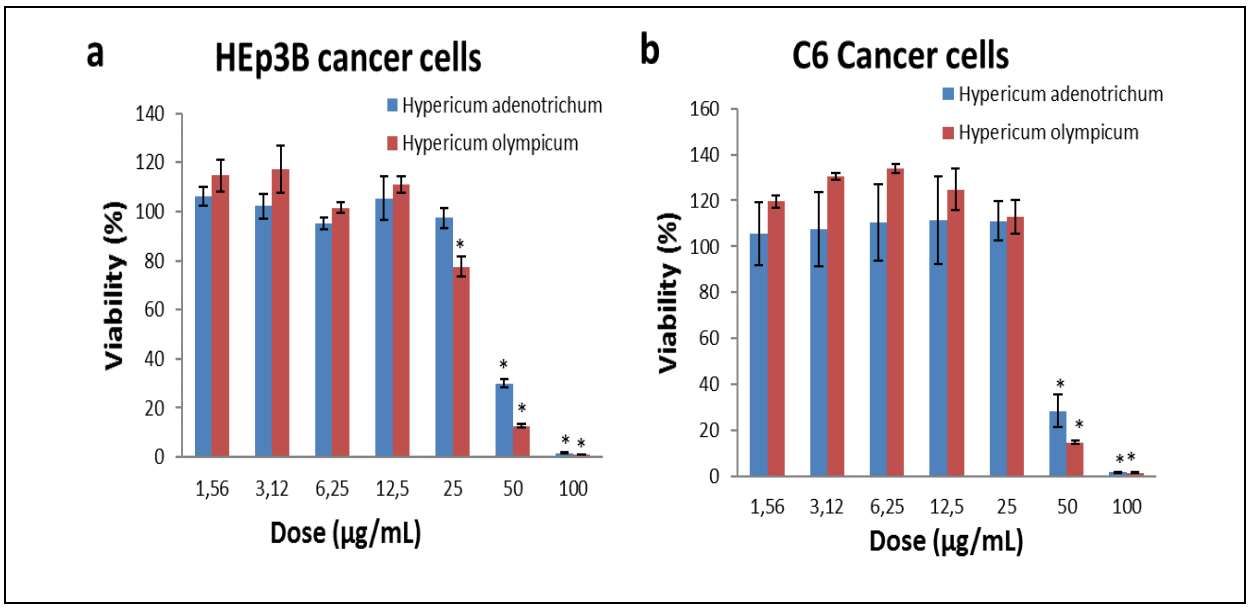

Figure 2. The anti-growth effects after the treatment with varying doses of *Hypericum adenotrichum* extract and *Hypericum olympicum* extract for 72 h against Hep3B (a) and C6 (b) cancer cell lines by the ATP assay. *Denotes statistically significant differences in comparison with control (p<0.05).

Table 1. The IC_{50} and IC_{90} values of the *Hypericum adenotrichum* extract (HAE) and *Hypericum olympicum* extract (HOE)

Cell Line	Extact	MTT Assay		ATP Assay	
		*IC_{50} (µg/ml)	**IC_{90} (µg/ml)	*IC_{50} (µg/ml)	**IC_{90} (µg/ml)
Hep3B	**HAE**	42.04	>100	42.60	85.28
	HOE	26.30	>100	35.62	61.84
C6	**HAE**	78.38	>100	43.46	84.44
	HOE	40.17	>100	41.02	68.23

IC_{50}** is defined as the dose inhibiting 50% of viability, *IC_{90}** is defined as the dose inhibiting 90% of viability

Table 1. Cancer cells treated with increasing doses of HAE and HOE (1.56-100 µg/ml) for 72 h resulted in explicit decrease of cell viability in a dose-dependent manner. According to MTT assay results, the cell viability is significantly reduced at 25, 50 and 100 µg/ml doses (p<0.05) (Figure 1). On the other hand, results obtained from ATP assay revealed that cell viability is reduced more significantly at 50 and 100 µg/ml doses (p<0.05) (Figure 2) in Hep3B and C6 cell lines. HOE exhibited much better cytotoxic effect with IC_{50} value of 26.30 µg/ml whereas HAE with IC_{50} value of 42.04 µg/ml in Hep3B cells. However, the higher IC_{50} values were determined in C6 cells after treatments with HOE (40.17 µg/ml) and HAE (78.38 µg/ml) (Table 1).

Based on morphological evaluation by phase contrast microscopy, prominent cytotoxic activity was observed in both Hep3B and C6 cells with HAE and HOE (100 µg/ml, 72 h), respectively (Figure 3). These examinations were found in accordance with the viability results.

Non-apoptotic Cell Death Induced by Hypericum adenotrichcum and Hypericum olympicum Extracts

Following determination of potential anti-growth activity of HAE and HOE (100 µg/ml) in cancer cells, we further investigated the mode of cell death at first by fluorescence imaging based on nuclear morphology. In this context, cells were incubated with Hoechst dye 33342, which stains both alive and dead cells after treatment with HAE and HOE (50 and 100 µg/ml) for 48 h. We observed that the nucleus of dying cells does not have pyknosis and/or chromatin condensation, which are well-known features of apoptosis. Subsequent evaluation of phosphatidylserine (PS) translocation to the outside of membrane as a hallmark of early apoptosis was performed via Annexin V-FITC staining in addition to

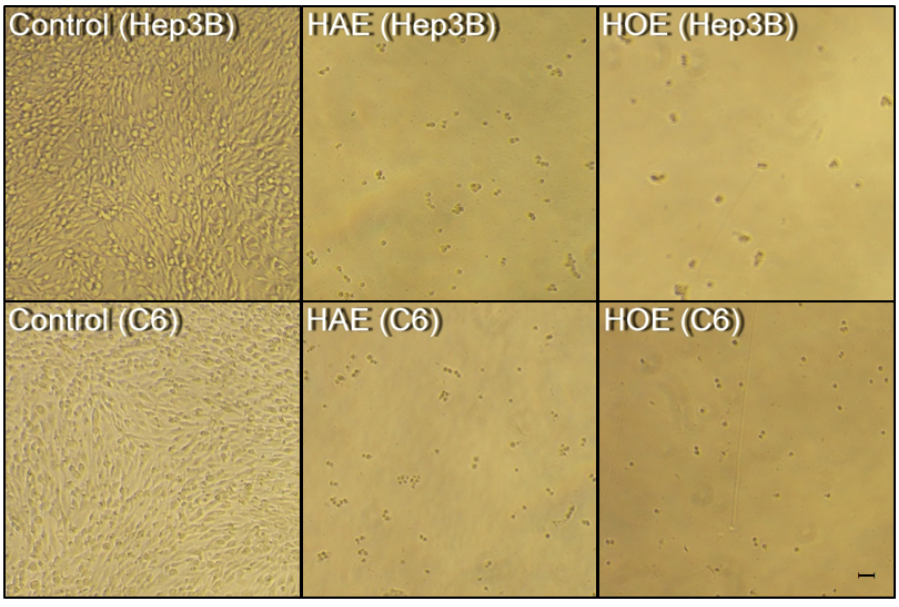

Figure 3. Images of Phase Contrast Microscopy. Cells were treated with 100 µg/ml *Hypericum adenotrichum* extract (HAE) and *Hypericum olympicum* extract (HOE) for 72 h. Controls included untreated cells. A scale bar represents 10 µm.

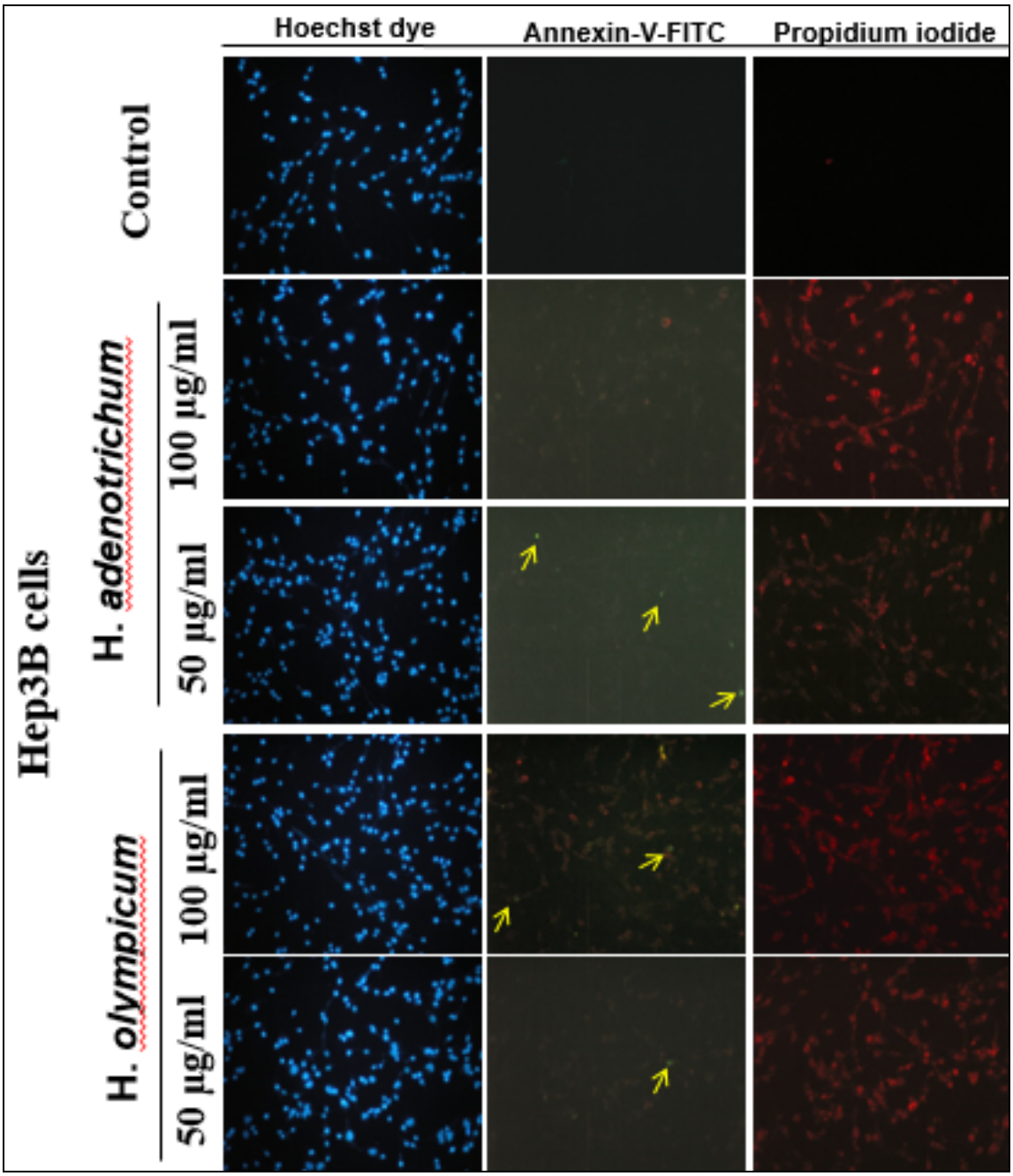

Figure 4. Fluorescence images of nuclei stained with Hoechst dye 33342 (left column, blue), Annexin-V-FITC (middle column, green) and propidium iodide (right column, red) after treatment with 50 and 100 µg/ml *Hypericum adenotrichum* and *Hypericum olympicum* for 48 h in Hep3B cells. Yellow arrows show the presence of Annexin-V-FITC staining.

PI staining in the assessment of plasma-membrane integrity. We observed prominently increment in the PI stained cells compared only Annexin-V-FITC stained cells (early apoptotic cells) as well as positivity for both of them (Annexin +/PI+) indicating late apoptotic and/or necrotic cells (Figures 4 and 5). When considering the lack of pyknosis and/or chromatin condensation, we suspected that the cells were actually dying by necrosis. Activation of caspases and presence of the caspase cleaved cytokeratin 18 (ccK18, M30) and/or cleaved poly (ADP-ribose) polymerase (PARP) are also hallmarks of apoptosis. As shown in Figure 6, we found that neither the caspase activation nor the cleavage of CK18 and PARP occur after treatment with HAE and HOE (100 µg/ml), implying that these cells do not undergo apoptosis with this treatment (Figure 6).

Discussion

Cancer is a serious ailment that has been estimated as the second leading cause of death in humans [26].

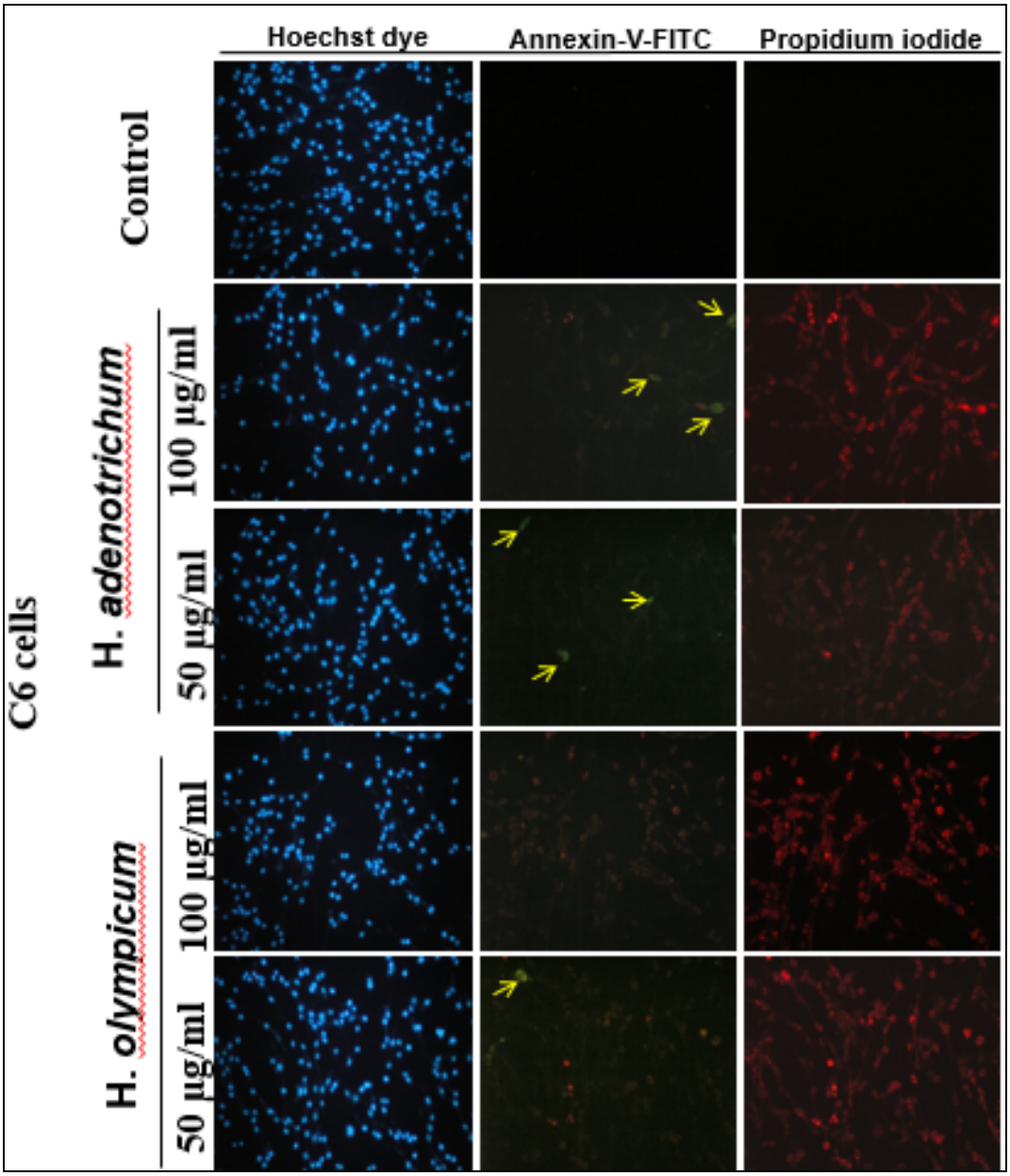

Figure 5. Fluorescence images of nuclei stained with Hoechst dye 33342 (left column, blue), Annexin-V-FITC (middle column, green) and propidium iodide (right column, red) after treatment with 50 and 100 µg/ml *Hypericum adenotrichum* and *Hypericum olympicum* for 48 h in C6 cells. Yellow arrows show the presence of Annexin-V-FITC staining.

For this reason, there has been an extensive research on various biological sources for an effective treatment. In this regard, natural products as a source of effective anti-cancer agents have attracted considerable attention from scientists. Today, a substantial number of anticancer agents used in the clinic are derived from natural sources including plant [27, 28]. Since the plants are used in traditional medicine worldwide and several have been screened for their anticancer properties, we evaluated the possible cytotoxic activities of the *Hypericum adenotrichum* (endemic) and *Hypericum olympicum*, which are still used in Turkish folk medicine. In addition, we investigated that the total phenolic content and antioxidant capacity of *Hypericum adenotrichum* and *Hypericum olympicum* extracts. We found that the total phenolic content and antioxidant capacity were considerably higher in HOE than HAE. To our knowledge, there is no data the phenolic content and antioxidant capacity of HAE and HOE in literature. Therefore, we performed a detailed literature review of the *Hypericum* genus. Alipour *et al.* [29] showed that the total phenolic content of extract of *Hypericum fursei* was exhibited 274 ± 9.6 mg GAE/g. The total phenolic content of water extracts of *Hypericum undulatum* was found to be

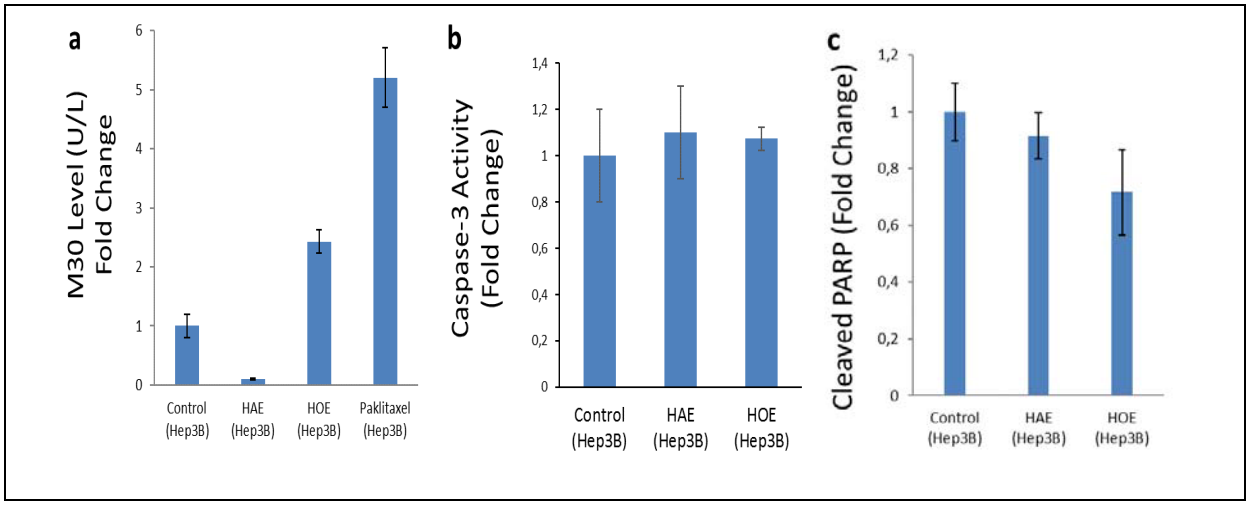

Figure 6. Apoptosis-inducing activities of HAE and HOE on Hep3B cancer cells. M30 levels (U/L) (a) Caspase-3 activity (b) and PARP cleavage (c) after treatment with 100 µg/ml *Hypericum adenotrichum* extract (HAE), *Hypericum olympicum* extract (HOE) and 3.12 µM Paclitaxel (as a positive control) for 72 h.

ranged from 119.90 to 191.77 mg GAE/g TE [30]. Zorzetto *et al.* [31] determined the antioxidant capacity of *Hypericum* species by ABTS method and found 251.2±29, 218.3±9.4, 323.1±49.9 and 766.5±43.3 µmol/g TE for *Hypericum reflexum Ifonche, Hypericum reflexum La Esperanza, Hypericum canariense* and *Hypericum grandifolium* respectively.

There are several studies on the anticancer activity of various *Hypericum* species against different type of cancer. For example, in a study, the protective effects of water extracts of *Hypericum perforatum*, *Hypericum androsaemum* and *Hypericum undulatum* were shown in colon cancer cells [32]. *Hypericum sampsonii* extract was found anti-growth and apoptotic effects on lung, liver and stomach cancer cells [33]. *Hypericum perforatum* extract have showed significantly inhibited prostate tumor growth [34]. Recently, Li *et al.* [14] examined that *Hypericum ascyron* extract has cytotoxic activity against different cancer cell lines. In our previously study, we demonstrated that the extract of *Hypericum adenotrichum* and *Hypericum olympicum* have cytotoxic activity on lung cancer cells by inducing apoptosis [19]. In this study, we showed that HAE and HOE exhibited significant anti-growth activity against human hepatoma (Hep3B) and rat glioma (C6) cell lines in a dose dependent manner. HOE was found more effective to cancer cells than HAE as the IC_{50} value (Table 1). The cytotoxic effects of HAE and HOE may be due to composition of plants. It is known that *Hypericum adenotrichum* and *Hypericum olympicum* contains compounds such as hypericin, pseudohypericin, hyperforin [35, 36]. Hypericin and hyperforin have a potent cytotoxic effect through inducing apoptosis in cancer cells [37, 38].

In our study, we investigated the mode of cell death resulted from HAE and HOE (50 and 100 µg/ml) for 48 h by fluorescence imaging. Late apoptotic/necrotic cells (positivity for PI staining, and negativity for Annexin-V-FITC staining) were observed both in HAE and HOE treatments. Also, it is showed that the nucleus of cells did not have pyknosis and/or chromatin condensation, any increment of PARP and M30 level in Hep3B and C6 cancer cells after treatment. These results demonstrated that the cells dying by necrosis after the treatment with HAE and HOE. In our previously studies, we found that HAE and HOE have cytotoxic effects by inducing apoptosis in human breast and lung cancer cells [19, 20]. In another study, Ozmen *et al.* [39] reported that petroleum ether extract of *Hypericum adenotrichum* induced apoptosis through on caspase 3 activation and PARP cleavage in HL-60 cells. It has implied that HAE and HOE may induce different cell death modes in different cell lines. The possible reasons for this outcome may be related to the genetic and phenotypic differences between the cell lines.

Conclusions

In conclusion, *Hypericum adenotrichum* and

Hypericum olympicum have potential anti-growth activity against human hepatoma (Hep3B) and rat glioma (C6) cell lines and they induce cell death via necrosis. Therefore, the potential cytotoxic activity of these plants needs further in vitro and in vivo experiments to elucidate the mechanism of action.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Preventive effect of selenium pretreatment against cisplatin-induced oral mucositis in rats

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ABSTRACT

Objectives. The aim of the present study was to investigate the protective role of selenium against cisplatin-induced oral mucositis in rats. ***Methods.*** Healthy wistar albino rats (n=21) were randomly divided into three groups: Cisplatin (Cis), cisplatin and selenium (Cis+Se) and control (C). Cisplatin was administered for 3 days to Cis and Cis+Se groups. Cis+Se group received selenium 5 days before cisplatin injection and continued for 11 consecutive days. Malondialdehyde (MDA) levels of the rats were determined before and at the end of experimental protocol. The tongues of rats were harvested for immunuhistochemical examinations. ***Results.*** In biochemichal analysis, MDA levels significantly increased in the Cis group (p=0.018). On the contrary, there was no significant difference between pretreatment and posttreatment MDA levels in Cis+Se group (p=0.128). In the immunohistochemical examinations of lingual tissues stained with anti-caspase-3, when the Cis and Cis+Se groups were compared, there were significantly more immunopositivity in the Cis group and significantly less immunopositivity in the Cis+Se group (p<0.05). ***Conclusions.*** Selenium might have played a protective role against cisplatin-induced oral mucositis in rats. Further studies are necessary before its clinical use in patients.

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Keywords: Cisplatin; oral mucositis; selenium; toxicity

Introduction

Oral mucositis is a common side effect of chemotherapy and radiotherapy regimens and has negative effects on patient's quality of life. It may cause swallowing and nutrition difficulty on patients; accordingly it may require parenteral nutrition by leading to anorexia, cachexia, dehydration and malnutrition [1]. Oral mucositis results in chewing, swallowing and speech difficulties due to edema and inflammatory lesions in the mouth. In some patients these side effects may necessitate termination or reduction of the chemotherapy dose [2]. Due to increased preference of chemotherapy and radiotherapy especially in treatment of patients with head and neck malignancy, mucositis is a serious

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problem in these patients and needs for the solution of this problem increased in recent years [3]. Cisplatin is an effective chemotherapeutic drug for a variety of malignant solid tumors including head and neck cancers, lung cancers, esophageal cancers, osteosarcoma, urogenital system cancers, central nervous system tumors, and neuroblastoma [4, 5]. The well-known toxicities of cisplatin are nephrotoxicity, myelotoxicity, neurotoxicity, ototoxicity, and gastrointestinal toxicity. Oral mucositis is one of the toxic effects of cisplatin. The rate of oral mucositis is increased when combined with radiotherapy. Generation of oxidative stress and reactive oxygen species by cisplatin is the primary accepted event in most pathways leading to mucositis and other side effects [6, 7]. Therefore, the effects of various antioxidants were evaluated for the prevention of cisplatin-induced oral mucositis [8]. But any accepted treatment modality entered into clinical use has not been developed yet.

Selenium plays an important role in cellular redox state regulation and essential to the function of glutathione peroxidase, because it is a structural component of the active site of selenoenzyme which has critical role in protecting cellular components from oxidative damage [6-8]. Although protective effect of selenium against some side effects of cisplatin has been shown previously, as much as we know, this is the first study investigating the efficacy of Se against cisplatin-induced oral mucositis.

Methods

Animals and experimental design

The study's protocol was approved by the institutional animal care and use committee, and the animals were treated in accordance with protocols approved by this committee. Twenty-one adult male Wistar albino rats weighing 280-300 g were used. All of the rats were maintained under conditions of 12 h light/dark cycle environment (lights on 07:00 AM-07:00 PM) at a temperature of 22±1°C and 50% humidity. Rats had free access to food and water ad libitum. The rats were randomly divided into the following three groups (n=7 in each group): Cisplatin (Cis), cisplatin and selenium (Cis+Se) and control (C). Cisplatin (Sigma–Aldrich Co, Germany) was administered to rats in the Cis and Cis+Se groups at a dose of 12 mg/kg body weight/day, intraperitoneally for 3 consecutive days. Moreover, 3 mg/kg body weight/day selenium (sodium selenite, Sigma–Aldrich Co, Germany) was given by oral gavage to rats in the Cis+Se group twice a day as 1.5 mg/kg for 11 consecutive days, starting 5 days before cisplatin administration. On the other hand, the C group received only saline intraperitoneally and orally at the same volume and the same time. Before and after treatment, blood samples of animals were collected for biochemical analysis. At the end of the experimental protocol, the animals in all groups were sacrificed under anesthesia using 30 mg/kg of ketamine (Ketalar®, Eczacibasi, Istanbul, Turkey) and 4 mg/kg xylazine (Rompun®, Bayer, Istanbul, Turkey). Their tongues were excised for pathological and immunohistochemical examinations. All surgical procedures were performed with sterilized instruments.

Lipid peroxidation assay

Malondialdehyde (MDA) values were measured for the evaluation of lipid peroxidation. Thiobarbituric acid (TBA) reaction was used as described previously in the literature (16). The principle of the method depends on the evaluation of the pink color appeared by the TBA and MDA interaction. The pink color absorbance was measured at 532 and 520 nm. MDA levels were measured as nmol/mg protein.

Histological and immunohistochemical analysis

The tongues of the rats were fixed in 10% neutral buffered formalin for 24 h at +4C temperature. Afterwards, the specimens were embedded in paraffin and then mounted in order to obtain multiplane cuts. Sections of 4 μm of thickness were collected on glass slides and stained with haematoxylin and eosin. Immunohistochemical staining was performed by using the DAKO Autostainer Universal Staining System (Autostainer Link 48 DAKO, Glostrup, Denmark). Firstly, the sections with the thickness of 4 μm were taken onto positively charged lames. Then, the sections, which were de-paraffinised with xylol, were exposed to an alcohol series and dehydrated. Afterwards, antigen retrieval was conducted in the thermostatic bath at 96°C (10 mM/L citrate buffer, pH: 6) for 40 minutes (PT Link). Sections were incubated with Caspase-3 (CPP 32-Novocastra™ Lyophilised Mouse Monoclonal Antibody Product Code; NCL-(CPP 32): by using the tonsil tissue recommended by the Premier antibody manufacturer as a positive

control tissue) for 60 minutes. An automation system was used with the Streptavidin-biotin immunoperoxidase technique (K8000 Envision Flex, DAKO, Glostrup, Denmark). Immunoreactions were shown with Diaminobenzidin tetrachloride (DAB) in order to obtain the view that would give the color. Negative staining was applied to the sections with haematoxylin for ground staining. Sections were respectively exposed to an alcohol series at increasing proportions for dehydration and covered with balsam in the automatic tissue closing device after the transparentation in xylol. Following the staining step, the sections were examined by only one pathologist, blind to clinical information, under the light microscope (Olympus BX51, Tokyo, Japan) and at the magnifications 4, 10, 20 and 40. Considering the number of the cells stained without taking the staining density into account, the following assessment was made in the histopathologic examination: 0=no staining (less than 5% of the cells stained, +=slight (5-10% of the cells stained), ++=medium (11-20% of the cell stained), and +++=severe (staining of more than 20%).

Statistical Analysis

Data analysis was performed using the statistical package for the social sciences (Version 16; SPSS, Chicago, IL). Values of $p<0.05$ were considered statistically significant. Mann-Whitney U and Kruskall-Wallis tests were used in the comparison of inter group measurements. Comparisons of pretreatment and posttreatment measurements were performed by Wilcoxon signed-rank test.

Results

The MDA levels measured before and after treatment are shown in Table 1. In biochemichal analysis, MDA levels significantly increased in the Cis group rats ($p=0.018$). On the contrary, the treatment with selenium decreased the elevation of MDA levels in Cis+Se group rats and there was no statistically significant difference between pretreatment and posttreatment MDA levels in this group ($p=0.128$) (see Table 1).

In the immunohistochemical examinations of lingual tissues stained with anti-caspase-3 antibody, there were no immunopositive cells in the lingual tissues of the control group, however, a significantly higher degree of immunopositivity was found in tissues of the Cis group. In the Cis group, 14.2% of specimens showed no staining, 42.9% of specimens showed medium staining (+), and 42.9% of specimens showed medium staining (++). Fewer immunopositive cochlear cells were found in the Cis+Se group compared to the Cis group. In the Cis+Se group, 71.4% of specimens showed no staining (0), 28.6% of specimens showed slight staining (+). When the Cis+Se group and Cis group were compared, significantly less immunopositivity occurred in the Cis+Se group ($p<0.05$). Semi-quantitative scores and evaluation for the immunopositive cochlear cells are presented in Table 2.

Discussion

Oral mucositis frequency reported in the literature varies between 30-40% and 100% in different series. Since there are no standardized scoring systems, there are no sufficient data about prevalence and incidence of oral mucositis based on chemotherapy and/or radiotherapy [9, 10]. In patients undergoing hematopoietic system transplantation, this rate is about 65-85%, in conventional chemotherapy patients 20-40%, and in head and neck radiotherapy patients it is about 100% [11, 12]. Severity and duration of

Table 1. Pre- and posttreatment malondialdehyde values of groups

	Cis group (n=7)	Cis+Se group (n=7)
Mean MDA value, nmol/mg (Pretreatment)	12.60	15.40
Mean MDA value, nmol/mg (Posttreatment)	20.67	16.00
p	0.018*	0.128

*Wilcoxon signale-ranked test. Cis=cisplatin, Cis+Se=cisplatin+selenium

Table 2. Evaluations and semi-quantitatively scoring of immunopositive cells in the lingual tissues of all groups

	Cis group		Cis+Se group		C group		Total	
	n	%	n	%	n	%	n	%
0	1	14.2	5	71.4	7	100.0	13	61.9
+	3	42.9	2	28.6	0	0.0	5	23.9
++	3	42.9	0	0.0	0	0.0	3	14.2
+++	0	0.0	0	0.0	0	0.0	0	0.0
Total	7	100.0	7	100.0	7	100.0	21	100.0

Cis=cisplatin, Cis+Se=cisplatin+selenium, C=control, n=the number of rats, 0=no staining, +=slight staining, ++=medium staining, +++=severe staining

mucositis varies depending on the received chemotherapy and concomitant radiotherapy. The risk factors in development of oral mucositis are based on chemotherapy drug and dosage and mode of therapy (radiation, chemotherapy, or combined chemo-radiotherapy) applied to patient. Due to morbidity caused by oral mucositis in patients having cancer therapy, many agents have been tried for prevention of this toxicity. One of the drugs used to prevent mucositis development is a free-radical scavenger amifostine. It is an agent showing mucoprotective effect by reducing salivary gland damage and oral dryness. However results of studies conducted with amifostine are conflicting [13, 14]. Other agent studied for prevention of mucositis is N-acetyl cysteine having antioxidant activity. It is shown that N-acetyl cysteine reduces the incidence and duration of severe mucositis [15]. Palifermin (keratinocytes growth factor 1) is an agent used to prevent from formation of oral mucositis. Ability of palifermin to inhibit mucosal damage capability depends on its effects on glutathione activity also it reduces oxygen-free radical damage by upregulating palifermin NRF 2 and exhibit anti apoptotic effect [16]. In addition to palifermin, studies for prevention of mucositis continue on growth factors such as sargramostim, filgrastim, and velafermin. Although there are studies conducted on drugs that increase TNF production and inflammatory cytokines such as benzydamine HCL and pentoxifylline, results are controversial [17]. Despite all these studies oral mucositis continues to exhibit serious toxicity that may increase morbidity during treatment of cancer patients and lead to disruptions in the treatment process. Therefore there is a need for new studies on the subject and the development of new treatment modalities.

The mechanism of cisplatin-induced oral mucositis is not completely understood, however many studies have suggested that toxic effects of cisplatin are related to the depletion of antioxidant enzymes (glutathione reductase, superoxide dismutase and glutathione peroxidase) with an increase in lipid peroxidation (MDA levels) [18]. Increased MDA levels may activate caspases pathway resulting in breakdown of DNA and apoptosis [19]. Caspase-8 and caspase-9 activates caspase-3, resulting in chromosomal DNA fragmentation and the cellular morphological changes of apoptosis. Activated caspase-3 is important for morphological changes in apoptotic cells and plays a pivotal role in the terminal phase of apoptosis [20, 21]. The results of this study showed that, the administration of cisplatin resulted in an increase in MDA levels, which is partially inhibited by selenium pretreatment. Moreover cisplatin treatment increased caspase-3 expression, which was significantly inhibited by selenium treatment, suggesting that selenium decreased cisplatin-induced lipid peroxidation and cell death in the oral mucosal tissues of rats.

Conclusions

To our knowledge, this is the first study that investigates the preventive effect of selenium against cisplatin-induced oral mucositis. It is our opinion that selenium might have played a protective role against cisplatin-induced oral mucositis in rats, as shown with biochemical and immunohistochemical analyses. Although the results confirmed that selenium reduced cisplatin-induced apoptosis in the oral mucosal tissues of rats and prevented oral mucositis, its clinical utility in patients remains uncertain. Finally, further studies before its clinical use against cisplatin-induced oral mucositis in patients are required.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Incidence and risk factors of contrast-induced nephropathy after diagnostic or interventional coronary angiography

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ABSTRACT

Objectives. Contrast-induced nephropathy (CIN) is the third most common cause of acute renal failure that occurred in the hospital. In Turkey, there is not enough data about the frequency of CIN in cardiological interventions. Increased contrast volume and creatinine value are related with CIN. We also investigated the CIN predictors. ***Methods.*** A total of 2604 patients who underwent coronary angiography or percutaneous coronary intervention (PCI) in our hospital were prospectively evaluated in terms of CIN. The definition of CIN includes absolute (≥0.5 mg/dl) or relative increase (≥25%) in serum creatinine at 48-72 h after exposure to a contrast agent compared to baseline serum creatinine values. ***Results.*** CIN was detected in 13.6% (355 patients) of 2604 patients. According to the procedure; CIN rate was 13.3% (280 of 2108 patients) in coronary angiography, 13.08% (50 of 382 patients) in elective PCI and 21.49% (25 of 114 patients) in primary PCI. Compared with each of these three groups patients, CIN rate was significantly higher in primary PCI group than coronary angiography (p=0.009) and elective PCI (p=0.02) groups. In multivariate analysis, age (odds ratio [OR]=1.04; 95% confidence interval [CI], 1.02-1.06; p<0.001), glomerular filtration rate (OR=0.99; 95% CI, 0.98-0.99; p<0.001), contrast volume (OR=1.14; 95% CI, 1.007-1.21; p<0.006), contrast volume to creatinine ratio (OR=1.01; 95% CI, 1.009-1.02; p<0.001), three vessel disease (OR=1.77, 95% CI, 1.24-2.51; p=0.001) were independent predictors of CIN. ***Conclusions.*** In our patient population, the incidence of CIN was found to be 13.6% in cardiological interventions. In emergency interventions, incidence of CIN was increased. We found that contrast volume to creatinine ratio is predictor of CIN.

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Keywords: Contrast-induced nephropathy; coronary angiography; percutaneous coronary intervention; renal failure; contrast media

Introduction

Contrast-induced nepropathy (CIN) is one of the cause of acute kidney injury which developes after use of intravascular contrast agent and which can not be defined by another reason. Today, because of the

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increasing cardiovascular procedures, the use of contrast agent has increased, as well. The actual CIN incidence is not known exactly, the frequency ranges between 1% and 25% in terms of the used CIN definition and preprocedural renal functions [1]. Although the mechanism of CIN development is being complicated, direct toxic effects of contrast agent for the renal cells and developing medullary ischemia and metabolic changes as a result of renal glomerular hemodynamic changes are the basis of pathophysiology. Studies have shown that CIN is the third most common cause of acute kidney injury in hospital [2]. The duration of hospitalization is prolong in patients with CIN because of needing renal replacement therapy. In this group of patients, morbidity and mortality frequency is increasing [2]. The main factors that influence the incidence of CIN are older age, pretreatment decrease in renal function (decreased glomerular filtration rate [GFR], increased creatinine level), heart failure, hypertension, diabetes mellitus, contrast volume, contrast osmolarity and ionic charge of contrast agents [1, 2]. Among the factors, changes may be done only in amount and features of contrast agent but it is not possible to change other risk factors. For this reason, numerous studies have been carried out to prevent and predict CIN. But, apart from hidration, benefit of other treatment modalities is still controversial. The use of contrast agents for diagnosis and treatment along with advances in interventional cardiology is rapidly increasing with each passing day. But, there is not enough study in our country in which cardiological interventions related CIN was evaluated. Therefore, we investigated the incidence of CIN that due to invasive cardiac procedures in our clinic and the predictive value of contrast volume to creatinine ratio.

Methods

Patient Selection

A total of 2604 patients who underwent coronary angiography or percutaneous coronary intervention (PCI) in our hospital were prospectively included in the study between January 2010 and February 2012. Patients with chronic kidney disease and, as a result, to whom hemodialysis or peritoneal dialysis was applied and patients who were given to bypass surgery within 48 hours, patients who were included the study before were excluded from the study. Elective PCI defined as; the patients who coronary angiography performed at least 1 week before. All patients gave written inform consent that was approved by Bursa Yuksek Ihtisas Training and Research Hospital Ethics Committee protocol.

Study Patients

The demographic characteristics of the patients were examined and physical examinations were performed. Before the process, patients' biochemical values, risk factors were recorded and blood preassure of each patient was measured. Patients whose sistolic blood pressure (SBP) ≥140 mmHg, or whose diastolic blood pressure (DBP) ≥90 mmHg and patients who use anti-hypertensive medication were accepted as hypertension. Patients were defined as diabetic if fasting blood glucose level was ≥126 mg/dL blood on two consecutive measurements or if they used oral antidiabetics/insulin. In accordance with echocardiographic evaluation, patients whose ejection fraction was below 40% were accepted as systolic heart failure.

Weight and height measurements of patients were made. Body mass index (BMI) were calculated according to body weight (kg)/height of the square (m2). GFR was calculated with Cockcroft-Gault formula; [(140-age) x body weight (kg)] / [72 x serum creatinine] (if women x 0.85) [3]. If serum creatinine values were ≥1.5 mg/dl, intraveneous hydration was performed with 0.9% sodium chloride (1 ml/kg/h) before the procedure in elective coronary angiography and elective PCI cases. The hydration dose was reduced (0.5 ml/kg/h) in patients with heart failure. Drugs of the patients were not modified before the procedure. The contrast volume to creatinine ratio was calculated as; used contrast volume/baseline creatinine level.

Interventional Procedure

All coronary angiography and percutan coronary interventions were performed with transfemoral approach. Over 50% stenosis on coronary angiography was accepted as a lesion. Before the PCI, 10.000 unit bolus heparin was applied to all patients. Conrast dose, angioplasty technique , stent and pharmacological medications which were used during the process were left to preferance of the operator. In all procedure, the non-ionic, low osmolar contrast agent (Omnipaque 350; 350 mgI/mL (iohexol) was used.

Follow-up

Necessity of urgent hemodialysis was decided

accordance to oliguria be longer than 48 hours or failure responce to forced diuresis for 24 hours. Urea and creatinine values were checked between 48-72 hours after the procedure to assess the development of CIN in patients. Early discharged patients were called for checking the biochemical parameters.

Definition of CIN

CIN was defined absolute (≥0.5 mg/dl) or relative (≥25%) increase in serum creatinine at 48-72 hours after exposure to a contrast agent compared to baseline serum creatinine values in the absence of other reasons which cause kidney failure.

Statistical Analysis

Statistical evaluation was performed using the SPSS program (Statistical Package for the Social Sciences ver. 10.0, SPSS Inc, Chicago, Illinois, USA). Numerical variants were defined as mean ± standart deviation and categorical variables were defined as percentage. In the comparision among the groups ; in the variables showing a normal distribution, student t test was used and in the variables not showing a normal distribution Mann-Whitney U test was used. Categorical variables were compared with chi-square test or Fisher's exact chi-square test. Univariate and multivariate logistic regression analyses were used to determine significant predictors of CIN. Receiver operating characteristics (ROC) analysis was used to determine the sensitivity and specificity of contrast volume to creatinine ratio to predict CIN. In all evaluations, $p<0.05$ was accepted statistically significant.

Results

The baseline demographic, echocardiographic, and biochemical characteristics of the study cohort are shown in Table 1. The age of 2604 patients were between 17 and 91 and the mean age was 59.5 years; 34.8% (906) of patients were female and 65.2%

Table 1. Characteristics of patients with and without CIN

	CIN (+) (n=355)	CIN (-) (n=2249)	*p*
Age (year)	60.96±11.25	59.34±11.38	0.01
Gender			
Male	215 (60.7)	1483 (65.9)	0.04
Female	140 (39.4)	766 (34.1)	
BMI (kg/m^2)	28.01±5.58	28.19±5.59	0.57
Hypertension	211 (59.4)	1163 (51.7)	0.007
Diabetes mellitus	79 (22.3)	395 (17.6)	0.03
EF (%)	52.88±11.88	54.54±10.99	0.009
GFR (ml/min)	98.91±34.04	113.34±44.37	<0.001
Urea (mg/dl)	33.99±14.99	34.76±15.63	0.38
Creatinine (mg/dl)	0.95±0.32	0.81±0.38	<0.001
Amount of contrast (ml)	109.05±73.95	99.64±54.75	0.004
Contrast volume to creatinine ratio	148.37±110.41	111.09±66.22	<0.001
Drugs			
ACEI	97 (27.3)	666 (29.6)	0.37
ARB	52 (14.6)	313 (13.9)	0.86
Statin	78 (22.0)	425 (18.9)	0.17
Diuretic	26 (7.3)	130 (5.8)	0.25
Metformin	52 (14.6)	221 (9.8)	0.006
Sulfonylurea	33 (9.3)	143 (6.4)	0.04
Insulin	20 (5.6)	91 (4.0)	0.16
Number of arteries with lesion >50%			
No lesion	107 (30.1)	849 (37.8)	0.001
One artery with lesion	103 (29.0)	670 (29.8)	
2 arteries with lesion	48 (13.5)	311 (13.8)	
3 arteries with lesion	97 (27.3)	418 (18.6)	
Procedure			
Coronary angiography	280 (78.9)	1828 (81.3)	0.03
Elective PCI	50 (14.1)	332 (14.8)	
Primary PCI	25 (7.0)	89 (4.0)	

Data are given as mean±standard deviation or number (%). ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, BMI=body mass index, CIN=contrast-induced nepropathy, EF=ejection fraction, GFR=glomerular filtration rate, PCI=percutaneous coronary intervention

(1698) of patients were male. In the study patients, mean body mass index was 28.1. In the study group 474 patients (18.2%) were diabetic, 1374 patients (52.8%) were hypertensive and 450 patients (17.3%) had heart failure history. Before the procedure, the mean creatinine values was 0.93 mg/dl and the mean calculated GFR was 100.86.

In admission, 3.3% (86) of patients creatinine value was ≥1.5 mg/dl. Contrast agent was used maximum 650 ml and minimum 20 ml and mean was 100.9 ml. The used contrast volume of the 97 (3.7%) patients were exceeded the threefold of creatinine clearance. Coronary angiography was performed 81% (2108), elective PCI was performed 14.7% (382) and primary PCI was performed 4.4% (114) of the study patients (2604).

CIN was found in 13.6% (355) of 2604 patients. CIN developed in 13.3% (280) of 2108 patients to whom coronary angiography was applied, in 13.1% of 382 (50) patients to whom elective PCI was applied and in 21.9% (25) of 114 patients to whom primary PCI was applied (see Table 1). Twenty-three (0.9%) of the 2604 patients was requiring dialysis due to CIN. CIN rate was 2.6% (67 patients) according to absolute increase of creatinine (≥0.5 mg/dl) and 13.5% (352 patients) according to relative increase of creatinine (≥25%) at 48-72 hours.

When comparing these three groups of patients (coronary angiography, elective PCI, primary PCI) in terms of CIN incidence, primary PCI group CIN incidence was significantly higher than coronary angiography group (p=0.009) and elective PCI group (p=0.02) (Figure 1). The CIN incidence was similar between coronary angiography and elective PCI group (p=0.91) (see Figure 1).

According to baseline characteristics; in CIN developed patients, women gender (p=0.04), hypertension (p=0.007) and diabetes mellitus (p=0.03) were significantly higher than in patients without CIN (Table 1). No significant difference was found in use of angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) in both groups (p=0.37 and p=0.86).

The use of metformin (p=0.006), sulfonylurea (p=0.04) and number of arteries with lesion was significantly higher (p=0.001) in CIN group (see Table 1). In CIN patients, the values of left ventricular ejection fraction (p=0.009) and GFR (p<0.001) were significantly lower, age (p=0.01), initial creatinine values (p<0.001), amount of contrast agents (p=0.004) and contrast volume to creatinine ratio (p<0.001) were significantly higher than in patients without CIN (Table 1).

Using a univariate and multivariate regression models, the patients's age, gender, hypertension, diabetes mellitus, ejection fraction, GFR, urea, creatinine, contrast volume, contrast volume to creatinine ratio, medications (drugs), number of arteries with lesion and procedure were included as predictor variables for CIN (Table 2). In univariate

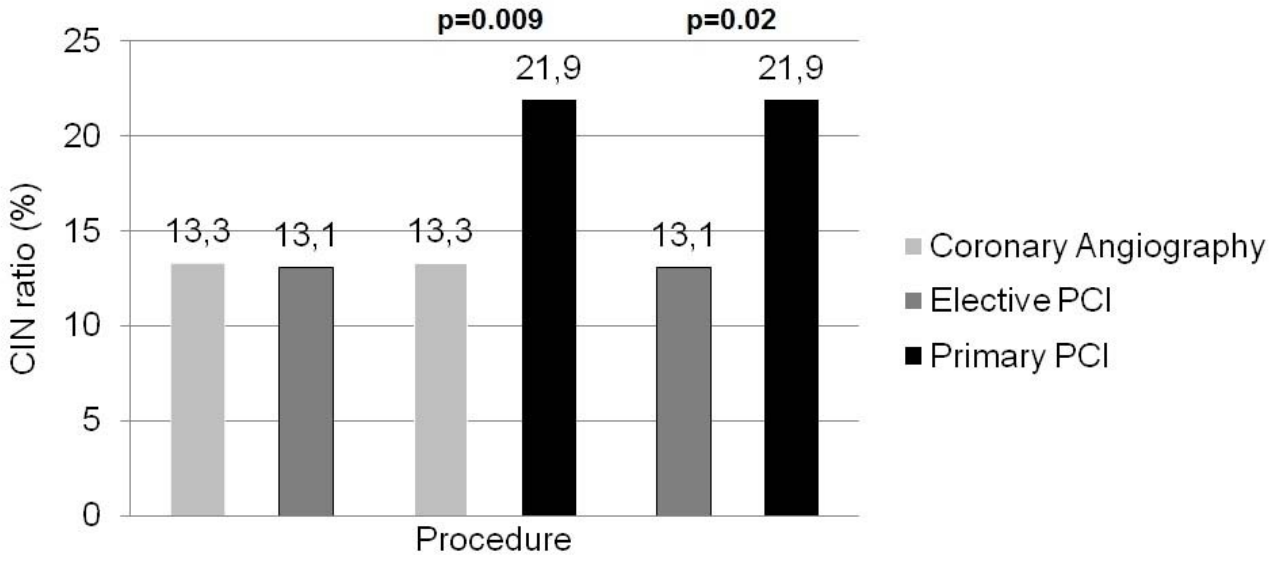

Figure 1. Comparison of the CIN incidence. CIN=contrast-induced nepropathy, PCI=percutaneous coronary intervention

Table 2. Univariate and multivariate analysis of CIN predictors

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.01 (1.003-1.02)	0.01	1.04 (1.02-1.06)	<0.001
Gender	1.26 (1.002-1.58)	0.04	1.04 (0.77-1.40)	0.78
Hypertension	1.36 (1.09-1.71)	0.007	0.92 (0.71-1.19)	0.56
Diabetes mellitus	1.34 (1.02-1.76)	0.03	1.03 (0.66-1.61)	0.88
EF	0.98 (0.97-0.99)	0.009	0.99 (0.97-1.001)	0.08
GFR	0.98 (0.97-0.99)	<0.001	0.99 (0.98-0.99)	<0.001
Urea	0.99 (0.98-1.004)	0.38		
Creatinine	1.90 (1.84-1.95)	<0.001	1.30 (0.66-2.57)	0.43
Amount of contrast	1.002 (1.001-1.004)	0.005	1.14 (1.007-1.21)	<0.001
Contrast volume to creatinine ratio	1.005 (1.004-1.006)	<0.001	1.01 (1.009-1.02)	<0.001
ACEI	1.11 (0.87-1.43)	0.37		
Statin	0.82 (0.63-1.08)	0.17		
Diuretic	1.28 (0.83-1.99)	0.25		
Metformin	1.57 (1.13-2.18)	0.006	0.87(0.53-1.44)	0.59
Sulfonylurea	1.50 (1.01-2.24)	0.04	0.95(0.57-1.59)	0.86
Insulin	1.41 (0.86-2.32)	0.17		
Number of arteries with lesion				
1-0	1.22 (0.91-1.62)	0.17	1.06 (0.74-1.52)	0.73
2-0	1.22 (0.85-1.76)	0.27	1.14 (0.74-1.74)	0.54
3-0	1.84 (1.36-2.48)	<0.001	1.77 (1.24-2.51)	0.001
Procedure				
Coronary angiography – Primary PCI	1.83 (1.15-2.90)	0.02	1.49 (0.85-2.61)	0.16
Coronary angiography – Elective PCI	0.98 (0.71-1.35)	0.91	0.82 (0.53-1.26)	0.38

ACEI=angiotensin converting enzyme inhibitor, CI=confidence interval, CIN=contrast-induced nepropathy, EF=ejection fraction, GFR=glomerular filtration rate, OR=odds ratio, PCI=percutaneous coronary intervention

analysis; age, gender, hypertension, diabetes mellitus, ejection fraction, GFR, creatinine, contrast volume, contrast volume to creatinine ratio, metformin, sulfonilurea, three vessel coronary artery disease and procedure were significant predictor of CIN. In multivariate analysis, age (odds ratio [OR]=1.04; 95% confidence interval [CI], 1.02-1.06; $p<0.001$), GFR (OR=0.99; 95% CI, 0.98-0.99; $p<0.001$), contrast volume (OR=1.14; 95% CI, 1.007-1.21; $p<0.006$), contrast volume to creatinine ratio (OR=1.01; 95% CI, 1.009-1.02; $p<0.001$), three vessel disease (OR=1.77, 95% CI, 1.24-2.51; $p=0.001$) were independent predictors of CIN (see Table 2)

According to ROC analysis, the area under the curve (AUC) of the contrast volume to creatinine ratio for CIN was 0.625 (95% CI, 0.59-0.65; p<0.001) for all the study groups, was 0.618 (95% CI, 0.58-0.65; $p<0.001$) for coronary angiography group, was 0.713 (95% CI, 0.64-0.78; $p<0.001$ for elective PCI group, was 0.58 (95% CI, 0.44-0.71; $p=0.22$) for primary PCI group (Figure 2).

Discussion

In this study, we found that; the CIN frequency that developed as related to interventional cardiological processes was 13.6%, the CIN incidence according to process was 13.3% in patients who underwent coronary angiography, 13.1% in elective PCI and 21.9% in patients who underwent primary PCI. In multivariate analysis, we showed that age, GFR, contrast volume, three vessel coronary artery disease and contrast volume to creatinine ratio were significant independent predictors of CIN.

The incidence of CIN with a retrospective analysis of 7320 patients was found as 14.8% (1069 patients) [4]. The risk factors of CIN has been found as age, diabetes mellitus, hypertension, peripheral vascular disease, ejection fraction less than 40%, multivessel PCI requirement, the presence of hypotension before, after and at the time of procedure [4]. When assessed by multivariate analysis it was found that most of these parameters is an independent risk factor for CIN. In our study, we found the overall incidence of CIN as

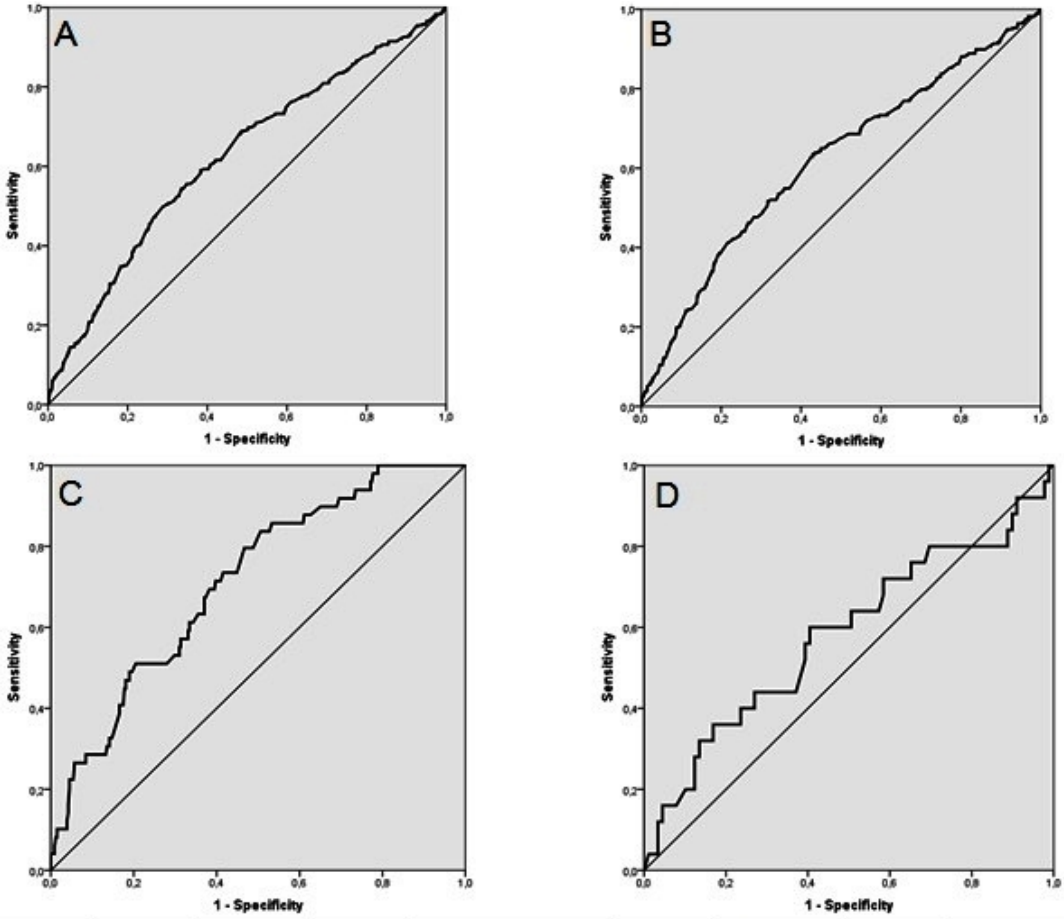

	Figure	AUC	P value	95% CI		Figure	AUC	P value	95% CI	
				Lower bound	Upper bound				Lower bound	Upper bound
Contrast volume / Creatinine	A	0.625	<0.001	0.59	0.65	B	0.618	<0.001	0.58	0.65
	C	0.713	<0.001	0.64	0.78	D	0.580	0.22	0.44	0.71

Figure 2. ROC and AUC of the study population including all of the study population (A), coronary angiography group (B), elective PCI group (C) and primary PCI group (D). AUC=the area under the curve, PCI=percutaneous coronary intervention, ROC=receiver operating characteristics

13.6%. In multivariate analysis age, GFR, contrast volume, three vessel disease and contrast volume to creatinine ratio were independent predictors of CIN.

In retrospective analysis on a large group of patients to whom PCI has been applied, it has shown that, similiar to our study, factors such as age, amount of contrast agent, high level of serum creatinine, diabetes mellitus, peripheral vascular disease, heart failure, hypertension, reference as acute myocardial infarction (MI) increase incidence of CIN, hospitalization and mortality [5, 6]. The score systems in recent studies showed that age, low GFR, low ejection fraction, hypertension, diabetes mellitus and contrast volume were predictors for CIN [7, 8].

Patients with CIN were older than patients without CIN (60.96±11.25 vs. 59.34±11.38; p=0.01). Some studies reported that 70 years and older is an independent risk factor for CIN [9]. In another study, compared with younger patients, elderly patients (>60 age) was significantly higher incidence of CIN (4% to 17%) [10]. Older age associated with sodium and water loss depending on the decrease in renal mass, function and perfusion. In addition lost in kidney functions related to age, the presence of multivessel disease, calcification, requires a greater amount of contrast agent due to tortuosity and embolic events can be accounted as factors that increase risk of CIN devolopment.

In our study, we found the value of basel serum creatinine higher and GFR values lower in CIN patients (p<0,001). The relationship between CIN and creatinine and GFR values is an expected data [4, 9].

The development of acute kidney injury is common after exposure to contrast patients with impaired renal function. Rihal *et al.* [5] have identified the value of the baseline serum creatinine as an independent predictor for CIN development. Hall *et al.* [11] had compared patients whose baseline serum creatinine is above 2.0 mg/dl and patients whose serum creatinine is 1.2 mg/dl and below and they have shown that incidence of CIN has increased 30 times in group with high creatinine. The creatinine clearance is an independent predictor for the development of CIN requiring dialysis after cardiac interventions.

Another well-defined risk factor for CIN is diabetes mellitus. In our study, diabetes mellitus frequency was found in a higher rate in CIN developed patients compared to those CIN hasn't developed (22.3% vs. 17.6%; p=0.03). Clinically serious CIN development was generally seen in diabetic patients who have kidney failure [5]. In our study in univariate analysis diabetes mellitus was a predictor of CIN however in multivariate analysis it was not. Our study diabetic population creatinine value was not different from non-diabetic population (0.95±0.37 vs. 0.93±0.33; p=0.69). This result may be related with this point. Parfery *et al.* [12] had shown that CIN frequency in diabetic patients whose have normal renal functions, in the absence of other risk factors is comparable with healty society.

Many studies revealed clearly that there is a significant positive correlation between the amount of contrast agent and the development of CIN [13]. In our study, patients with CIN has received a greater amount of contrast agent too (109.5±73.95 vs. 99.64+54.75; p=0.004) and ın multivariate analysis contrast volume was an independent predictor.

We evaluate the adjusted contrast amount according to creatinine value (contrast volume/baseline creatinine) and found that the contrast volume to creatinine ratio was significantly higher in the CIN group (111,09±66,22 vs. 148,37±110,41; p<0,001). The contrast volume to creatinine ratio was independent predictor for the development of CIN in univariate and multivariate analysis. In recent studies calculate the maximum allowable contrast volume according to creatinine level and showed that the incremental use of contrast beyond the maximum allowable contrast volume is associated with an increased risk of CIN [14]. These studies results support our trial findings. The contrast volume according to creatinine level is one of the most important factor for CIN.

According to ROC analysis; the contrast volume to creatinine ratio had reasonable AUC for predicting the CIN. In subgroup ROC analysis for the CIN prediction of contrast volume to creatinine ratio showed that the AUC value was the highest level in elective PCI group; however it was not reach the significant p value in the primary PCI group. This point could explain with the few number of patients in primary PCI group. Indeed; the contrast volume to creatinine ratio was higher in CIN group of primary PCI patients (170.49±88.16 vs. 201.74±115.57; p=0.14).

Incidence of CIN has been seen higher (21.9%) in our patients with primary PCI can be associated with hemodynamic theory which takes place in CIN pathophysiology. Primary PCI patients are processed without preservative evaluations; renal perfusion is impaired as a result of developing acute cardiac failure. After undergoing primary PCI, the risk of CIN development is higher when compared to elective patients, even in patients with normal renal functions [9]. In the randomized controlled clinical trial done by Marenzi *et al.* [15], CIN was developed as 19% in patients who applied primary PCI and this value is higher than expected general incidence. In our study, as well, incidence of CIN in patients whose applied primary PCI was higher than general incidence (13.6% vs. 21.9%). In univariate analysis primary PCI was a significant predictor for CIN however in multivariate analysis it was not. Narula *et al.* [16] showed that GFR is the most important factor for CIN in patients with primary PCI (according to propencity score analysis). In our study GFR levels significantly higher in primary PCI group than other patients (100.16±35.05 vs. 90.96±40.59; p=0.01). This result could be explain with this point.

One of another factors which create risk for CIN development is low EF of left ventriculi. In various studies, it has been shown that ejection fraction less than 40% is an independent risk factor for CIN. In our study, too, it has been found that patients whose ejection fraction was below 40% had a higher CIN incidence than above 40% (16.7% vs. 12,9%; p=0,02).

In patients with low ejection fraction have reduced renal perfusion and use a large number of pharmacological agents, explain the increase in the risk of developing CIN.

While in our study CIN incidence in 1374 hypertensive patients was found as 15.4% (211 patients) , the rate in 1230 patients without hypertension was found as 11.7% (144 patients). CIN incidence in hypertensive patients was statistically significant higher (p=0.007). Consistently high glomerular filtration pressure in hypertensive patients impairs renal function. Hypertensive nephropathy causes a reduction in the number of the functioning nephrons. The risk of CIN increases in patients with hypertension. Also, excessive activation of renin-angiotension system and the reduction of NO release are disturbed the renal autoregulation which predispose to the development of CIN. In the studies, hypertension was found to be an independent risk factor for CIN [17]. According to our study, in univariate analysis hypertension was a risk factor for CIN; however, in multivariate analysis it was not. Mehran *et al.* [7] showed similir results with us, according to univariate analysis hypertension was a risk factor for CIN but in multivariate model it was not.

In our study, the number of female patients have been much more in CIN developed group (39.4% vs. 34.1% p=0.04). In retrospective analysis by Iakovou *et al.* [17], women gender has been found to be an independent risk factor for CIN. Ovarian hormones may lead to an increased risk for CIN in women by affecting renin-angiotensin system and renal blood flow. We also found multivessel disease with increasing incidence of CIN. This may be related to the use of high volumes of contrast media for visualisation the coronary lesion and already compromised renal vessels due to atherosclerosis [13].

We found that the use of oral antidiabetic, especially metformin, is more frequent in patients with CIN. In univariate analysis, sulfonilurea and metformin were predictor for CIN; however in multivariate analysis they were not. As a result of decrease in renal functions following contrast media exposion, metabolism of metformin affected so may lead to increased accumulation in the body and adverse effects. Following contrast application, there is an increase in lactic acidosis risk in patients who use metformin. Lactic acidosis also cause development of CIN. However the metformin adverse effect dependent on renal function. In patients with normal renal function metformin did not increase the CIN risk. Guidelines recommend that this medication should not be taken for 48 hours by the patients who have a high risk in terms of CIN [18].

In the analysis of 7741 patients whose PCI applied, CIN which requires dialysis had developed in 51 patients (0.66%) [19]. A great deal of patients who requires dialysis are women, diabetic, patients with CRF and they have low ejection fraction and history with previous PCI or CABG. In-hospital morbidity (non-Q MI, CK-MB elevation, pulmonary edema and vascular complications) was significantly higher in patients who need dialysis. In our study, CIN that require dialysis has been found in 0.9% patients.

In our patients we used non-ionic, low osmolar contrast agent (iohexol). The contrast agent characteristics affect the CIN incidence. The iso-osmolar, non-ionic contrast agent has low CIN risk and this agent should use especially in patients with preexisting renal insufficiency or those at high risk for CIN is debatable. However the data is not accurate which contrast agent is the ideal agent about the CIN protection in patients with normal kidney function [20].

Recently, one of the trial showed that baseline chronic kidney disease, acute MI presentation, prior heart failure, prior cardiac arrest, prior cardiovascular disease, cardiogenic shock, anemia, age, contrast volume and diabetes mellitus are independent factors associated with acute kidney injury in patients with PCI [21]. Most of these factors were defined as risk predictor for CIN after PCI and a risk score was identified for CIN [7]. These studies result and the indentified risk score was support our study finding. Contrast volume to creatinine ratio was evaluated for CIN in our study. To the best of our knowledge, our study is the first study in literature which evaluate the contrast volume to creatinine ratio for prediction of CIN. These two parameters (creatinine and contrast volume) are accurate value of the patients. They do not need any formula such as GFR. Our findings could guide for new trials in different patients group.

There are important increases morbidity and mortality in patients with CIN [2]. But in our country there is not enough data showing the incidence of CIN is caused by the interventional cardiology procedures.

The exact evaluation incidence of CIN is highly difficult. Since in many clinics patients are discharged a few hours or a day after the interventional procedures, it can't be evaluated whether CIN is developed or not in early discharged patients. As the studies are in selected groups or search for the effects of the treatment regime, it is not possible for incidence of CIN to be evaluated exactly.

The Limitations of the Study

First; our study population include different patients group such as coronary angiography group, primary PCI group and elective PCI group however the groups were not similar size. Second; we did not use creatinine clearance value based on 24-h urine collection during a true baseline clinical condition, and our GFR calculation is subject to limitations due to the formula used and the possibility that patients may not be at their true baseline condition before interventional procedure, because of dehydration or cardiac illness.

Conclusions

Incidence of CIN which was developed as related to cardiological interventions in our clinic was defined to be similar to data throughout the world. Incidence of CIN was seen to increase in emergency interventions. Identified risk factors for CIN was found to increase the incidence of CIN in our society, as well. We found that contrast volume to creatinine ratio is predictor of CIN especially in elective PCI group.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Prevalence of corneal astigmatism and axial length in cataract surgery candidates in Turkey

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ABSTRACT

Objectives. To analyze the corneal astigmatism and axial length values in cataract surgery candidates. ***Methods.*** The files of patients who undergone cataract surgery between November 2012 and November 2013 were retrospectively selected and reviewed. The preoperative corneal keratometry measurements in the flat and steep axis and the axial lengths of the patients were recorded. ***Results.*** The study comprised of 449 eyes of 449 patients with a mean age of 68.6±9.8 (range; 40-90) years. The mean axial length value was 23.1±1.0 mm; mean corneal astigmatism was 1.00±0.70 D. The corneal astigmatism was 1.00 D or less in 315 eyes (70.1%); between 1.00 and 2.00 D in 99 eyes (22%); and 2.00 D or more in 35 eyes (8%). With-the-rule astigmatism was present in 51% of the patients, against-the-rule astigmatism was present in 32% of the patients, and oblique astigmatism was present in 17% of the patients. We observed an increase in against-the-rule astigmatism (p=0.032) and oblique astigmatism with age (p=0.040). ***Conclusions.*** The current study is the most populous study in this field of research ever carried out in our country. The mean axial length in our study in comparison to Chinese and German populations was found to be shorter.

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Keywords: Astigmatism; keratometry; axial length

Introduction

The only treatment of cataract is surgery and that is the most prevalent surgery all over the world [1]. Patients' expectations about postoperative vision quality are progressively increasing [2]. Astigmatism is probably the most important factor affecting vision quality, following the cataract surgery [3]. One of the significant markers of astigmatism values that emerge in the postoperative period is the corneal astigmatism values in the preoperative period. Detection of these values and adaptation of the cataract surgery procedure based on these values will enhance the postoperative vision quality. While preoperative values have been widely researched in many countries in the world [4-7], data as to preoperative corneal astigmatism values in surgery candidates are insufficient in our country. The purpose of our study was to measure the values of corneal astigmatism and axial length values in cataract surgery candidates.

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Methods

Four hundred and forty-nine eyes of 449 consecutive cataract patients hospitalized at the Bursa Yuksek Ihtisas Training and Research Hospital between November 2012 and November 2013 were included in our study. The files of the patients were retrospectively analyzed. Patients with cataract, Caucasian, aged 40 years and older were included in the study. Exclusion criteria for the study were previous ocular, refractive or intra-ocular surgery, history of ocular inflammation, pterygium, ocular trauma, and endothelial, ocular surface disorders. This study was approved by the local Ethics Committee. All procedures were in adherence with the tenets of the Declaration of Helsinki.

The patients were divided into two groups based on their ages. The group aged 59 and under was referred to as the Group 1 and those aged 60 and above were gathered under Group 2. For better understanding effects of aging in elderly age groups, the patients aged over 60 were further divided into three groups; those aged between 60-69; between 70-79 and the ones who were 80 and older. The auto refractokeratometric measurements made in the preoperative period were evaluated. Canon RK-F2 (Canon Inc., Tokyo, Japan) autorefractometer was used to obtain keratometry and Opticon Pacline (OPTIKON 2000 S.p.A, Rome, Italy) was used to perform ocular axial length. The corneal keratometry measurements in the steep and flat axis were recorded based on the Canon RK-F2 (measurement range 33.75 to 67.5 D) autorefractometer outputs and also the axial lengths were noted based on the Opticon Pacline output. All patients were tested by the same experienced examiner. Corneal astigmatism was accepted as with-the-rule when the axis of correcting minus cylinder was within 180±30 degrees (the steep meridian of the cornea being within 90±30 degrees in this case), against-the-rule when the correcting minus cylinder axis was within 90±30 degrees, and oblique if it was neither with-the-rule nor against-the-rule.

Statistical Analysis

In the definitive statistics set of the data, standard deviation, lowest, highest median, frequency, and rate values have been utilized. All analyses were performed using SPSS software (version 18.0, International Business Machines Corp.). Kolmogorov-Smirnov and Kruskal-Wallis tests were used and *p* values less than 0.05 were considered significant.

Results

This study enrolled 449 patients (250 female, 199 male). The mean age was 68.6±9.8 years (range; 40-90 years). The mean axial length was 23.1±1.0 mm and the mean corneal astigmatism was 1.0±0.7 Dioptry (D). Corneal astigmatism was present in 315 eyes (70.1%) with a value of 1D or less; between 1 and 2 D in 99 eyes (22%), and 2 D or higher in 35 eyes (8%). No significant difference was observed in the amount of axial length, flat K and steep K, and corneal astigmatism values between Group 1 and 2 ($p>0.05$) (Table 1).

The patients aged older 60 years, on the other hand, were divided into ten-year groups amongst themselves and were analyzed. The patients' groups and their comparison in terms of the regularity of astigmatism are illustrated in Table 2. While the rate of against-the-rule astigmatism increases with the age ($p=0.032$), after 80 years old against-the-rule astigmatism decreases and it was seen that oblique astigmatism also increases ($p=0.040$) (see Table 2). The mean corneal astigmatism values in each age group and the mean steepest axes are illustrated in Table 3. Distribution of the type of astigmatism in age groups was not statistically significant ($p=0.522$). No significant difference in term of astigmatism was

Table1. Ocular biometric parameters of the groups

	Group 1 (<59 years) (n=77)	Group 2 (≥60 years) (n=372)	*p*
Age	52.57±5.31	71.92±6.81	
Axial length	23.08±0.92	23.14±1.01	0.647
K1	42.96±1.56	43.06±1.58	0.644
K2	44.06±1.80	44.02±1.53	0.817
Astigmatism	1.10±0.85	0.97±0.70	0.161

Data are shown as mean±standard deviation. K1=flat keratometry, K2=steep keratometry

Table 2. Distribution of astigmatism in the age groups

	≤59 years	60-69 years	70-79 years	≥80 years
Against-the-rule astigmatism	20 (26)	41 (27.5)*	64 (38.8)*	20 (34.5)
With-the-rule astigmatism	47 (61.0)	83 (55.7)	76 (46.1)	23 (39.6)
Oblique astigmatism	10 (13.0)	25 (16.8)**	25 (15.1)**	15 (25.9)

Data are shown as number and percent. *p= 0.032, ** p= 0.040

Table 3. The mean corneal astigmatism values and the steepest axes in each age group

	≤59 years	60-69 years	70-79 years	≥80 years	*p*
Astigmatism	1.10±0.85	0.98±0.7	0.98±0.7	0.93±0.7	0.522
Steepest astigmatic meridian	83°	90°	85°	80°	83°

Data are shown as mean±standard deviation.

found between the groups (p=0.161) (see Table 1). The distribution of patients within the groups was similar regarding gender and in terms of which eye was being examined. No significant difference was found between the groups (p>0.05).

Discussion

The results obtained in the after the cataract surgery have become almost perfect thanks to certain new techniques being applied in cataract surgery and new-generation lenses [20, 21]. However, astigmatism still appears as the most important problem that we are confronted with, affecting patient satisfaction and vision quality in the postoperative period pursuant to surgery of cataract, which is a particular old age disease [8, 9]. In order to minimize this current problem, corneal relaxing incisions and toric intraocular lenses eliminating the astigmatism when placed on a specific axis are being utilized [10]. Nevertheless, despite these methods, success cannot always be granted and problems about postoperative vision quality may occur. In this study, we investigated preoperative corneal astigmatism values, which were very important for the vision quality in the postoperative period after a cataract surgery, by classifying them according to the ages of the patients.

Type and distribution of astigmatism is different in country. In a study by Ferrer-Blasco *et al.* [5] (Spain), examining the 4,540 eyes of 2,515 patients, they found out that corneal astigmatism was 1.0 D and higher in 35% of the patients. In a study by De Bernardo *et al.* [19] (Italy), examining the 757 eyes of 380 patients, they found out that roughly 50% of the eyes have more than 1 D of astigmatism. In the study in which Hoffmann and Hutz [14] (Germany), noted a corneal astigmatism rate of over 1.0 D 36% rate in 23.239 eyes. Gunes [12] (Turkey) examined 240 eyes of 163 patients. In their study, corneal astigmatism proved over than 1 D in 27.1 %. Khan *et al.* [9] (England) found that over 1 D astigmatism rate 40% in 1230 eyes. Chen *et al.* [8] investigated 2849 Chinese patients; they reported that over than 1 D astigmatism in 41% of the patients. In present study, 29.9% of eyes had corneal astigmatism of 1.00 D or more, which is less than other country.

Against-the-rule astigmatism increased with age and this result was known [3, 5]. The reasons for this were the changes in the eyelid along with aging and also the pressures of these changes on the cornea leading to astigmatic changes on the cornea [17]. Guan *et al.* [6] investigated 827 Chinese patients, and less than 1 D astigmatism was found in 54.5% of patients and against-the-rule increased and linear regression with age. Chen *et al.* [8], and Khan and Muhtaseb [9] were found similar result. Moreover, our study also showed that against-the-rule astigmatism increased with age, in contrast over the 80 age astigmatism

decreased. This result was different from other study results. This may occur due to different eyelid structures [18] or nutrition disorders and the structural differences based on ethnic characteristics. We calculate total corneal astigmatism with autokerotometry, didn't measure the posterior astigmatism. Keratometric astigmatism overestimates total corneal astigmatism in eyes with with-the-rule astigmatism and underestimates total corneal astigmatism in eyes with against-the-rule astigmatism [22].

Axial lengths is important factor for intraocular lens calculation, the average axial length in our population was measured as 23.1±1.0. In the study that Cui *et al.* [13] carried out on the 6,750 eyes of Chinese patients, it was measured as 24.07±2.14 mm. In their study in which they examined 23,239 eyes in Germany, Hoffmann *et al.* [14] measured the mean axial length as 23.43±1.51 mm. In a study conducted on 80 patients fromTurkey by Kamis *et al*. [11], the mean axial length of the patients was found out to be 23.63±0.76 mm (22-25 mm). The axial length in our study, on the other hand, was shorter than the axial length in the Chinese and German populations. Furthermore, our study also pointed out that axial length decreased as the age increased. Similar results were also found in a study involving Chinese population in Singapore, and it was explicated that this outcome might come out due to the effort to compensate for the increasing refraction that happens more frequently with an increasing age [15,16]. In our study, the mean flat keratometry 43.03 D and steep keratometry 44.02 D was found. Ferrer-Blasko et al. [5] reported flat and steep keratometry 43.48 D and 44.08 D, respectively. Khan et al. [9] also reported 43.43 D and 44.46 D. Our keratometry values were lesser than these studies.

Conclusions

In the present study, we found out that against-the-rule astigmatism and oblique astigmatism increased by age and after 80 ages against-the-rule astigmatism decreases; 29.9% of eyes has corneal astigmatism of more than 1.00 D, we found no significant difference in the distribution of astigmatism forms by decades. Our keratometric and axial values were lesser than other studies. Since we could not find a comprehensive study in which Turkish population was also studied, the ethnicity-related discussion of our data is limited. This study reason is benefit for astigmatism management in Caucasian population.

Conflict of interest

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Laparoscopic cholecystectomy in childhood: a review of twenty-four consecutive cases

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ABSTRACT

Objectives. The experience with laparoscopic cholecystectomy in children remains limited. Therefore, we aimed to present our experience with this procedure. ***Methods.*** Between April 2011 and June 2016, retrospectively, data points of children who underwent laparoscopic cholecystectomy reviewed included demographics properties, indication for cholecystectomy, surgical technique, operative time, complications, and length of hospital stay. ***Results.*** Twenty-four children (5 were males with ages ranging from 2 to 17 years, mean: 10.5 years) underwent laparoscopic cholecystectomy. The indication for surgery was associated to symptomatic gallstones in all patients. The surgery was performed under general anesthesia and classical 4-port approach was done in twenty-two patients, and 2-port approach in combination with 2 portless 2.3-mm percutaneous graspers was used in two patients. The operating time ranged between 45 and 90 minutes (mean: 60 minutes). Two patients ended by open surgery. No complications occurred. Hospital stays ranged from 1-3 days. ***Conclusion.*** Laparoscopic cholecystectomy is safe and effective in children, and shows the same advantages reported in adult series.

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Keywords: Laparoscopy; cholecystectomy; cholelithiasis; children

Introduction

Gallbladder disease, which is rarely seen in children, is generally accompanied with hemolytic disorders, biliary dyskinesia, parenteral nutrition, cystic fibrosis and recently seen increased obesity in children [1]. Cholelithiasis as one of the gallbladder disease is the most common disorder affecting the biliary system. If cholelithiasis causes symptoms or complications, cholecystectomy is necessary. Even though open cholecystectomy was the generally accepted conventional method, many pediatric surgery centers have started performing laparoscopic cholecystectomy [2]. Most of the series published on laparoscopic cholecystectomy represent adult cases, and the practice on pediatric patients is still limited.

In this study, we intended to present the clinical characteristics of our patients who had undergone laparoscopic cholecystectomy due to cholelithiasis in the light of the literature.

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Methods

We retrospectively analyzed the demographic data, clinic features, cholecystectomy indications, preoperative approach, operative technique, complications, duration of hospital stay and postoperative follow-up data of the patients who had undergone laparoscopic cholecystectomy between April 2011 and June 2016.

Procedure

After obtaining an informed consent, the patients prepared for elective laparoscopic cholecystectomy. All procedures were performed under general anesthesia and endotracheal intubation. A single dose of antibiotics (first generation cephalosporin) was given for prophylaxis. The patients were positioned on the supine position. The surgeon and the assistant stand on the patient's left side, and scrub nurse stands on the right. The monitor and laparoscopy rack were placed on right side of the patient's head. The operation was carried out by the same surgical team using the conventional 4-port method in patients. We inserted 10-mm trocar through the umbilicus for telescope, 5-mm trocar through the left abdominal upper quadrant for hook cautery and clip applier, 5-mm trocar through midclavicular line and below arcus costarum for retraction of liver and gallbladder, and 5-mm trocar at the level of umbilicus and on the anterior axillary line for the dissectors to be used for retraction of the infundibulum. In two patients, portless 2.3-mm percutaneous graspers were used for retraction of the gallbladder instead of the last two ports (Figure 1A). Laparoscopic cholecystectomy was performed by the conventional method (Figures 1B, C, D, E, F, G, and H). Non-steroidal anti-inflammatory drugs were administered to relieve postoperative pain and oral nutrition was started at the 6th hour. The patients were followed-up for 3-36 months postoperatively.

Results

During the period of 52 months, laparoscopic cholecystectomy was performed on a total of 24 patients, 5 of whom were male. Table I summarizes the demographic characteristics together with the symptoms of our patients. The mean age of the patients was found as 10.5 years (ranging from 2 to 17 years). The six patients aged over 15 years were obese. Cholelithiasis in 10 (41.6 %) patient was diagnosed during the evaluation of acute abdominal pain with the abdominal ultrasonography. In the other patients, it was diagnosed by ultrasonography during the evaluation of different complaints, such as fever, vomiting, and urinary tract infection. It was ascertained that three patients had received ceftriaxone therapy due to previous urinary tract infection. All

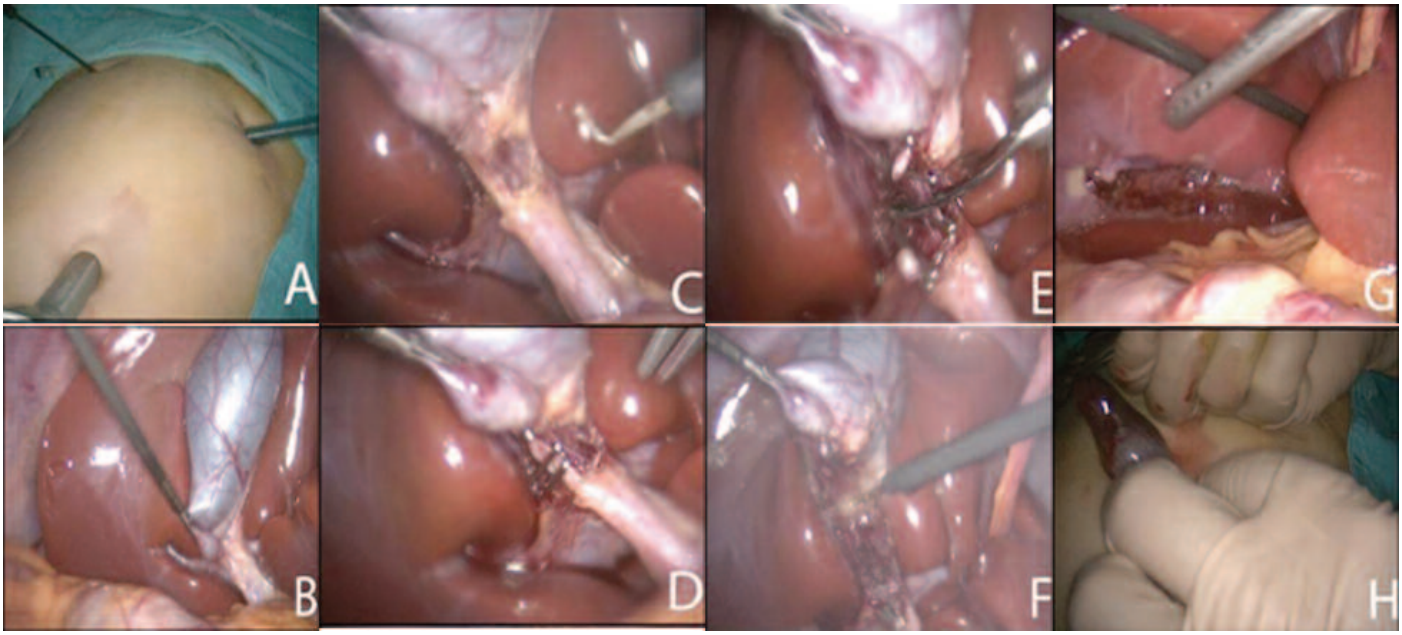

Figure 1. Laparoscopic stages of cholecystectomy. The placement of instruments (A), expose triangle (B), the dissection of cystic duct and vessels (C), the clip placed (D), the cutting of duct and artery (E), the gallbladder is freed from its bed (F), the control of bleeding and bile leakage (G), and the gallbladder is removed through the umblicus (H).

Table 1. The demographic characteristics and symptoms of patients

Patient No	Gender	Age	BMI	Symptom
1	F	12	N	Abdominal pain
2	F	13	N	Fever/vomiting
3	F	2	N	Abdominal pain
4	F	17	H (27.2)	Abdominal pain
5	F	13	N	Fever/vomiting
6	M	4	N	Fever/vomiting
7	F	15	H (20.7)	Abdominal pain
8	F	11	N	Fever/vomiting
9	F	6	N	Fever/vomiting
10	M	11	N	Abdominal pain
11	F	7	N	Abdominal pain
12	F	13	N	Fever/vomiting
13	F	7	N	Fever/vomiting
14	F	7	N	Fever/vomiting
15	F	10	N	Abdominal pain
16	F	13	H (27.1)	Abdominal Pain
17	F	16	H (33.29)	Abdominal Pain
18	M	6	N	Fever/vomiting
19	F	15	N	Abdominal pain
20	F	6	N	Fever /vomiting
21	F	15	H (37.64)	Fever/vomiting
22	M	9	N	Fever/vomiting
23	F	15	H (33.29)	Fever/vomiting
24	M	7	N	Fever/vomiting

F=female, H=high, M=male, N=normal

patients had a history of acute cholecystitis episode at least once. The diagnosis of cholelithiasis was made via ultrasonography for the patients who had applied to an external medical center with the complaints of vomiting and abdominal pain. All patients were evaluated regarding their hematologic and gastrointestinal disorders. Some of the patients referred from the gastroenterology departments had been receiving ursodeoxycholic acid therapy; however, they could not benefit from the therapy. In six patients who had high body mass index, there wasn't find any risk factors for cholelithiasis except for obesity. The serum amylase and alkaline phosphatase were elevated in two patients. These blood values were reduced before surgery.

The mean duration of the operation was 60 minutes (ranging from 45 to 75 minutes). In a female patient, there was a cystic artery variation originated from left hepatic artery. In two patients, the procedure was converted to open surgery because of cystic duct could not actually differentiate due to severe intra-abdominal adhesions and a big stone located on the choledochocystic junction. None of the patients experienced a complication during laparoscopic cholecystectomy in our series. More than half of the patients needed analgesics for more than 24 hours. Vomiting, shoulder pain, and pain at incision sites were the most common postoperative complaints. The duration of hospital stay ranged from one to three days. Acute abdominal pain episode, characterized by the increase of liver function test values, was observed in one patient three months after the operation; however, it was able to be managed through conservative follow-up.

Discussion

The prevalence of cholelithiasis is very low in children. Although it has been reported to be usually

related to hemolytic diseases (10-40% higher as compared to normal population), the leading cause of gallbladder stone is generally idiopathic in published series and reported to be detected incidentally while investigating other abdominal pathologies [3]. On the other hand, it may also be seen in premature babies or children who have encountered severe nutritional problems and parenteral nutrition, serious abdominal surgery, familial predisposition, cystic fibrosis, ceftriaxone therapy, obesity, dehydration, endocrine disorders, genetic liver diseases or it may be diet-induced [4, 5]. The patients included in this study had undergone hematologic and gastroenterologic investigations preoperatively; no hemolytic, endocrinologic or metabolic disorder was detected. However, it was found out that the patients aged less than six years had received ceftriaxone therapy because of urinary tract infection. Obesity has been reported to be a potential cause of gallbladder stone in children; however, only six of our patients were obese [1, 5]. Nevertheless, it has been claimed that the process of gallstone formation is different in children under the age of 10 when particularly compared to adults, because in pediatric patients, the larger part of the gallbladder stone is composed of pigment stones while the smaller part is of cholesterol stones [6].

Related studies in the field have suggested that 80% of the gallbladder stones is symptomatic in adults whereas only 10-33% is symptomatic in children [4]. Esposito *et al.* [3] stated that non-calcified stones may spontaneously resolve within 3-6 months. Nonetheless, symptomatic or incidentally detected asymptomatic calcified stones should be intervened through a surgical procedure. Although all of gallbladder stones in our series were symptomatic, we detected only 10 (41.6%) patients who have specific symptoms.

Although ultrasound imaging is sufficient for the diagnosis of gallbladder stones, scintigraphy (for ejection fraction) and magnetic resonance cholangiopancreatography have been claimed to be necessary to display bile ducts and the flow of the bile in patients having episodes of cholangitis or biliary dyskinesia [1, 7, 8]. In our series, the diagnosis was made using ultrasonography for all patients. No pathology was detected related to the bile flow in two patients that brought their scintigraphy results from external centers.

There are differences between adults and children regarding the cholecystectomy indications and results. While cholecystectomy is frequently performed due to acute inflammation in adults, the main reason for cholecystectomy in pediatric patients without inflammation signs is the prophylactic removal of gallbladder stones [7, 9]. In recent years, large series in which cholecystectomy was performed in the presence of biliary dyskinesia, diagnosed by advanced scintigraphic investigations, have been published [8, 10, 11]. However we haven't enough detecting technology for biliary dyskinesia diagnosis but all of our cases have symptomatic gallbladder stone.

Conventional cholecystectomy is performed through the open technique using a subcostal or midline incision; however, extended hospital stay and prolonged wound healing are inevitable in open procedures [4]. Since 1987, the year when it was first performed on an adult patient; laparoscopic cholecystectomy has been increasingly used in gallbladder pathologies [12]. In 1991, laparoscopic cholecystectomy was reported to be safe and effective to use in pediatric patients for the first time [13, 14]. After that date, laparoscopic cholecystectomy has become a standard method implemented in children. Moreover, laparoscopic cholecystectomy can also be performed through the single-incision laparoscopic surgery technique despite the need for longer time and difficulty of the manipulation of the anatomical structures [15]. Notwithstanding, the 4-port laparoscopic cholecystectomy is considered as the gold standard for treatment of gallbladder pathology [16]. It is recommended that if there is need for the transition from open method to the single-incision method, the performer should transit to laparoscopic cholecystectomy first, and then start using the single-incision technique [16]. In the present series, all patients were intervened using the 4-port technique. It is possible to use small-diameter tools; however, large ports are still essential for extraction of both clip appliers and the gallbladder. Similar to the process in adults, the pediatric laparoscopic cholecystectomy is completed with dissection of the gallbladder of the liver bed through identification of the Calot's triangle and subsequent binding of the cystic duct and the cystic artery. However, it should always be kept in mind that the biliary system can vary from patient to patient in the pediatric group just like in the adults [3]. In the present study, one patient had cystic artery variation.

Bile duct injury is a frequently reported complication of cholecystectomy in adult patients [3, 9]. However, the bile duct and cystic canal junction can be easily observed in children by exposing the

Calot's triangle during binding the cystic canal. The presence of stone in the bile duct is another problem. Although intra-operative cholangiography can be performed in such cases, it is not always a necessity, since this situation is relatively rare. None of our patients needed intra-operative cholangiography during laparoscopy. Postoperative endoscopic retrograde cholangiopancreatography has been suggested to be performed following laparoscopic cholecystectomy in patients in whom such a situation is suspected [3, 9]. If the surgical team encounters difficulties related to previous cholecystitis (e.g. bleeding, perforation of the gallbladder), they may use the alternative of open procedure; however, the open technique was not necessary for any of our patients [9].

Conclusions

In conclusion, as adult population the gallbladder diseases requiring surgery is increasing in childhood. Nonetheless this laparoscopic cholecystectomy procedure can be applied easily in a wide age range. Laparoscopic cholecystectomy is an efficient method for gallbladder pathologies with the advantages it provides in children and surgeons should be encouraged to perform laparoscopic cholecystectomy.

Conflict of interest

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Evaluation of child and adolescent psychiatry consultations in a tertiary university hospital

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ABSTRACT

Objectives. The aim of this retrospective study was to examine referral pathways to department of Child and Adolescent Psychiatry in a tertiary university hospital for consultation-liaison and to identify patterns associated with demographic characteristics of children, referral sources, the presenting problems, diagnoses and the treatments. ***Methods.*** The consultation demands from inpatient and outpatient clinics of our hospital between October 2015 and October 2016 were screened retrospectively. ***Results.*** Psychiatric consultations were demanded for 263 child and adolescent patients who were treated in inpatient and outpatient units for one-year period. The children consulted were primarily females (52.5%) and who were in 12 or older age group (62%). Children were referred mostly because of mood and anxiety related complaints. Major depressive disorder was the most common diagnosis. Children were referred mostly from the pediatric emergency service. The intensive care, oncology, hematology and endocrinology departments of pediatrics were also the common referral sources. Psychotropic medications were recommended for 22 percent of children. Psychotherapeutic interventions were conducted in approximately half of the children. ***Conclusions.*** Pediatricians have to pay an extra attention to female adolescents. Emergency service demands for suicide attempts are higher than the other departments and there is a need for more collaboration with emergency service. Future studies of child and adolescent psychiatry consultants need to be aware of the growing body of literature supporting the biopsychosocial model of understanding the process of adjustment to chronic childhood illness and the experience of hospitalization.

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Keywords: Consultation; liaison; psychiatry; child; adolescent

Introduction

According to Lipowski [1], consultation-liaison psychiatry is the field of clinical psychiatry that involves all diagnostic, therapeutic, teaching and research activities for psychiatrists in the non-psychiatric parts of the hospitals.

There is a severe lack of child and adolescent psychiatrists in the United States [2] and is likely to remain present for the predictable future [3]. The availability of professionals specifically trained in the area of child and adolescent psychiatry to meet the

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high demand of services required is still a problem in all over the world. Although primary care providers usually refer children to child and adolescent psychiatry clinics for psychiatric treatment, significant barriers present to referral, including lack of available child and adolescent psychiatry specialists, insurance problems, appointment delays, and stigma [4].

High psychiatric disturbance rates have been seen in children admitted to pediatric clinics [5]. Chronic medical illness in childhood and adolescence period increases the psychiatric disturbance risk. Compared to healthy controls, rates of psychiatric disorder are up to four times greater in children with chronic physical illness [6, 7]. Emotional problems might complicate the management of organic pathologies [5]. Treating the psychiatric comorbidity of the physically ill child could facilitate the adjustment of the child to his/her illness [8].

Psychiatric disorders in physically ill children are more likely to occur when risk factors such as premorbid psychopathology, infancy age period, chronic illness and multiple hospitalizations, parents' inappropriate attitudes, and poor parent-child relationship are exist [9]. Child's developmental stage, social factors, such as the parents' response to the child's condition, and physiological issues, such as the characteristics of pain and nature of the chronic illness are known to be the factors that affect the child's psychosocial adjustment to his/her illness [10, 11].

Data about rationales for child and adolescent psychiatry consultation, psychiatric diagnosis and treatment to date is critical to better evaluate existing child needs and the current functioning of child and adolescent psychiatry services [12].

The aim of this retrospective study was to examine referral pathways to department of Child and Adolescent Psychiatry at our university hospital for consultation-liaison and to identify patterns associated with demographic characteristics of children, referral sources, the presenting problems, diagnoses and the treatments.

Methods

This is a retrospective study of a sample including all inpatient and outpatient units of Ankara University School of Medicine up to the age of 20 who had a consultation with child and adolescent psychiatry department between October 2015 and October 2016. Data about the child's age, gender, medical history, primary diagnosis, psychiatric evaluations, treatments were extracted from the patient file database. A total of 263 consultations were presented and retrospectively screened. The IRB/Ethics Committee had ruled that approval was not required for the study. Clinical diagnosis was based upon DSM IV-TR criteria [13].

The assessment of the child may require multiple interviews with the child, parents, service doctors, nurses and child's teacher as needed. In our department, treatment planning is made by the child and adolescent psychiatry team according the biopsychosocial approach for every child. Treatment recommendations include psychoeducation on medication and illness and diagnostic issues, physical exercise, relaxation tecniques, medical therapy or psychological testing as needed. Supportive psychotherapy, preparation for hospitalization, surgery, transplantation and diagnostic procedures, arrangement of follow-up care, coping-strategies intervention, helping the patient/family communicate with medical staff and with each other, cognitive behavioral intervention, crisis intervention, grief intervention, therapeutic play, occupational therapy, behavioral modifications, group therapy, liaison, and arrangement of health reports of disabled children for special education are also provided by the child and adolescent psychiatry team as needed.

Statistical Analysis

For the categorical variables, the descriptive statistics were calculated as frequencies. The categorical data were expressed as number (n) and percentage (%). All statistical analyses were performed using IBM SPSS Statistics 20.0 software (IBM, Armonk, NY, USA).

Results

Psychiatric consultations were demanded for 263 child and adolescent patients who were treated in inpatient and outpatient units of our university hospital for one-year period. The mean age was 11.7 and the standard deviation was 4.77. There were 125 boys (47.5%) and 138 girls (52.5%) in our study.

Figure 1 shows the percentage distribution of children ages. The overall frequency of referrals for the adolescent group (n=163, 62%) was greater than the other age groups.

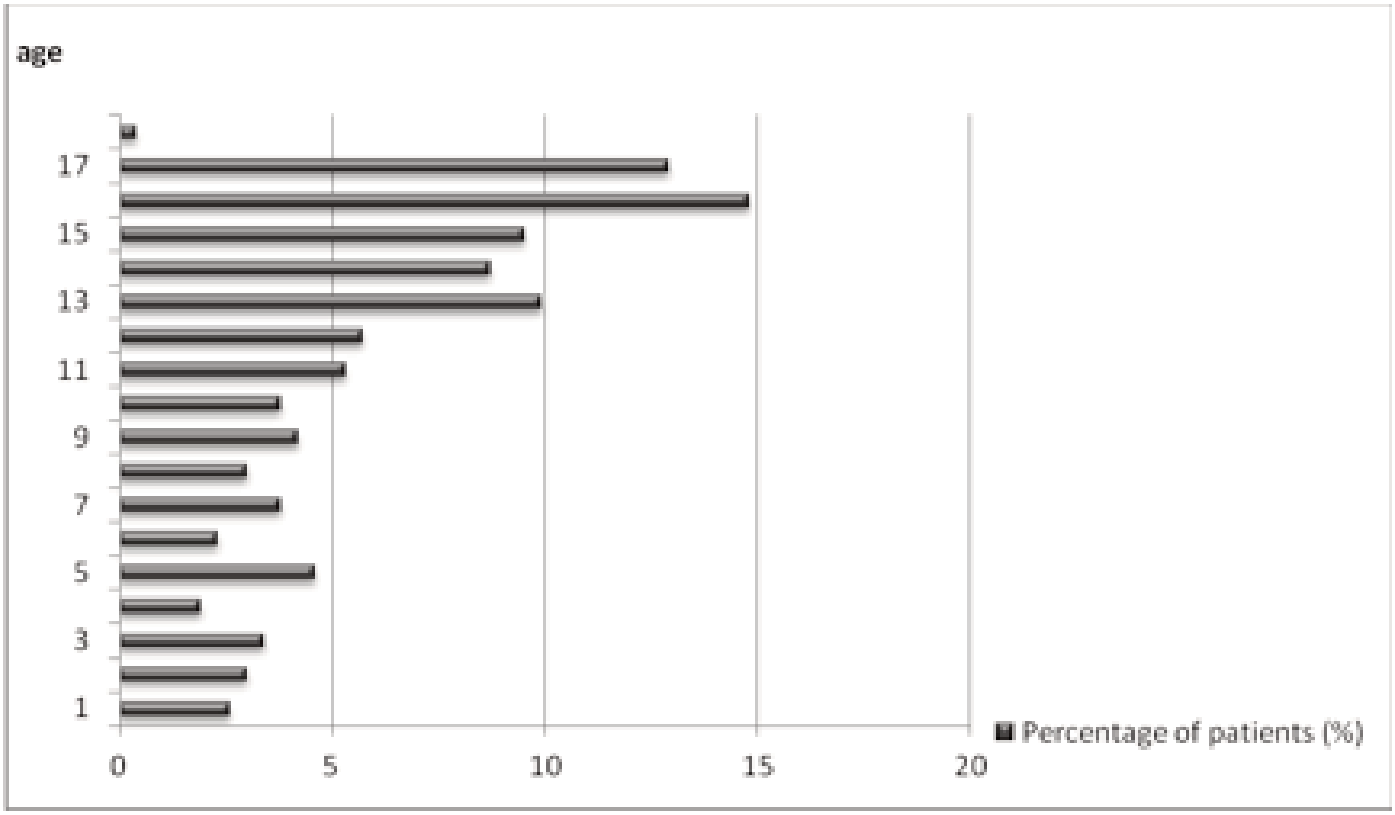

Figure 1. Distribution of the children according to ages

As shown in the Figure 2, children were referred mostly from the pediatric emergency service. The intensive care, oncology, hematology and endocrinology departments of pediatrics were also the common referral sources. Pediatric surgery was the most common referral source from the surgery departments of our university hospital. The other surgery departments labeled as 'others' in Figure 2, consisted of brain surgery, orthopedic surgery, urology, plastic surgery and ophthalmology.

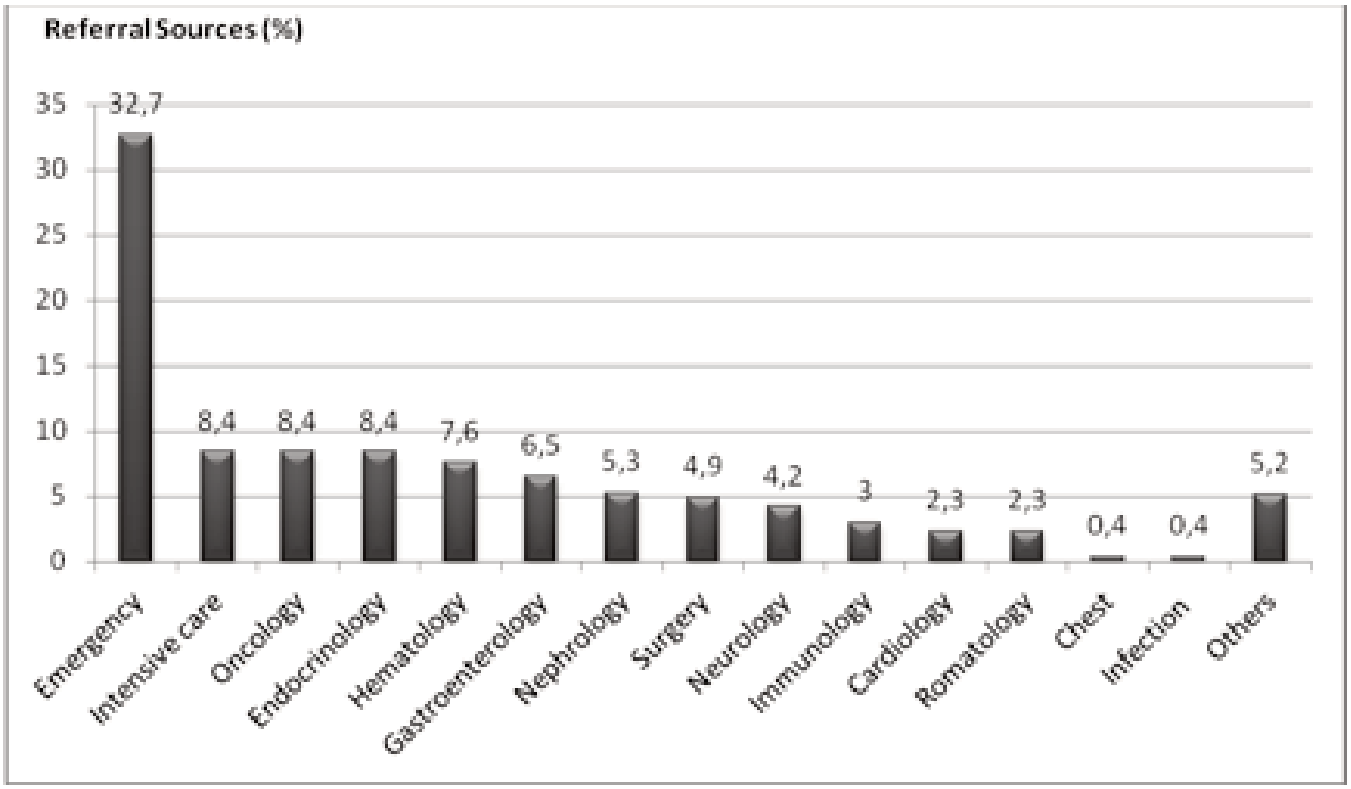

Figure 2. Distribution of the referral sources

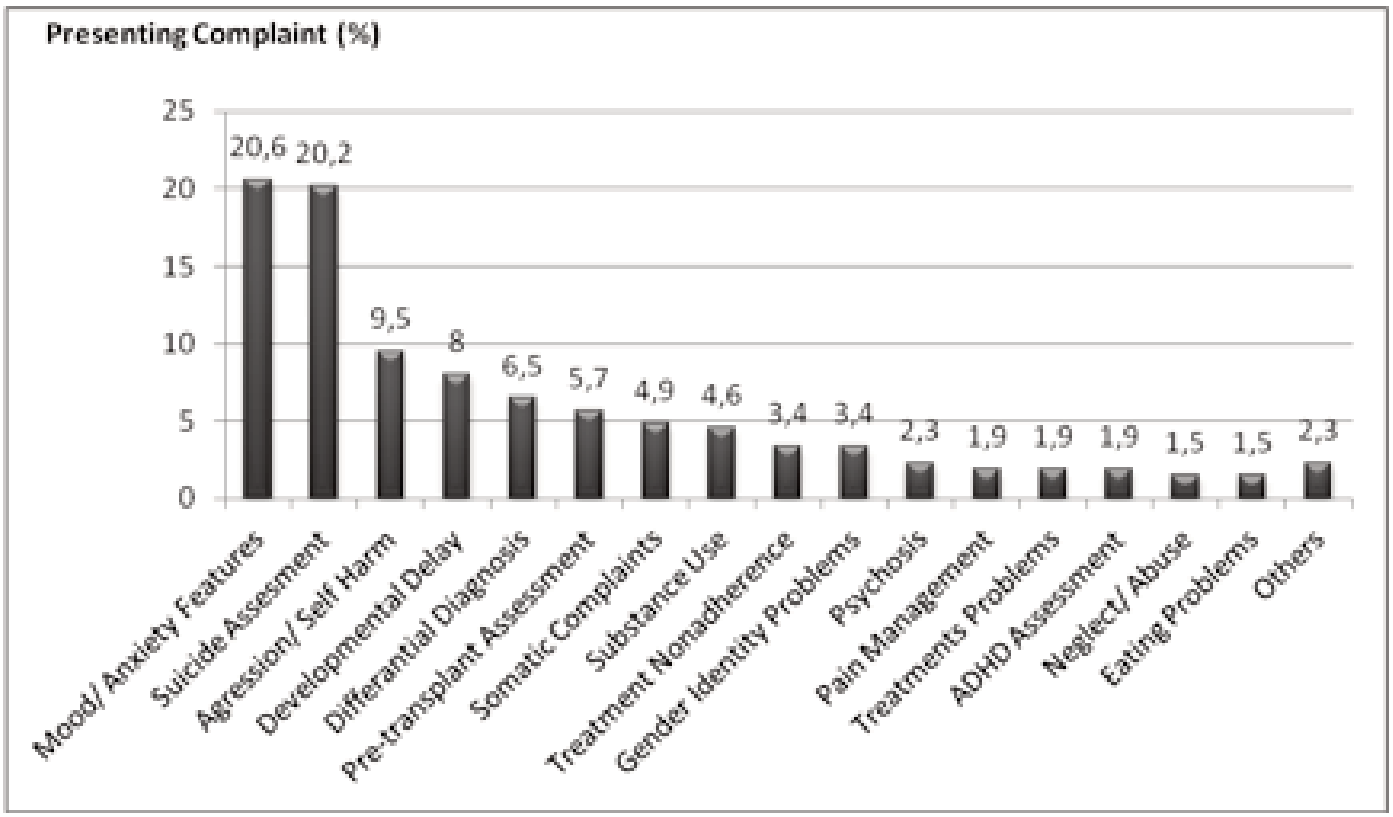

Figure 3. Distribution of the presenting complaints of the children

Children were referred mostly because of mood and anxiety complaints. Half of the presenting complaints were consisted of mood/ anxiety problems, suicide attempts, aggression, disruptive behaviors and self-harm. The main complaints were presented in Figure 3.

There was a DSM-IV diagnosis for 188 out of a total of 263 children. There were ongoing psychiatric assessments and further evaluations for these 75 (28.5%) undiagnosed children. The diagnosis distribution is presented in Figure 4. Forty-seven (17.9%) cases were not qualified for a DSM-IV diagnosis. Major depressive disorder was the most common diagnosis given by the child adolescent psychiatrist. Approximately one fifth of children in our study were diagnosed as mood or anxiety disorders. Psychological assessment demand for determining the developmental delay or mental retardation in child who has a suggestive symptom was one the common referral reason. Developmental delay/mental retardation was detected in 9.5% of the children in our study.

Of the group of 263 children, 46 (17.5%) were seen on more than one occasion by the child and adolescent psychiatrist. 58.7% of the multiple consultations were undertaken within 30 days and 28.3% of the multiple consultations were undertaken within 31-90 days from the initial consultation.

In the light of the child and adolescent psychiatry consultations which were demanded in the study period, 127 (47%) cases were referred to follow-up sessions and to further evaluations like psychological testing and no medication was recommended for this group. Combined psychotropic medications with any kind of psychotherapeutic interventions (which were detailed in the method section) were conducted in 60 (22%) cases. Among these cases, selective serotonin reuptake inhibitors (SSRI) as a medication was suggested to 39 (65%) children and antipsychotic medication was suggested to 20 (7%) children and benzodiazepine medication was suggested to 1 (1.7%) child. Any kind of psychotherapeutic interventions without a psychiatric medication were conducted in 65 (23%) children. Eighteen (5.5%) children were referred to special education centers due to developmental delay/mental retardation. Ten (2.5%) children were referred to the inpatient psychiatry unit due to his/her persistent suicide ideation.

Discussion

The aim of this study was to get an overview of the number and characteristics of child and adolescent

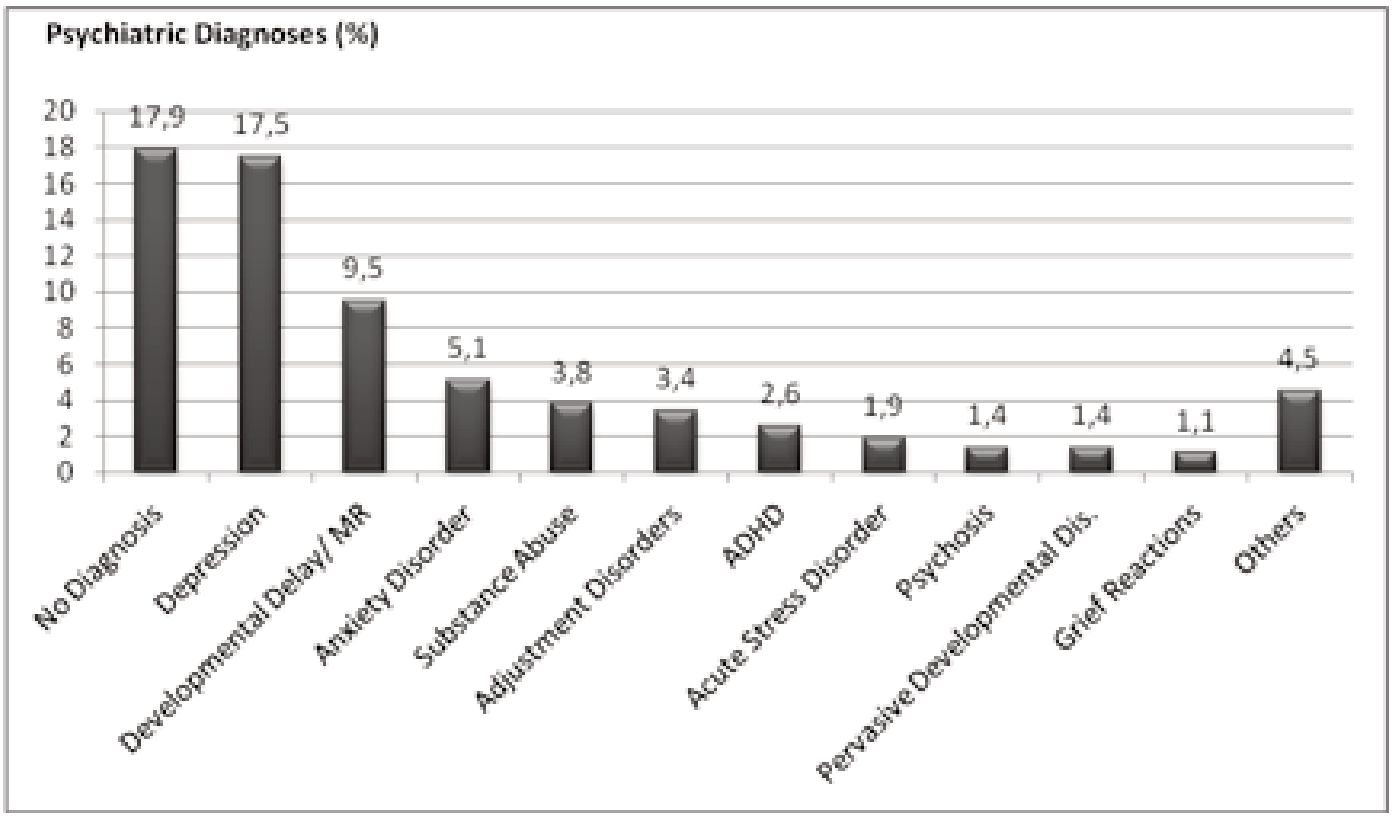

Figure 4. Distribution of the diagnoses of children given by child and adolescent psychiatry. ADHD=attention deficit hyperactivity disorder, MR=mental retardation

psychiatry consultations at our university hospital within one-year period and to determine the service property that was offered. In this retrospective study, we assessed the child and adolescent psychiatry consultations, demanded for 263 child and adolescent patients who were treated in inpatient and outpatient units of our university hospital for one-year period. Our study results showed that female adolescents were more likely to be referred to child and adolescent psychiatry clinic. The results from this study are parallel to the current literature [14-17]. This is of particular significance for mental health intervention, due to the increase in emotional and behavioral problems and the onset of psychiatric disorders that arise during adolescence [18]. Anxiety and depressive disorders are joined under the category of internalizing disorders, while aggressive behavioral disorders and attention deficit hyperactivity disorder are regarded as externalizing disorders. In our study, most of female adolescents had internalizing disorders. As for gender differences, previous studies showed that female adolescents have higher prevalence of internalizing disorders than male adolescents [19]. It has been reported that sex difference in internalizing problems is associated with sex differences in stress reactivity [20]. Cortisol secretion is closely related with age, puberty, and sex [20]. Increased doses of basal cortisol and increased response to interpersonal stressors have been shown among adolescents with internalizing problems [20]. Furthermore, high doses of estrogen can augment stress response [20]. Abovementioned explanations seem to have roles in the vulnerability of female adolescents to external stressors [20].

Children were referred mostly because of their mood and anxiety complaints. Half of the presenting complaints were consisted of mood/anxiety problems, suicide attempts and aggression, disruptive behaviors and self-harm. The most common diagnosis was depression and the most common complaint was suicide attempt. This finding is parallel to the literature on the pediatric patients [21]. Suicide attempt age has been reported as 13 to 18 years [22, 23]. It is indicated that 50% of adult psychiatric disorders have their onset in adolescence period [24]. It was reported that mood disorders have shown low prevalence until the early teens followed by a roughly linear increase through late middle age [25]. Results of a national survey in which 144 pediatric child and adolescent psychiatry services in United States were included, showed that the majority of the child and adolescent psychiatry consultations have been demanded for depression and anxiety [21, 26]. Consistent with both national and

international large studies results, the majority of the referrals came from pediatric emergency services, general pediatrics, and pediatric hematology/oncology departments [14, 15, 21, 27]. In our study, child and adolescent psychiatry consultations which were demanded by pediatric endocrinology were higher than the previous studies [5, 14]. This result might be the reflection of the specialty collaboration due to the common gender identity council in which child and adolescent psychiatry and endocrinology both participate.

Aggression, disruptive behaviors and self-harm are commonly main features of agitated depression. In our sample, depression is the most common diagnosis. The routine physical activity of the child is precluded during the hospitalization. Long hospitalization may negatively influence the child and may cause aggression. Due to the abovementioned possible explanations, aggression, disruptive behaviors and self-harm were at the top places of the chief complaint list.

Developmental delay/mental retardation was one of the most referral causes. This result is parallel to the literature [14, 28]. Etiological agent of the disease may affect negatively the perception, attention and central nervous system of the chronically ill children in pediatric units. Exposure of the physical illness/ agent during the vulnerable time like intrauterine period can cause mental retardation. Furthermore, long hospitalization may cause absenteeism from school and sensory deprivation, and also may decrease the amount of information retrieval. These abovementioned possible causes can explain the high frequency rate of developmental delay/mental retardation diagnosis.

Collaboration need is extremely important for differential diagnosis of the patients. In our study, 6.5% of the child and adolescent psychiatry consultation demands were undertaken as a result of pediatrician's indecision about the diagnosis of his/her patient. Forty-seven (17.9%) of the children in our sample were not qualified for a DSM-IV diagnosis. This result is consistent with previous study results in our country [14, 29]. According to pediatricians' perspective, severity of a psychiatric symptom can be more important when dealing with a stressful situation.

In our clinic, treatment planning is considered according to the biopsychosocial approach for every child when dealing with chronic and life-threatening diseases. Therapeutic intervention starts with the assessment. Sometimes the psychiatric intervention is limited to giving psycho education to the child and to his/her family about the illness. We play an important role in actions such as preparation for hospitalization, surgery, transplantation and diagnostic procedures of the child. Supportive psychotherapy, coping-strategies intervention, cognitive behavioral intervention, crisis intervention, grief intervention, therapeutic play behavioral modifications, individual therapy, occupational therapy, group therapy, liaison, and arrangement of health reports of disabled children for special education are also provided by the child and adolescent psychiatry team as needed.

Combined psychotropic medications with any kind of psychotherapeutic interventions (which were discussed above) were conducted in 60 (22%) cases. SSRI medication was suggested in two thirds of these cases. The rates of mood/anxiety disorders and suicide attempts were high in our sample. Mostly SSRIs were suggested as a psychotropic medication. This result is consistent with previous study results [14, 15]. Our psychotropic medication rate is relatively lower than the previous studies [21]. In literature, antidepressants are mainly chosen in self-poising attempts [30, 31]. This is consistent with our clinical experience. In the light of this reality and our clinical experience, our consultant team does not initially suggest antidepressants in these cases. We prefer to start the treatment with psychotherapeutic interventions for this special group and then add antidepressants after following visits. This can be the reason for our lower SSRI usage in instances of suicide attempt survivors. Any kind of psychotherapeutic interventions with or without a psychotropic medication were conducted in 125 (45%) children. Psychotherapeutic interventions were conducted in approximately half of the children. This ratio is similar to international study findings but higher than the rates of national study findings [14, 21]. It takes time to conduct any kind of psychotherapeutic interventions. One study result showed that 43% of consultation-liaison programs have reported inadequate staffing to meet the clinical need, and 42% have reported difficulties recruiting child psychiatry staff and faculty, consistent with the overall national lack of child and adolescent psychiatrists. For optimum child and adolescent psychiatry assessments, there has to be adequate educated staff to meet the expectations of children, families and the pediatricians. Aysev *et al.* [32] evaluated the child and adolescent psychiatry consultations of 115 child and adolescent patients who

were treated in inpatient and outpatient units of our university hospital between 1992-1993. When we compare our study result (n=263) with this previous study result (n=115), we see that the current consultation demand becomes 2.3 times higher than the mentioned year. Our result is parallel to the results of a large national study conducted in the Unites States [21]. It was indicated that the increased level of medical acuity and shorter lengths of stay have led to increased work demands, most of programs reporting an increase in the amount of consultation requests [21]. According to this study result, 57% of programs reporting an increase in clinical service requests over the past 5 years. Our finding is favorable for child and adolescent psychiatry and for children. This attitude could be the result of increased awareness of pediatricians about child and adolescent psychiatry and the increase in consultation demands. Most of the children in our study were seen on one occasion by a child and adolescent psychiatrist. The possible explanation of this finding could be the increased amount of consultation demands and limited time.

The approximate ratio of pediatric departments' consultation demands to the surgery departments' consultation demands is 9:1 in our study. This finding is consistent with Aysev *et al.* [32] study finding of ratio 10:1. This outcome might be the result of the shorter length of hospitalization in surgery. Also this marked discrepancy in the referral rates between these departments might be related to the variation of the degree of awareness about child and adolescent psychiatry consultations.

The Limitations of the Study

Limitation of our study is the absent of follow-up process of the children and adolescents due to the retrospective study design. Further prospective studies are needed to highlight the psychopathologies of chronically ill children and to highlight the influences of hospitalization on children's psychology.

Conclusions

To sum up our study results, child and adolescent psychiatry consultations were demanded mostly for female adolescents. Common psychiatric diagnoses among these children and adolescents were depression, developmental delay/mental retardation and anxiety disorders. Half of the presenting complaints were consisted of mood/ anxiety related problems, suicide attempts, aggression, disruptive behaviors and self-harm. The majority of referrals came from pediatric emergency services, general pediatrics, pediatric hematology/oncology and pediatric endocrinology departments. Psychotherapeutic interventions were conducted in approximately half of the children. The most common psychotropic medication was SSRI medication and it was suggested in two thirds of the cases in our study. Our study has given some understanding of the current approach. The findings have highlighted that it appears difficult to cover all pediatric consultations by consultation-liaison services. Identifying children "at risk" early in the child's hospitalization may help reduce the psychiatric morbidity and prevent behavioral disturbances that interfere with medical treatment and recovery [33].

Pediatric consultation-liaison is a growing aspect of psychiatric divisions in academic field, clinical care for children and families, and support for pediatric staff. It is indicated that future studies of child and adolescent psychiatry consultants need to be aware of the growing body of literature supporting the biopsychosocial model of understanding the process of adjustment to chronic childhood illness and the experience of hospitalization [34]. Providing sustainable resources to support staff training, inter-professional education, evaluation strategies and research is critical. Further studies are needed to understand how to promote these important services within the rapidly changing healthcare system.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Clinical value of neutrophil to lymphocyte ratio in the region of lower extremity deep venous thrombosis

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ABSTRACT

Objectives. Many studies have demonstrated a significant association between cardiovascular disease and neutrophil to lymphocyte ratio (NLR). To our knowledge, no study has been reported in patients with deep venous thrombosis (DVT) which affecting proximal or distal leg. In this study we analyzed proximal and distal DVT according to the NLR. ***Methods.*** This retrospective study was obtained from patients' records of a tertiary university hospital between May 2011 to January 2014. A total of 57 patients with the diagnosis of acute primary DVT and 30 patients as control group included in the study. All of them were confirmed with lower extremity venous duplex examinations. Of these, 37 examinations with the diagnosis of proximal DVT were compared to 20 examinations with distal DVT. The groups compared regarding to complete blood counter values. ***Results.*** Mean eosinophil level was higher in the distal DVT group (0.28±0.24 vs. 0.12±0.01, p=0.001), whereas median NLR were higher in the proximal DVT group than the distal DVT group (3.5 [0.5-4.3] vs. 2.3 [1.2-9.7], respectively; p=0.002). In addition, median NLR, leukocyte and neutrophil counts were statistically lower in the control group than the others (p=0.014, p=0.027 and p=0.004, respectively). ***Conclusion.*** NLR, an inexpensive and easily measurable laboratory variable, was independently and significantly associated with the presence and severity of DVT, especially acute proximal DVT.

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Keywords: Deep venous thrombosis; neutrophil to lymphocyte ratio (NLR)

Introduction

Deep venous thrombosis (DVT), a part of clinical diagnosis called venous thromboembolism, is an important cause of morbidity and mortality. Various predisposing clinical conditions for higher risk of DVT are prolonged immobility and postoperative bed rest, malignancy, advanced age, cardiorespiratory and other organ failures, neurological disorders, and a wide variety of inherited and acquired hematological disease [1].

DVT commonly affects the leg veins, such as the femoral vein or the popliteal vein, or the deep veins of the pelvis [2]. Proximal DVT is related pulmonary embolism and the mortality. In case of proximal DVT

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identified, anticoagulant treatment should initiate immediately [2, 3]. Doppler ultrasonography is the gold standard technique for diagnosis it is noninvasive and safe [4].

Blood neutrophil to lymphocyte ratio (NLR) could be an important measure of systemic inflammation as it is cost effective, readily available and could be calculated easily. Recently, the NLR has become an emerging marker of inflammation, and a useful marker of cardiovascular disease as well as an independent predictor of cardiac or non-cardiac mortality [5].

High NLR levels show that inflammatory response occurs in patients with DVT. According to our knowledge no studies have been performed in patients with complete blood counter analysis to detect the DVT whether proximal or distal. We aimed to demonstrate any association between NLR and DVT with respect to presence and location.

Methods

Study Population

From May 2011 to January 2014, 57 consecutive patients with first time acute DVT which confirmed by venous duplex examinations in Evliya Celebi Training and Research Hospital were included to the study retrospectively. Thirty-seven patients with proximal acute DVT and 20 patients with distal acute DVT included in the study group. Thirty consecutive patients who came to the hospital with varicous veins complaints without venous thrombosis were added as control group to the study. The local ethical committee approved the study protocol.

Clinical evidence of cancer, acute coronary syndrome, congestive heart failure, chronic obstructive lung disease, chronic inflammatory disease, or any systemic infection that occurred during the first 48 hours after admission was excluded. Patients whose hospital records were incomplete, who were under the age of 18 were also excluded.

Laboratory and Radiologic Analyses

Venous Doppler ultrasonography was performed in our hospital radiology department. In this study, only patient which proximal and distal DVT corrected with lower extremity venous duplex examinations were considered in DVT group.

Complete blood count, leukocyte count, neutrophil, lymphocyte, eosinophil, mean platelet volume and NLR were recorded by using Beckman Coulter LH780. Patient clinical findings were also recorded.

Statistical Analysis

Continuous variables were shown as mean ± standard deviation. While, the mean differences between groups were compared by Student's t test, Mann-Whitney U test was applied for comparisons of the median values. Whether the distributions of continuous variables were normally or not was determined by Kolmogorov Smirnov test. Categorical data were analyzed by Pearson's Chi-Square test. The optimal cut-off points of NLR to determine both proximal and distal DVT was evaluated by receiver operating characteristic (ROC) analysis as giving the maximum some of sensitivity and specificity for the significant test. Predictive effect of NLR on the DVT was evaluated by binary logistic regression analyses after adjustment for all possible confounding factors. Odds ratios and 95% confidence intervals for each independent variable were also calculated. p value less than 0.05 was considered statistically significant. Data analysis was performed using SPSS for Windows, version 21 (SPSS Inc., Chicago, IL, United States).

Results

Clinical and laboratory characteristics of the patients with DVT were summarized in Table 1. There was no significant difference between proximal and distal DVT groups regarding age, sex, clinical risk factors including hypertension, diabetes and smoking. Laboratory parameters including leukocyte, red cell distribution width, neutrophil, mean platelet volume and platelet count were also similar in both DVT groups (see Table 1).

The mean age of the patients with proximal DVT and distal DVT groups were 49.4±6.3 and 55.9±13.3, respectively; p=0.148. Patients with distal DVT were predominantly older and also were predominantly males compared to the proximal DVT group patients but statistical significant difference was not found (p=0.237) (see Table 1).

Mean eosinophil level was higher in the distal DVT group (0.28±0.24 vs. 0.12±0.01, p=0.001); in contrast the median value and the interquartile range (25^{th} and 75^{th}) of NLR were higher in the proximal DVT group than the distal DVT group (3.5 [0.5-4.3] vs. 2.3 [1.2-9.7], respectively; p=0.002) (Table 1, Figure 1).

Table 1. Demographic features of the patients with deep venous thrombosis

Variables	Proximal DVT group (n=37)	Distal DVT group (n=20)	*p*
Age (years)	49.6±16.3	55.9±13.3	0.148
Female	19 (51.3%)	7 (35%)	0.237
Leukocyte ($X10^9$/L)	8.05 (3.1-17.5)	8.1 (3.6-13)	0.904
MPV (fL)	8.2±0.9	8.5±0.7	0.078
Hemoglobin (g/dL)	13±1.9	14.1±1.3	**0.003**
Smoking	23 (62.1%)	8 (40%)	0,178
Hypertension	19 (51.3%)	8 (45%)	0,623
Diabetes mellitus	4 (64%)	4 (64%)	0,432
RDW (%)	13.5 (12-18)	14.6 (12-19)	0.146
Lymphocyte ($X10^9$/L)	1.7 (1-4)	2.3 (1-5)	**0.001**
Neutrophil ($X10^9$/L)	5.4 (2-14)	5 (1-8)	0.260
NLR	3.5 (0.5-4.3)	2.3 (1.2-9.7)	**0.002**
Eosinophil ($X10^9$/L)	0.12±0.01	0.28±0.24	**0.001**
Platelets ($X10^9$/L)	265 (85-464)	247 (85-410)	0.477

Data are shown as mean±standard deviation or median (interquartile range) or number (%). DVT=deep venous thrombosis, MPV=mean platelet volume, NLR=neutrophil to lymphocyte ratio, RDW=red cell distribution width

Median NLR, leukocyte and lymphocyte counts were statistically lower in the control group than the others (p=0.014, p=0.027 and p=0.004, respectively) (Table 2). The other variables including gender, age, lymphocytes, and eosinophil were similar in patients with or without DVT. According to the ROC curve analysis, the optimal cut-off value of NLR to predict proximal DVT was ≥1,9637 with 75% sensitivity and 65% specificity (area under curve=0.778, CI=95%) (Figure 2).

According to the binary logistic regression analysis, lymphocyte count, hemoglobin level, NLR were able to define patients with proximal DVT compared to the other two groups independently (Table 3).

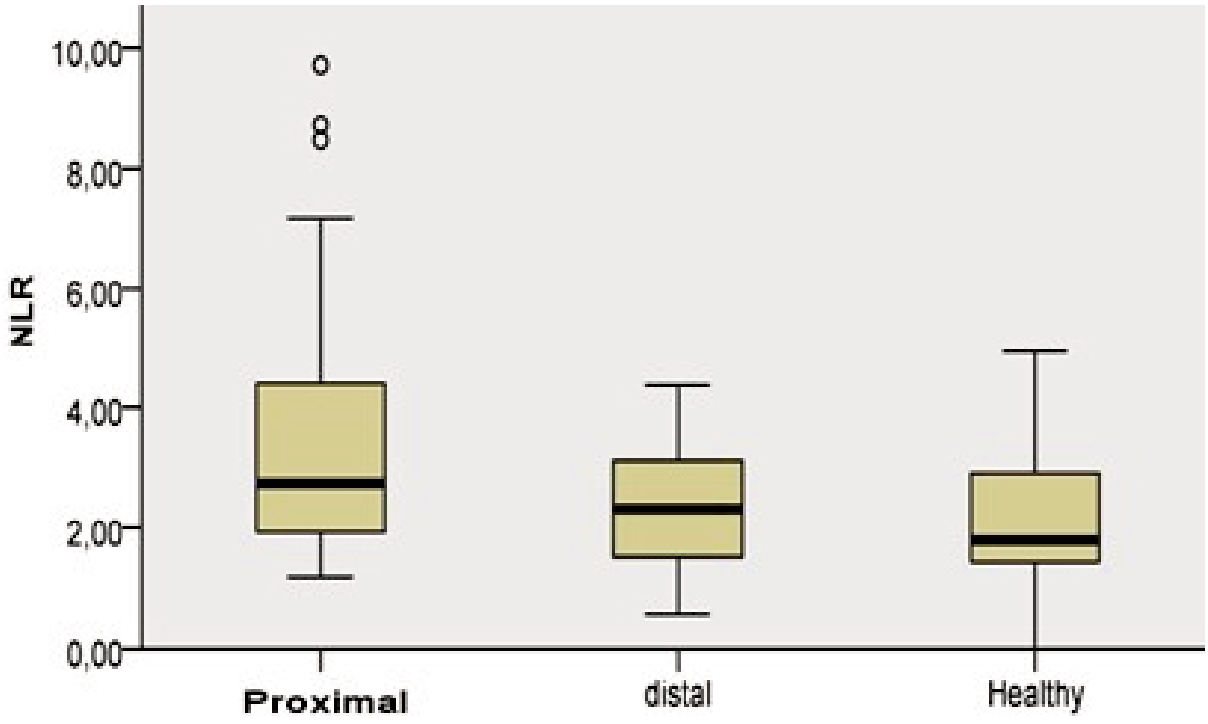

Figure 1. Kruskal-Wallis test for NLR in the healthy and DVT groups. The median value and the interquartile range (25th and 75th) of NLR (%) level were higher in proximal DVT group. DVT=deep venous thrombosis, NLR=neutrophil to lymphocyte ratio

Table 2. Demographic features of the patients with or without DVT

Variables	Control group (n=30)	DVT group (n=57)	*p*
Age (years)	49.3±15	51.7±15	0.499
Female	15 (50%)	26 (45.6%)	0.697
Leukocyte ($X10^9$/L)	6.7 (3.8-11)	8.3 (3.1-17.5)	**0.027**
MPV	8.4±0.9	8.3±0.9	0.446
Hemoglobin	13.2±1.6	13.4±1.7	0.331
RDW	13.6 (12-19)	14.8 (12-19)	0.104
Lymphocyte ($X10^9$/L)	1.8 (1-4)	1.8 (1-5)	0.881
Neutrophil ($X10^9$/L)	3.7 (1-8)	5.6 (1-14)	**0.004**
NLR	1.88 (0.1-4.9)	2.6 (0.5-9.7)	**0.014**
Eosinophil ($X10^9$/L)	0.13 (0-3.3)	0.12 (0-1.1)	0.316
Platelets ($X10^9$/L)	221 (109-528)	230 (85-723)	0.382

Data are shown as mean±standard deviation or median (interquartile range) or number (%). DVT=deep venous thrombosis, MPV=mean platelet volume, NLR=neutrophil to lymphocyte ratio, RDW=red cell distribution width

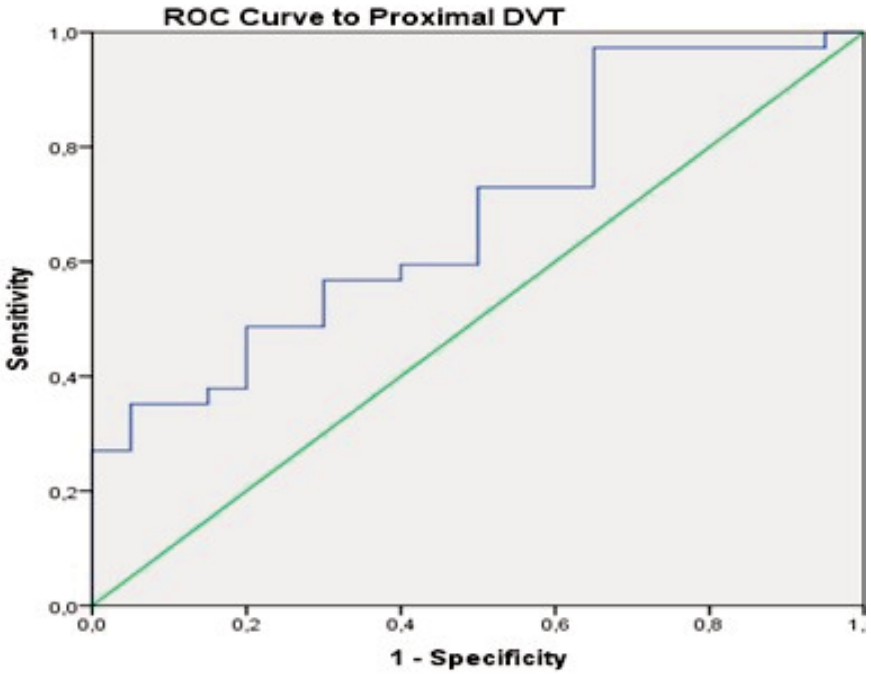

Figure 2. According to the ROC curve analysis, the optimal cut-off value of NLR to predict proximal DVT was ≥1,9637 with 75% sensitivity and 65% specificity (area under curve=0.778, CI=95%). CI=confidence interval, DVT=deep venous thrombosis, NLR=neutrophil to lymphocyte ratio, ROC=receiver operating characteristic

Discussion

In this study we evaluated the relationship between NLR and the presence proximal DVT in 57 patients with acute DVT. The findings of the present study indicated for the first time that NLR, lymphocyte, hemoglobin, and eosinophil are independent predictor of proximal DVT in patients.

The number of leukocytes and the ratio of their subtypes are regarded as markers of inflammation in all cardiovascular disease [5, 6]. NLR is an indicator of subclinical inflammation. Elevated NLR means higher neutrophil count compared to lymphocyte count in response to stress such as infection and inflammation. This ratio, which can be calculated easily, may be used as an independent prognostic factor in DVT whether it affect proximal or distal.

Previous studies had shown its prognostic

Table 3. Binary logistic regression analysis to define patients with proximal DVT

Variables	Score	*p* value
Gender	1.393	0.273
Hemoglobin	4.239	**0.040**
Lymphocytes	5.00.	**0.025**
NLR	5.980	**0.014**
Eosinophil	8.496	**0.004**

DVT=deep venous thrombosis, NLR=neutrophil to lymphocyte ratio

significance in cardiovascular disease including heart failure, stable and acute coronary artery disease [7-9]. It also shows that mortality increased with the increase in NLR in patients with acute coronary syndrome and those who underwent cardiovascular intervention [7, 10]. In some studies, elevated neutrophil count was found to be associated with decompensated heart failure related to acute myocardial infarction [8].

In this study, there are high NLR values in proximal DVT. Previous studies showed that pulmonary embolism and mortality is associated with high NLR values. In previous studies thrombus development is associated with vein wall inflammation marked by an early extravasation of leukocytes and elevation in pro-inflammatory mediators. In particular, neutrophils are the first leukocytes to be found in the damaged intravascular area. Pro-coagulants are secreted locally by leukocytes that contribute to oxidative and proteolytic injury especially in case of pulmonary embolism [11, 12].

After the acute phase the monocyte and macrophages cells are accumulated in the inflammation area including leg vein wall, pulmonary artery wall or lung parenchyma. These cells likely play an important role in embolism resolution.

The majority of pulmonary embolism cases were reported to be between the ages of 60-70 years and in clinical studies and between the ages of 70-80 years in autopsy series [13-15]. Mortality rate in males was found to be higher. Mortality difference between males and females is more prominent after the age of 40 years [13]. In the present study, the number of males was higher than the number of females in the patients with distal DVT. In addition distal DVT group was more prominent advanced age.

The Limitations of the Study

Our study was a single institution, retrospective study, which had a relatively small sample size, so subject to various unaccounted confounders inherent in such an analysis. We could not compare NLR with other inflammatory markers, such as C-reactive protein because of they were not routinely obtained in our study population.

Conclusions

In conclusion, increased NLR as a simple non-specific marker of inflammation is associated with proximal DVT. With its universal availability, it may serve as an inexpensive new tool for deep venous thrombosis clinical property. Further large-scale and randomized prospective studies are required to clearly understand the exact role of NLR in the pathophysiology of DVT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Unnecessary computed tomography and magnetic resonance imaging rates in a tertiary care hospital

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ABSTRACT

Objectives. The actual rate of unnecessary imaging is unknown in our country. In this study we aimed to detect unnecessary computed tomography (CT) and magnetic resonance imaging (MRI) rates and the radiological quality of these examinations in our hospital. ***Methods.*** CT/MRI request documents of 1,713 patients who had multidetector CT or MRI examination in a 2-month period at a single tertiary care hospital were obtained. We evaluated that whether the disorder that mentioned in request document was present or not in multidetector CT or MR images from the picture and archiving communicating system of our hospital. Scoring was done as follows; score 0 (there is no pathologic finding), score 1 (suspicious findings), and score 2 (presence of mentioned pathology). The radiological quality of the examinations was scored as follows; grade 0 (poor quality), grade 1 (moderate quality), and grade 2 (good quality). ***Results.*** There was not any pathologic finding in 35% of the patients included in the study (score 0, unnecessary imaging). There was/were finding(s) regarding to the disorder that mentioned in the request document in 43% of the patients (score 2). Suspicious findings were existed in the remaining patients (score 1). In the assessment of radiologic quality of the examinations that included in the study; 94% of the radiologic examinations had good quality and the remaining had moderate (0.2%) and poor (5.5%) quality. ***Conclusions.*** Unnecessary CT or MRI rate was detected as 35% in our hospital. Unnecessary imaging causes increased nephrogenic systemic fibrosis, contrast-induced nephropathy and/or radiation risks, and total cost. It may also cause reduced patient compliance and prolongation of therapy period.

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Keywords: Ionizing radiation, medical education, radiological examinations, health policy, imaging utilization, repeat imaging, CT, MRI, health care

Introduction

Unnecessary radiologic examinations leads to increase in the health expenditure and those examinations may also lead to development of nephrogenic systemic fibrosis (NSF), contrast-induced nephropathy (CIN), malignancy, reduced patient compliance and prolongation of treatment time [1]. According to Gimbel *et al.* [1], approximately 50% of advanced medical imaging in USA is unnecessary.

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There are many factors including patient age and sex, underlying disease, health care delivery model, access to high-cost imaging modalities, hospital characteristics, radiologist recommendations, national medical education status, and styles of practice can contribute to unnecessary imaging. Reducing the unnecessary CT or MR imaging can save healthcare resources, significantly.

In our country, the actual rate of unnecessary imaging is unknown. The primary aim of this study is to detect the rate of unnecessary CT and/or MR imaging at a single tertiary care hospital radiology department. Our second aim is to make a group for the reasons of CT and MR examinations and radiological quality of those examinations. Our last aim is to detect the correlation between unnecessary CT and MR imaging and intravenous (i.v.) contrast media administration in our hospital.

Methods

Local ethical committee approval or informed patient consent was obtained for this retrospective study. All of the patients (n=2,064) who had CT or MRI examination within two-month period of time were found from the picture and archiving communicating system (PACS) of our hospital. Also, MR or CT imaging request document of those patients were obtained. The patients who did not have request document or whose request form did not include enough clinical information and the patients who had time interval more than 2 weeks between the date of fulfilling the request form and CT/MR acquisition, were not included in the study. Also, CT and/or MR exams for oncologic follow-up were excluded from the study. If a patient had multiple radiologic examinations, only the most recent CT or MRI examination was enrolled in the study. As a result, CT or MR examinations of 1,713 patients that composed of 820 (47.9%) men and 893 (52.1%) women were included in the study. The mean age of men was 49.36±17.67 years, the mean age of women was 49.41±16.29 years and the mean age of all patients included in the study was 49.38±16.96 years. All of the patients who meet our study criteria were selected randomly and analyzed.

All of CT and MRI examinations were performed in the same unit. CT examinations were performed with 16-slice CT machine (Somatom Perspective, Siemens, Erlangen, Germany), and MRI examinations were obtained with 1.5-tesla MR unit (Achieva; Philips Healthcare, Best, The Netherlands). CT and MRI protocols of our hospital were described previously in our publications [2-6].

We scored that whether the disorder that mentioned in the request document was present or not in MDCT or MR images as follows:

Score 0 (there is no pathologic finding): When all of the images of the patients were evaluated, there was not any pathologic finding regarding to the possible diagnosis mentioned in the request document or any other pathologic finding.

Score 1 (suspected findings): There were suspicious findings regarding to the possible diagnosis mentioned in the request document or there were some other findings which were not related with the pre-diagnosis or patient complaint in the radiologic images of the patients.

Score 2 (apparent pathology): There were findings related with the pre-diagnosis that mentioned in the request form at CT or MR examination of the patient.

The radiological quality of the 1,713 examinations mentioned above was scored as follows;

Grade 0 (poor quality): The quality of examination was not sufficient for radiological assessment.

Grade 1 (moderate quality): Interpreting of the examination was possible however the image quality was suboptimal.

Grade 2 (good quality): Radiological reporting confidence was perfect. There was not any problem with image quality.

In addition, it was noted that whether the contrast media was administered intravenously for each of the examination or not (score 0: no contrast-material administration, score 1: contrast-media +). The results of these measurements were recorded in study table subsequently.

All of the scorings were performed by one radiologist who had an experience of 5 years (M.K.) to detect the findings mentioned above. The assessment duration of CT or MR exams was not limited, and all of the images were evaluated in same PACS system by using the same computer and same screen. All cases reviewed independently.

Statistical Analysis

For statistical analysis, all of the groups and subgroups were calculated in percentage form. The parametric data was given by mean ± standard deviation. The categorical variables were presented as frequency with related percentage.

Table 1. Examination types of the study group

Examination types	Patients (n)
Brain MRI	192
Spinal MRI	171
Extremity MRI	155
Abdominal MRI	24
Sacroiliac MRI	21
Pituitary MRI	2
Brain+cervical MRI	1
Abdominal MDCT	328
Brain MDCT	275
Thorax MDCT	263
Paranasal Sinuses MDCT	73
Temporal bone HRCT	41
Neck/Cervical MDCT	54
Thoracoabdominal MDCTA	35
Cardiac MDCTA	23
Extremity MDCT	19
Brain MDCTA	18
Thorax MDCTA	6
Thoracoabdominal MDCT	6
Neck+thorax MDCT	1
Pelvis MDCT	1
Sacroiliac MDCT	1
Maxillofacial MDCT	1

HRCT=high resolution computed tomography, MDCT=multidetector computed tomography, MDCTA=multidetector computed tomography angiography, MRI=magnetic resonance imaging, n=number of the patients

Results

The numbers and types of the CT or MR examinations which were assessed in this study were given in Table 1. There was not any pathologic finding in 35% of the patients that included in the study (score 0). There was at least one finding regarding to the disorder that mentioned in the request document in 43% of the patients (score 2). There were suspicious findings in the remaining patients (score 1) (Table 2) .

Table 2. Results of the study examination reports

Reporting Scores	Number (%)
Score 0 (there is no pathology)	595 (34.7%)
Score 1 (suspected findings)	389 (22.7%)
Score 2 (apparent pathology)	729 (42.6%)
Total	1,713 (100%)

In the evaluation of radiologic quality of CT/MR images that included in the study; 94.3% of the examinations had good quality, and the remaining part of the examinations had moderate (5.5%) or poor (0.2%) quality (Table 3).

Table 3. Radiological quality grades of the study population

Quality Grades	Number (%)
Grade 0 (poor)	4 (0.2%)
Grade 1 (moderate)	94 (5.5%)
Grade 2 (good)	1,615 (94.3%)
Total	1,713 (100%)

CT and MR examinations were performed without administration of contrast media in 904 (53%) patients while i.v. contrast-media was administered in 809 (47%) patients. There was not any pathologic finding in 162 of the patients who had i.v. contrast-media administration. There was at least one finding regarding to the disorder mentioned in the request document in 413 of the patients who had i.v. contrast-

media administration. Finally there were suspicious findings (score 1) in the remaining 234 patients (Table 4).

Table 4. Radiological quality grades of the study population

Scores	I.V. Contrast administration		Total
	No	Yes	
Score 0	433	162	595
Score 1	155	234	389
Score 2	316	413	729
Total	904	809	1,713

Contrast media was administered intravenously 27% (n=162) of the examinations which had no pathologic finding (score 0) while contrast media administration was not performed in 73% (n=433) of the examinations. Contrast media administration was not performed in 43% (n=316) of the examinations which had at least one finding regarding to the disorder that mentioned in the request form (score 2) while i.v. contrast media was administered in the remaining 57% (n=413) of the examinations (Table 4).

Discussion

All over the world, the numbers of radiologic examinations and national health expenditure have been increased due to the progression in CT and MR technology, excessive health insurance coverage and increase in geriatric population [7-10]. In our country, 11 million CT and 9 million MR examinations were performed at 2013 while 12.4 million CT and 10.3 million MR examinations were performed at 2014 [8, 10]. Three hundred and eighty million radiologic procedures (including 67 million CT scans) were performed in the USA only at 2006 [9]. According to our Ministry of Health 2014 reports, there are 1100 CT devices and 800 MR devices in our country [10-12].

When we look at the distribution of the examinations that included in the study, we detected that the most requested CT imaging types were abdomen, brain and thorax MDCT examinations respectively. The most requested MR examinations were brain, spinal and extremity MR examinations respectively as well (Table 1). According to our observations and the literature; the reasons for requesting these examinations were primarily neurologic disorders, trauma, and malignancy [13]. Thus, the task of preventing unnecessary or repeated CT/MR examinations falls on especially neurologist, neurosurgeons, oncologist, emergency unit doctors, and orthopedists.

In this study, we aimed to detect unnecessary imaging rates and evaluate the radiological quality of CT and MR examinations in our country. There was not any pathologic finding (score 0) in CT or MR examinations of 595 (35%) patients included in the study. Therefore, we can suggest that 35% of the CT or MR examinations that performed in our hospital was unnecessary (Table 2). This ratio is similar with others in literature [1].

Many factors contribute to unnecessary imaging, including patient age and sex, underlying disease, health care delivery model, access to high-cost imaging modalities, hospital characteristics, styles of practice, lack of adequate interest of doctors, social/individual preferences, national medical education status, knowledge gap regarding the safety/cost of cross sectional imaging, and radiologist recommendations [1, 14]. The repetitive use of CT and MR techniques is the main unnecessary imaging reason. Chen *et al.* [13] detected that 20% of all CT or MR examinations which were performed in a period of 90 days were repetitive imaging. Also; in this study, repetitive imaging rates were altered due to the diagnosis of the patients and hospital characteristics [13].

Preventing unnecessary cross-section examinations is crucial for decreasing health expenditure, improving health care quality, preventing the delay in treatment of the patients, avoiding of ionizing radiation (for CT exams), prevention of contrast-material related diseases (such as NSF or CIN) [14]. Obtaining the history of the patients appropriately and completely, performing optimal physical examination, and continuing education about radiation exposure risk and evidence-based principles of cross-sectional imaging to the doctors can be useful in preventing side effects which may be develop due to unnecessary or increased CT/MR imaging [9]. Gimbel *et al.* [1] decreased the number of unnecessary imaging to 50% after the education regarding to safety and cost information.

CT examinations are the main cause of medical related radiation exposure [11]. The radiation exposure applied to the patients for each CT examination has increased approximately 6 times due to the

development in technology [9]. Increasing in awareness of future cancer risk from radiation exposure was illustrated in previous studies and previous CT exposures cause approximately 15,000 deaths annually [9, 11, 15]. There are 2 main methods which may reduce cancer development due to CT examinations. First is performing specific CT protocols with the lowest dose as possible and second method is reducing the number of unnecessary CT examinations [16]. Reducing the number of unnecessary CT examinations should be noticed since this can also reduce health expenditure, delay in establishing the diagnosis for the patients and the risk of contrast nephropathy development. For the optimization of CT scanning protocols, we should implement the recommendations of international societies including International Commission on Radiological Protection, the European Commission or national radiological societies precisely in a close cooperation with the medical physicists [11, 17]. Arslanoglu *et al.* [18] focused on the knowledge of doctors and intern-doctors about the radiation exposure applied to the patients for common radiological imaging procedures in their study. This study showed us that most of the doctors underestimated the real radiation exposure. Therefore, Arslanoglu *et al.* [18] proposed that continuous education about radiation protection is necessary for all doctors.

Application of radiation protection of the patient principles which were recommended by the international atomic energy agency (preventing other parts of body out of region of interest with a lead apron, using protective goggles, and performing efficient tests regularly and frequently for X-ray permeability of CT room and lead aprons) is crucial for preventing cancer development due to CT examinations for the patients (especially for pediatric and pregnant patients) as well as health workers [19, 20].

The radiological quality of CT and MR examinations was generally good in our study (Table 3). However the expected or predicted radiological quality of CT and MR examinations can be lower in smaller hospitals (primary or secondary centers) since our center was a tertiary care reference hospital. Unnecessary examinations increase with the decrease of radiological quality and this situation may bring all of the risks that mentioned above. We should keep in mind and follow the recommendations of radiology societies for achieving the optimal radiological quality of CT or MR examinations [13, 20]. Fulfilling of the request documents by the clinicians in detail or evaluation of the patient together with the clinicians may increase the radiologic quality and contribute patient management.

In our study, unnecessary i.v. contrast media was administered in 27% (162 cases) of 595 patients who had unnecessary CT or MR examination (score 0) (Table 4). Contrast-agents are distributed over intravascular and extracellular fluids, and eliminated by glomerular filtration in patients with normal kidney function [21]. However, i.v. CT contrast media (iodine-based agents) administration can lead to CIN and i.v. MR contrast media (gadolinium compounds) administration can lead to NSF and accumulation of gadolinium at brain in the patients who have lower estimated glomerular filtration level (eGFR) (<60 mL/min) [21, 22]. Those risks are increased in patients with GFR<30 mL/min [21-23]. Although immediate hemodialysis after contrast-agent injection reduce the risk of CIN or NSF development, the etiopathogenesis of CIN or NSF is quite complicated and prediction of which patient would have CIN or NSF development is very difficult due to patient-related risk factors [22, 23]. Although there are some suggestions about avoiding NSF and CIN development in literature; the most efficient, fast and cheapest method is avoiding the unnecessary or repetitive examinations [22, 23].

The Limitations of the Study

The main limitation of this study was lack of diagnosis and imaging types based unnecessary and repeat imaging numbers, and lack of data about complications (e.g. NSF, CIN or gadolinium accumulation in the brain) due to i.v. contrast-media administrations. Also, our major concern is that a 'normal' examination is presumed as unnecessary examination. Sometimes, a normal examination has a significant contribution to patient management. Many practitioners would not consider a normal examination as unnecessary examination. "Rule out" is a very common reason for performing radiologic examinations. If patient management would not be changed then we could argue that those examinations were unnecessary. New studies are necessary to assess the contribution of the imaging findings on management of these patients. According to some reviewers, this research should be a double-blind and multicenter study for more effective results. We are planning a new and comprehensive study for clarifying these issues.

Conclusions

The rate of unnecessary CT or MR imaging was 35% which was quite high in our country according to our study. Obtaining the history of the patients appropriately and completely, performing physical examination, continuing education issues including radiation exposure and health risk, imaging costs and implementation of evidence-based medicine imaging principles to the doctors can be useful in preventing side effects which may be develop due to unnecessary or increased CT or MR imaging. Continuous education about radiation protection (especially for dose and duration reduction of ionizing radiation) is necessary for all doctors.

Conflict of interest

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The impact of family functioning and expressed emotion on caregiver burden

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ABSTRACT

Objectives. Expressed emotion and family functioning have been reported as negative impacts of the caregiver burden, mostly in mental disorders. There are limited data available to explain how these factors affect caregiver burden particularly for those caring for rehabilitation patients. In this study, the relationship of family functioning and expressed emotion with the caregiver burden was examined. ***Methods.*** A total of 103 caregivers with a mean age of 43.1±13.8 years were participated in the study. The caregivers' demographic data, psychiatric symptomatology, subjective burden, expressed emotion, and family functioning were assessed using structured and semi-structured scales. ***Results.*** Expressed emotion level (R^2=0.361, p<0.001), family functioning (R^2=0.275, p=0.003) and caregiver gender (R^2=0.361, p=0.004) were determined as significant contributory factors with the subjective burden. ***Conclusion.*** Psychological intervention programs focused on both expressed emotion and communication skills in family should be developed to reduce the caregiver burden.

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Keywords: Caregiver burden; expressed emotion; family functioning

Introduction

According to World Health Organization, disability is a general term for impairments, activity limitations and participation restrictions, and refers to the negative aspects of the interaction between an individual and that individual's contextual factors. Whether temporary or permanent, almost everyone may experience a disability during his or her lifetime. More than one billion people worldwide have a disability in various forms and degree, and of these, nearly 200 million have severe functional difficulties [1].

Chronic diseases such as cardiovascular diseases (stroke and heart disease), mental illness, cancer, and respiratory diseases are the most common health conditions causing disability. It is expected that their prevalence rates will rise because of the ageing population, changing lifestyles related to tobacco, alcohol, diet, and physical activity [1-3]. Injuries such

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as traffic accidents, occupational injuries, and violence are also recognized as contributors to disability. Traffic accidents, violence, and conflict have been reported to account for approximately 1.5% of all years lived with disability [2].

Due to changing global healthcare systems, hospital stays have become shorter, and physicians and nurses are in short supply, which has resulted in community-based care [3, 4]. Support and care at home for disabled people is provided by family members [5]. Many non-disabled family members take responsibility for supporting and caring for their relatives with disabilities as informal caregivers [6]. Caregiving is a labor-intensive occupation and requires direct support of the caregiver in various activities such as assisting daily activities, administering medications, providing transportation, preparing meals, managing finances, advocating for health care and providing emotional support for the patient [7]. Research on informal caregivers indicates that some of these caregivers experience an intense emotional and physical burden [8]. This burden may negatively affect both the caregivers' health and quality of life, which may result in mental health disorders.

Several family-related factors including family functioning and expressed emotion have the potential of negative physical and psychological impact on caregivers, which may lead to psychopathology in the caregiver [9]. Emotional over-involvement and having a critical or hostile attitude are considered to be the core components of the emotion construct and an index of the emotional climate between the patient and the caregiver [10].

There is an interaction between family members with disabilities and the qualities and functioning of the family. Transactional patterns among the subsystems are suggested to be important in understanding individual behavior and coping capacities [11]. It has been reported that poorer family functioning is associated with higher rates of caregiver burden [12].

The physical burden can be treated in a classical medical way, but emotional problems are generally intrinsic in nature. This means they are not easily diagnosed and may cause more pathological experiences as a consequence. In this study, it was aimed to address the relationship of family functioning and expressed emotion with the caregiver burden in a population of caregivers of rehabilitation patients. Furthermore, the impact of the caregiver burden on psychiatric symptomatology and quality of life (QoL) was investigated.

Methods

Participants

Participants were recruited consecutively from a rehabilitation center between October 2012 and May 2013. A total of 125 family caregivers, older than 18 years, Turkish speaking, literate, and with no psychotic spectrum disorder were informed about the study. Informed consent was obtained from 122 caregivers were recruited and 113 completed the study (5 were discharged before completion of the study, 4 were lost to follow-up). Ethics Committee approved this study, which complied with all ethical requirements.

Procedure and Instruments

The demographic data of caregivers and patients were collected from the caregivers and medical records of the patients using a data collection form. The current and past medical histories of both caregivers and patients were also recorded on this form. The functional independence measure scores of the patients were calculated to measure the patients' current functional status severity, where higher scores indicate a greater level of independence [13]. Caregivers were asked how much time they spent caregiving and a measure of caregiving occupation rate was calculated by dividing the expressed amount of time by the total time of disability of their patient. The Zarit burden interview was used to assess the subjective burden of caregivers. It is a self-administered questionnaire containing 22 items including physical and psychological health, social participation, finances, and relationship with the patient. The participants rated each item on a 5-point Likert scale. Higher scores indicate a greater burden; 0-20 points: little or no burden, 21-40 points: mild to moderate burden, 41-60 points: moderate to severe burden, and 61-88 points: severe burden [14]. The Turkish version of the Zarit burden interview was used [15, 16].

Family functioning was assessed using the McMaster family assessment device. This has 60 items and seven subscales including problem solving, communication, family roles, emotional involvement, behavior control, emotional reactions, and general functioning. The participants rated each item on a 4-

point Likert scale. Higher scores indicate healthier family functioning [17]. The validated Turkish version of the original scale was used [18].

The expressed emotion scale was used to assess the caregivers' expressed emotion levels. It is a self-administered, 41 item true-false scale. In this study, the scale developed by Berksun [19] was used because of its simplicity and high reliability for the Turkish population [20].

The psychiatric evaluation of caregivers was performed in two steps. First, caregivers were interviewed for their possible psychiatric co-morbidities with the help of the Structured Clinical Interview for DSM-IV (SCID-I) form, which was administered by the research psychiatrist [21]. Second, symptoms of anxiety and depression were evaluated using the Hamilton anxiety (HAM-A) and Hamilton depression scales (HAM-D). A research psychologist who was blind to the caregivers' diagnosis administered both the HAM-A and HAM-D to the participants.

The evaluation was completed in four sessions: acquiring demographic data, self-reporting scale administration, psychometric evaluation, and psychiatric evaluation sessions.

Statistical Analysis

Statistical analyses were performed using a commercially available statistical software package (SPSS for Windows, Version 16.0. Chicago, SPSS Ltd., 2007). Descriptive features were described as mean ± standard deviation. Correlation coefficients and their significance were analyzed using the Pearson test. Possible factors identified in correlation analyses were further entered into the logistic regression analysis to determine independent predictors of the caregiver burden. Hosmer-Lemeshow goodness of fit statistics was used to assess the model fit. A 5% type-I error level was used ($p<0.05$) to infer statistical significance.

Results

Demographic Features of Participants

A total of 113 caregivers completed the study. The mean age of the participants was 43.1±13.8 years and 72.6% were female. The caregivers were mostly the mother (25.7%), spouse (20.4%) or daughter (16.8%) of the patient. Most caregivers had primary school education (38.9%) and were unemployed (73.5%). The mean caregiving duration was 19.9±35.3 months and caregiving occupation rate was found to be 86.9±27.9.

The mean age of the dependents of the caregivers was 40.8±21.3 years, and 62.8% were male. The primary diagnosis of the patients fell into four major diagnostic groups; cerebrovascular accident (46%), spinal cord injury (23%), traumatic brain injury (46%) and cerebral palsy (11.5%). The overall functional severity of the patients was assessed using functional independence measure and the mean score was 69.4±23.1.

Family Functioning and Expressed Emotion

The expressed emotion level was assessed with the expressed emotion scale and revealed that the level experienced by the caregivers was 20.8±4.2. Family functioning was assessed with family assessment device in seven subcategories and presented in Table 1.

Subjective Burden

The caregiver's subjective burden was evaluated with Zarit burden interview and the mean level was found to be 35.7±14.9. Correlations between demographic factors, family functioning and expressed emotion levels with the subjective burden were examined. A correlation was determined between caregiver gender, occupation, number of hospitalizations, location of caregiving, caregiving occupation rate, expressed emotion level and family assessment device subcategories of communication, affective involvement, behavior control and general functioning. Expressed emotion level (R^2=0.361, $p<0.001$), family assessment device general functioning (R^2=0.275, p=0.003) and caregiver gender (R^2=0.361, p=0.004) were determined to have a positive correlation with the subjective burden. Regression analysis showed expressed emotion, caregiver occupation, family assessment device communication subscale and caregiving occupation rate to be the most contributory factors to the subjective burden (Table 1).

Caregivers' Psychological Profile

A research psychiatrist who was blinded to the mental history interviewed the caregivers with the help of SCID-I and diagnosed co-morbid psychopathology using DSM-IV-TR diagnostic criteria. Twenty-five (22.1%) caregivers reported that they had a psychiatric diagnosis before they began caregiving. The

Table 1. Correlations of selected demographic factors, subjective burden, expressed emotion and family functioning domains on caregivers' anxiety and depression symptomology parameters

	ZCBI	HAM-A	HAM-D
Caregiver gender	**.271****	**.379****	**.372****
Caregiver occupation	**-.244****	**-.252****	**-.271****
Hospitalizations	**.190***	**.370****	**.363****
Hospitalization site	**.233***	**.278****	**.338****
COR	**.269****	**.237***	**.222***
Expressed emotion	**.361****	**.287****	**.208***
FAD problem solving	0.137	0.183	0.113
FAD communication	**.229***	**.331****	**.264****
FAD roles	0.13	**.196***	0.115
FAD affective responsiveness	0.144	**.201***	0.112
FAD affective involvement	**.213***	0.121	0.038
FAD behavior control	**.194***	**.252****	0.139
FAD general functioning	**.275****	**.365****	**.219***
ZBI	1	**.500****	**.592****

ZBI=Zarit burden interview, HAM-A=Hamilton anxiety scale, HAM-D=Hamilton depression scale, FAD=family assessment device, COR=caregiving occupation rate, * Correlation is significant at the 0.05 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed).

prevalence rates of reported previous psychiatric disorders were 15%, 4.4%, 3.5% for anxiety disorder, depressive disorder, and panic disorder, respectively. The diagnostic interview according to SCID-I revealed that 51.8% of the caregivers had at least one psychiatric disorder. The most common psychiatric disorders were anxiety disorder (n=20), obsessive-compulsive disorder (n=18), post-traumatic stress disorder (n=15), panic disorder (n=12), and depressive disorder (n=6), respectively.

The psychometric scores of the caregivers were 9.94±7.68 and 7.58±5.82 for HAM-A, and HAM-D, respectively. The correlation between the caregiver burden and psychometric symptomatology and calculated correlation coefficient was 0.500 for HAM-A, and 0.592 for HAM-D (p<0.001).

Discussion

Providing care for a disabled family member at an out-of-hospital setting is being promoted by current healthcare policies. Family members are the most common source of care provider (informal caregivers) for the disabled. Female family members are more often engaged as informal caregivers, which may be a result of their social role to nurture [22]. Furthermore, our sample showed that caregivers are mostly under-educated and unemployed. An investigation into the relationship between gender, education, occupational status, and acting as a caregiver may provide more information on the causality of being an informal caregiver.

The expressed emotion effect on the caregiver burden has been investigated mostly in mental and behavioral disorder studies [23]. The current study is one of the few studies investigating the expressed emotion effect on the caregiver burden and, as a consequence, psychiatric symptomatology and quality of life. Expressed emotion is the most contributory factor among family functioning and other demographic factors.

The impact of the emotional environment between patient and caregiver, which is reflected by expressed emotion, may vary depending upon the nature of the disorder [23]. However, no such variance was found regarding the patient diagnosis and severity of the disease. This finding suggests that expressed emotion is more likely to be related to the caregiver's personal traits. The findings of this current study support the evidence that high- and low- expressed emotion relatives may differ in the beliefs they hold about problems associated with the patient's illness [24].

The characteristic style of high-expressed emotion family members is that they are prone to be intolerant of their dependent's problems, intrusive, and use inappropriate strategies to deal with difficulties [25]. Greenley [26] reported that high expressed emotion is

associated with family members being more fearful and anxious. It has been suggested that relatives high in emotional over-involvement would be especially unlikely to blame patients for their disturbed behavior, instead viewing the patient as an unfortunate victim of a severe illness [27]. Also, emotionally over-involved relatives have made sense of the illness in terms of factors that are outside the patient's control. Therefore, high emotional over-involvement relatives attempt to ameliorate events by using themselves as a buffer between the patient and the outside world and, through their self-sacrifice and intrusive behavior, try to control events and people [28].

Published expressed emotion studies support the importance of family intervention programs for relatives of patients with schizophrenia. Relapse rates for patients with schizophrenia in high expressed emotion families was reported to be significantly reduced when family treatments are focused on reducing some aspects of high-expressed emotion behavior [29].

Several studies investigating the family functioning effect on the caregiver burden have reported that poor family functioning is related to higher levels of caregiver burden, particularly disturbances in roles and communication [12]. Communication is the exchange of information within the family. The finding of the current study of disturbances in communication among family members is correlated to previously published studies and adds new information on how family functioning may influence the caregiver burden in correlation with expressed emotion.

Associations between high expressed emotion and some chronic medical conditions have been reported [30], although to the best of our knowledge no data are available about caregivers of rehabilitation patients.

There are a limited number of studies using clinical psychiatric evaluation including diagnostic interviews, the caregiver burden has been proposed as a risk factor increasing the prevalence of psychiatric disorders along with psychiatric symptomatology [31]. In the current study, it was determined from the diagnostic interview that nearly half of the caregivers had at least one psychiatric disorder, and 12.6% had more than one psychiatric disorder. Post-traumatic stress disorder was the most remarkable diagnosis with a substantial prevalence rate of 13.4% among caregivers. In a recent meta-analysis, symptom prevalence rates of post-traumatic stress disorder were reported as 21% (13%-56%) and 35% in relatives of children and adult patients, respectively [32]. Prevalence rates of post-traumatic stress disorder have been reported as 7.7% and 40% in different populations [33, 34]. Variance in reported rates may be due to the study settings or study designs that use self-reporting psychometric tests, which could be limited in the ability to differentiate psychiatric diagnoses.

Although it was not the aim of this study to determine the impact of demographic factors on the subjective burden, the results showed that the caregiver occupation and caregiving occupation rate have a substantial impact on the subjective burden. This finding suggests that the caregiver's participation in activities other than caregiving may help to reduce the caregiver burden.

Several interventional programs have been developed to reduce the caregiver burden and increase quality of life in different populations. However, the effectiveness of these programs has been found to be beyond the expectations [35].

The Limitations of the Study

Even our study expands the knowledge for the contributory factors associated with caregiver burden of the rehabilitation patients by utilizing clinician administered psychometric tests. But contradictory, we couldn't assess the contributing personality factors associated with the caregiver burden and expressed emotion levels. Association of personality types with caregiver burden needs to be addressed in further studies.

The factors, which may be associated with expressed emotion and family functioning domains such as personality traits of the caregiver or the caregiver's past experiences including having been cared for at some time in their life, were not examined in this study. These limitations may lead further studies to help understand the contributory factors to expressed emotion and family functioning. Thus, more specific interventional programs for caregivers could be developed.

Conclusions

In an era of out-of-hospital care, these findings suggest that interventions focusing on reducing the caregiver's emotional over-involvement or critical/hostile manner to improve family functioning

should be incorporated into family education programs aimed at reducing the caregiver burden. Such a reduction in caregiver burden may decrease psychiatric symptomatology and improve quality of life for caregivers.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The diagnostic efficacy of clinical findings and electrophysiological studies in carpal tunnel syndrome

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ABSTRACT

Objectives. The aim of the study was to examine the relation between clinical findings, neurological examination and electrophysiological studies in diagnosing carpal tunnel syndrome (CTS) and share our institutional experience in patients with CTS. ***Methods.*** Patients presenting with complaints of pain, paresthesia, and weakness in hands who diagnosed CTS between 2014 and 2015 were examined retrospectively. Demographic characteristics, clinical and neurological examination findings and electrodiagnostic evaluations were analyzed. ***Results.*** A total of 348 patients were included to the study. Weight and height measurements were significantly higher in patients with CTS on the right side (p=0.05 and p=0.04, respectively). Right hand side was the most dominant lateralization in patients with CTS (p=0.001) but there was no significant correlation for left side (p>0.05). The score of visual analogue scale was positively correlated with the severity of CTS (p=0.001). Thenar atrophy, hypoesthesia, positivity of Tinel and Phalen tests were also related to bilateral CTS (p=0.001 for each). ***Conclusion.*** We agree that clinical features, neurological examination findings and electrophysiological studies are effective diagnostic means in patients with CTS.

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Keywords: Carpal tunnel syndrome, pain, paresthesia, weakness, electrophysiological study

Introduction

Carpal tunnel syndrome (CTS) is the most frequent mononeuropathy in human body. In general population the risk to develop CTS is about 10%. CTS is produced by the chronic compression of median nerve while passing through carpal canal. This syndrome mostly seen between 40-60 years is 3 times more frequent in women than men. Although symptoms are seen in dominant hand at first, later other hand is also effected. Nocturnal pain and paresthesia are the most important characteristics features of the syndrome. With the progression of the disease symptoms become evident in day time. After a while sensational complaints turn into sensational disturbances. As the disease progresses weakness and atrophy at thenar area can be seen [1].

In this study we aimed to investigate the association between clinical features, examination findings and electrodiagnostic studies in patients

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complaining about paresthesia in hands and diagnosed as CTS by electrodiagnostic studies.

Methods

Including and Excluding Criteria

A total of 348 patients over 18 years of age who had compliants of pain, paresthesia and weakness in their hands from our outpatient clinics between 2014 and 2015 were included to the study. Excluding criteria were polyneuropathy symptoms or findings, radicular pain and/or sensation loss, other neurological and neuromuscular diseases.

Clinical and Demographic Findings

For the diagnosis of CTS, American Academy of Neurology criteria were used [2]. These criteria include: 1) Pain and paresthesia in the symptomatic hand at nights, 2) Sensational complaints during flexion and extension movements of wrist, 3) Pain and paresthesia in the morning, 4) Phalen test positivity, 5) Sensation loss in median nerve innervation area, 6) Atrophy and weakness in median nerve innervated muscles. In the presence of at least one criteria the patient was accepted to have CTS. Gender, age, weight, height, dominant hand, marital status, education level and job were recorded. Sensation, muscle strength, Tinel and Phalen signs were identificated by detailed neurological examination. Pain, paresthesia, weakness, symptomatic hand, starting time of complaints, concomitant illnesses were recorded. To modify the severity of pain visual analogue scale (VAS) was used. According to this scale, 0 means no pain, 10 means severe pain. Additional to all these psychical activation like using computer, knitting, sewing, doing housework were recorded.

Electrophysiologic Test Procedure

Conventional electroneurographic study was done. Median and ulnar nerve conduction studies were done according to reference technics. Motor and sensorial onset latency, amplitude and nerve conduction velocity of median and ulnar nerves of both upper extremity were recorded. Motor nerve conduction studies were orthodromic where as sensorial nerve conduction studies were antidromic. Supra-maximal stimulation technique was performed with 0.1-1 msn duration time by using superficial electrode. For motor conduction studies low frequency filter (LFF) was determined as 2 Hz, high frequency filter (HFF) was determined as 10 Hz, sensitivity was determined as 2-5 Mv/division. For sensorial conduction studies LFF was determined as 20 Hz, HFF was determined as 2 Hz and sensitivity was determined as 10-20 µV/division.

Electrophysiological severity of CTS was classified as mild, moderate and severe according to following criteria. Mild CTS was determined as prolongation of distal latency and decrease in the amplitude of median sensorial nerve. Moderate CTS was determined as in addition to mild CTS criteria prolongation of distal latency of median motor nerve. Severe CTS was determined as no record of sensorial potential, prolongation of distal latency and decrease in the amplitude of median motor nerve [1]. Demographic characteristics, clinical features, comorbidity and hand using habituation were recorded.

Statistical Analysis

The description of parametric and non-parametric data was done by using kurtosis skewness test. The parametric data was given by mean ± standard deviation. For comparation of categorical variables between right and left CTS groups ki-kare test was used. We used Spielman correlation test for correlation of non-parametric variables with independent groups. We used one-way analysis of variance test for comparison of means of two independent groups. p value <0.05 was considered as statistically significant.

Results

There were 286 women and 62 men in the study. The mean age was 51.27±12.46. According to medical history, dominant hand was right in 334 (96%) patients, whereas in 14 (4%) patients it was left. There was no significant correlation between age, gender, marriage status, education level and electrodiagnostic CTS (p>0.05). Weight and height were both significantly higher in right handed CTS (p=0.05 and p=0.04, respectively) but there was no significantly correlation for left handed CTS (p>0.05). In the patients with right CTS mostly right hand was dominant (p=0.001) but there was no significant correlation for left side (p>0.05). Demographic characteristics and their correlations with electrodiagnostic CTS are summarized in Table 1.

Among 348 patients 292 (84%) had right CTS,

Table 1. Correlations of demographic datas due to electrophysiological findings

	Right CTS (n=292)			*p*	Left CTS (n=269)			*p*
	Mild	Intermediate	Severe		Mild	Intermediate	Severe	
Sex (F/M)	118/30	107/24	13/0	**0.06**	101/20	107/22	16/3	0.98
Age (years)	51.70±13	51.25±12	54.54±13	0.65	51.43±13	51.70±12	57.68±12	0.12
Weight (kg)	78±13	81±14	84±14	**0.05**	79±12	81±14	79±12	0.59
Height (cm)	163±8	161±6	158±5	**0.04**	162±7	161±7	161±8	0.32
Dominant hand (Right-Left)	145/3	129/2	12/1	**0.00**	112/9	126/3	17/2	0.09

Data are given as mean ± standard deviasyon or number. CTS=carpal tunnel syndrome, F=female, M=male

269 (77.2%) had left CTS and 214 (61.5%) had bilateral CTS. From the patients with right CTS 148 (42.5%) had mild CTS, 131 (37.6%) had moderate and 13 (3.7%) had severe CTS. From patients with left CTS, 121 (34.8%) had mild CTS, 129 (37.1%) had moderate and 79 (22.7%) had severe CTS. When we analyse patients with right CTS, we found out that 96 patients had symptoms only on the right hand and among this group 54 had mild, 36 had moderate, 6 had severe CTS. When we look at patients with left CTS, 66 had symptoms only on the left hand. Within this group 32 had mild, 27 had moderate and 7 had severe CTS. One hundred and seventy-seven (50.9%) patients had symptoms on both of the hands.

Symptomatic findings were summarized as follows; pain, paresthsia, weakness and sensation loss. VAS score was in positive correlation with CTS severity (p=0.001). While weakness was bilateral (p=0.001 for both left and right) correlated with increased CTS; sensation loss was correlated with increased CTS only on the right hand (p=0.05). The time of symptom starting was 0-6 months for 98 (28.2%) patients, 6-12 months for 123 (35.3%) patiens, 1-5 years for 105 (30.2%) patients, 5-10 years for 16 (4.6%) patients and more than 10 years for 6 (1.7%) patients. Thenar atrophy was correlated with CTS severity for both right and left hand (p=0.001). Weakness (p=0.001), hipoestesia (p=0.001), positivity of Tinel (p=0.001) and Phalen (p=0.001) tests were also correlated with CTS severity for both hands. The relation between clinical symptoms, neurological examinations and electrodiagnostic CTS is summarized in Table 2.

Psychical activation like using computer, knitting, sewing and doing housework was not significantly related with right and left CTS severity (p>0.05). We also investigated the effect of smoking and diseases like rheumatoid artritis, thyroide pathologies and diabetes mellitus and found out no significant relation between these status and CTS (p>0.05). The relation between risk factors and and electrodiagnostic CTS is summarized in Table 3. .

Discussion

CTS which is usually seen between 60-70 years is 3 times more frequent in women than men. Right hand is more affected than left hand as accepted [1]. Similar to literature the mean age of patients in this study was 51.27. Although CTS was seen more frequent in women, we found no significant correlation between

Table 2. Correlations of electrophysiological CTS findings with clinical symptoms and examination findings

	Right CTS (n=292)			*p*	Left CTS (n=269)			*p*
Positive	**Mild**	**Intermediate**	**Severe**		**Mild**	**Intermediate**	**Severe**	
Pain	137 (49)	127 (46)	12 (4)	0.24	112 (41)	124(48)	18 (7)	0.46
VAS score	6±2	7±2	8±2	**0.001**	6±2	7±2	8±2	**0.001**
Numbness	144 (50)	129 (45)	13 (5)	0.60	118 (44)	127 (48)	19 (8)	0.61
Sensorial deficit	119 (48)	117 (47)	13 (5)	**0.05**	98 (44)	110 (49)	17 (7)	0.54
Motor deficit	65 (41)	81 (51)	11 (8)	**0.001**	51 (34)	79 (54)	18 (12)	**0.001**
Thenar hypoestesia	18 (21)	56 (68)	9 (11)	**0.001**	17 (22)	46 (62)	12 (16)	**0.001**
Thenar atrophy	6 (10)	38 (67)	13 (23)	**0.001**	10 (17)	34 (58)	15 (25)	**0.001**
Tinel test positivity	97 (44)	112 (51)	11 (5)	**0.001**	82 (40)	108 (52)	17 (8)	**0.001**
Phalen test positivity	61 (34)	106 (60)	12 (6)	**0.001**	47 (29)	98 (60)	17 (11)	**0.001**

Data are given as mean ± standard deviasyon or number (%). CTS=carpal tunnel syndrome, VAS=visual analogue scale

Table 3. Correlation of risk factors with electrophysiological findings

	Right CTS (n=292)			*p*	Left CTS (n=269)			*p*
Positive	**Mild**	**Intermediate**	**Severe**		**Mild**	**Intermediate**	**Severe**	
DM	40 (52)	34 (44)	3 (4)	0.94	29 (42)	37 (53)	3 (4)	0.39
Cleaning labour	104 (52)	85 (42)	12 (6)	0.07	85 (46)	88 (47)	14 (7)	0.86
Knitting	79 (50)	69 (44)	8 (5)	0.82	63 (45)	64 (46)	12 (9)	0.53
Sewing	74 (51)	69 (46)	5 (4)	0.60	65 (44)	71 (51)	7 (5)	0.30
Computer/mouse occupation	15 (50)	13 (43)	2 (7)	0.84	8 (28)	18 (62)	3 (10)	0.12
Smoking	22 (48)	24 (52)	0	0.07	14 (39)	20 (55)	2 (5)	0.61
Hypothyroidism	13 (54)	9 (37)	2 (8)	0.57	10 (43)	12 (52)	1 (4)	0.81
Arthritis	1 (25)	2 (50)	1 (25)	0.28	3 (60)	2 (40)	0	0.60

Data are given as number (%). CTS=carpal tunnel syndrome, DM=diabetes mellitus

CTS and gender in this study. In patients with right CTS right hand was dominant but there was no correlation like this for the left side. If we look up the literature investigating the relation between obesity and CTS, it is mentioned that obesity is a risk factor for CTS in most of the studies [3, 4, 5]. De Azevedo *et al.* [6] investigated the profile of patients on sick leave with CTS and reported obesity with a ratio of 44% among these patients [6]. Similar to these studies in this study we recorded that weight and height was significantly higher for patients with right CTS. But there was no significant relation for the left side statistically.

As Tinel and Phalen tests are easily applicable, they are usually preferred in polyclinic practice. In spite of common use of them there are different results abought the sensitivity and specificity of these tests. This calls the question of 'what is the reliability of these tests?' to mind. In a study investigating the the prevalence of CTS in women in Iran the most common findings in physical exam were Tinel sign (58.9%) and Phalen sign (50.9%) [7]. Again in Iran in another study Phalen and Tinel signs were positive in 82.2% and 71.1% of patients, respectively [8]. A study investigating the correlation between physical examinations and clinical severity along with the electrodiagnostic findings by subjects with CTS both hand elevation test and Phalen test were correlated well with the severity of CTS where the correlation of Phalen was higher than that of hand elevation test [9]. In 2012, Ma and Kim [10] compared Phalen's test, Tinel's test, and carpal compression test with hand elevation test. Phalen's test had 86.7% specificity and 84.4% sensitivity. Tinel's test had 88.9% specificity and 82.2% sensitivity. Comparisons of specificity and sensitivity between Phalen's test, Tinel's test, hand elevation test and carpal compression test had no statistically significant differences [10]. As mentioned above the positivity of these tests are variable. In our study Tinel and Phalen test positivity were correlated with CTS in both right and left hand.

The most important property in CTS diagnosis is pain that awakes the patient from sleep and paresthesia. After a while these complaints spread to fore arm and shoulder. In order to decrease the severity of these complaints, the patients flail and shy the hands and these movements are distinctive for the disease. Waking up at nights with pain in the hands, decreasing or losing the symptoms with flexion and extension movements of hands is helpful in diagnosing the disease with a ratio of 93%. As the disease grow up paresthesia in the hands in day time start [1]. In a study comparing physical examination, ultrasonography and electroneuromyography in diagnosing CTS, pain was reported by 74% of the patients while paresthesia was reported by 50% [11]. When comparing to other symptoms pain is more frequently positive in diagnosing CTS. In this study we found out that VAS score was positively correlated with CTS severity.

Sensation examination is normal in thenar area in CTS patients. The reason of this is accepted that the palmary branch of median nerve leaves the nerve before carpal tunnel. Sensation loss is marked in second and third fingers front part. The most frequent and early symptom is hyposthesia in the third finger. The sensation examination in fourth and fifth fingers on the ulnar side is normal. Sensation examination in CTS patients may be normal with a ratio of 20-50% [1]. As we discussed in Tinel and Phalen tests above this finding have variable positivity ratios. In our study we found out that sensation loss is positively related with CTS.

There are only limited studies assessing the power of hands and fingers in CTS patients. In Turkey Ozdolap *et al.* [12] found out no relation between coupling power and electrodiagnostic findings. Their result suggests the idea that hand coupling powers are not heplful in diagnosing CTS. But in our study weakness was related to CTS both in right and left hands.

As the disease progresses thenar atrophy and breakdown can be seen. Abduction and opposition in the first finger can not be done [1]. Ozdolap *et al.* [12] found out no relation between thenar atrophy and electrodiagnostic findings. In their study they mentioned that the reason for this result may be the low number of hands with thenar atrophy [12]. In our study we found out that thenar atrophy was related to CTS severity for both right and the left hand.

Electrodiagnostic studies are done to definite CTS diagnosis and also to fix the level and severity of the disease. Although electrodiagnostic studies are very sensitive in CTS, there is no accordance between sensational complaints and sensory studies. The reason for this is most probably nocturnal pain and paresthesia, which occurs according to ischemia in the median nerve, are not related to focal demyelinization in the carpal tunnel. Prolong distal motor latency and loss in motor amplitude is related to thenar atrophy and paresis [1]. Although we usually expect abnormalities only in the sensory studies in early stages of CTS; Vahdatpour *et al.* [13] reported a contrary result in their study. According to their study the most sensitive electrophysiological finding in CTS patients was median nevre terminal latency index (TLI) (82%), but the most specific one was distal motor latency (98%) [13]. In 2015, Kanikannan *et al.* [14] compared the diagnostic accuracy of high-resolution ultrasonography with electrodiagnostic testing in patients with CTS. As a result of this study electrodiagnostic testing has been found to be more sensitive and specific in mild CTS [14]. As we see in clinical and examination findings there are different results about the reliability of electrodiagnostic studies.

Hobbies and jobs which lead to extension and flexion movements of the wrist may increase complaints about CTS [1]. In this study we found no significant effect of hobbies like knitting, sewing, doing house work and using computer on the severity of CTS for both the right and the left hand. In Turkey, Ciftdemir *et al.* [15] investigated the prevalence of CTS related to manuel tea harvesting and reported that manuel tea harvesting might be a risk factor for work related CTS. And also we found no significant effect of smoking, diabetes mellitus, thyroid disease and rheumatoid arthritis on the severity of CTS. In a study investigating the prevalence of CTS in rheumatoid arthritis, CTS was more frequent in these group patients [16].

Conclusions

We suggest that these data may be helpful for clinicians in order to decide which tests and clinical findings should be used in CTS diagnosis in daily practice. As a result we found out significant relations between clinical findings, examination evidence and electrodiagnostic studies. Although above we discussed may studies dealing with the negative correlations for CTS we still suggest these clinical findings and electrodiagnostic tests can be used in daily practice.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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How frequent is nocturia in medical students?

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ABSTRACT

Objective. Nocturia is the most common lower urinary tract symptom and its prevalence increases with age. The frequency of nocturia and related bother are not widely investigated in young adults in the literature. In this study we aimed to investigate frequency, bothersome and relation of nocturia with anxiety in medical students. ***Methods.*** A questionnaire consisting of 19 items were sent to medical students via social media by using Survey Monkey™ software. Questions include demographic characteristics, fluid intake habits, voiding symptoms, and bother score related to nocturia. Also, Beck Anxiety Inventory was used to measure level of anxiety. ***Results.*** A total of 221 students replied the survey. The mean age was 20.7±2.10. Forty-seven (21.3%) students had nocturia. The rate of nocturia was 27.4% and 13.4% in women and men, respectively (p=0.011). The frequency of nocturia per night was 80.2%, 17.3% and 2.2% (1, 2, 3 times; respectively). While the frequency of nocturia was found to be related with bother scores there were no relation of gender with degree of bother. ***Conclusion.*** Nocturia is frequent in medical students, especially in women. Commonly, nocturia do not cause bother in young adults with one episode and it is not related with anxiety.

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Keywords: Nocturia, young adults, bother

Introduction

Nocturia is a bothersome lower urinary tract symptom causing sleep disturbance. The International Continence Society (ICS) has defined nocturia as the complaint of up wake at night one or more time to void when each void is preceded and followed by sleep [1]. It is one of the most common lower urinary tract symptoms in adults. In a large scale study 48% of men and 54% of women found to have nocturia [2]. Despite the current definition of nocturia some researchers do not think only one void is clinically meaningful. In another study, the overall nocturia prevalence was 28.4% in 5,502 individuals with a definition of at least two wakes at night for voiding [3].

The number of voids per night increase with age however, young adults are not free of nocturia. According to the Third National Health and Nutrition Examination Survey (NHANNES III) the prevalance of nocturia in United States residents aging between 20 and 29 was 32% and 42% in men and women, respectively [4].

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Nocturia may have negative effects on day time productivity due to sleep fragmentation. Furthermore it may adversely affect the quality of life [5]. This is more important in young adults who are prone to the high volume of workload. Frequent nocturia episodes can result in increased levels of anxiety. The association of nocturia with anxiety and depression is bidirectional. This association is more clear for depression however there are limited data for association between anxiety and nocturia [6].

In this study we aimed to investigate the prevalence and bother of nocturia among medical students as a primary objective. Our secondary objective was to evaluate whether there is a relation between nocturia and anxiety.

Methods

A questionnaire consisting of 19 items were sent to medical students via social media by using Survey Monkey™ software between the dates 29th July 2016 and 3rd August 2016. The questions regarding demographic characteristics included gender, age, height, weight, smoking and alcohol use, history of a systemic disease, daily use of a particular drug, presence of lower urinary tract symptoms (urgency, incontinence, voiding difficulties), mean fluid intake and mean sleep time. A specific question concerning the presence of nocturia was added to the questionnaire. We asked the following question depending on ICS definition of nocturia : "Do you wake for voiding while sleeping and you continue to sleep?" The frequency of nocturia is also included if present. The bother of nocturia was determined with the following question: "What is your degree of bother due to this condition?". The answer for this question was constructed with number from 0 to 10; in which "0" representing no bother and "10" a tremendous bother.

The anxiety level of the responders were determined with Beck Anxiety Inventory (BAE). This is a self-administrated scale consisting of 21 questions. Each question has four possible score ranging between 0 to 3 (0: not at all, 1: it did not bother me much, 2: It was not pleasant at times, 3: it bothered me a lot.) [7]. The Turkish version of BAE was validated in university students by Tunay and Soygut [8].

Statistical Analysis

SPSS (v.23) software was used for statistical calculations. The descriptive data were quantitatively assessed, and given as numbers, and frequencies (%). The correlations between the groups and responses to questions were analyzed using an appropriate chi-square test (Pearson chi-square or Fisher-Freeman-Halton exact test). All normally distributed data were presented as mean and standard deviation and compared with either the student's t-test. Non-normally distributed data were presented as median (minimum-maximum) with mean and standard deviation and were compared with Mann-Whitney U test. $p<0.05$ was specified as the level of statistical significance.

Results

A total of 221 medical students replied our survey. The mean age of the responders was 20.7±2.10 years. Nighty-seven (43.89 %) were man and 124 (56.11%) were women. Forty-eight (21.7%)students reported nocturia. While 39 (80.2%) had a nocturia frequency of one, 8 (17.3%) had two and only one (2.2%) man had three times of nocturia (Figure 1). A total of 35 (28.2%) were women and 13 (13.4%) were man among the responders with nocturia ($p=0.009$).

Comparison of the factors with and without nocturia is presented in Table 1. None of the factors besides gender were statistically significant across the groups.

The bother scores of the responders according to frequency of nocturia episodes are presented in Figure 2. A total of 21 (43%) responders reported no bother (score of 0) of nocturia and 9 students (19.1%) replied a bother score more than 5 over 10. While the mean bother score in responders with a frequency of one was 1.31±2.14 (0-9); this was 5.22±2.95 in responders with two or three voids per night. This was found to be statistically significant ($p=0.001$). The comparison of the degree of bother in men and women is listed in Table 2. The mean level of bother was 2.17±2.73 (0-9) and 1.69±2.90 (0-10) in men and women, respectively and the results were not statistically significant ($p=0.451$).

Discussion

There are three main etiologic factors responsible for nocturia: i) nocturnal polyuria (over hydration at night, congestive heart failure), ii) decreased bladder capacity (neurogenic bladder, anxiety, bening prostatic

Table 1. Comparison of the demographic characteristics and Beck anxiety inventory

	Nocturia (+)	Nocturia (-)	*p*
Mean age (years)	20.9±1.9	20.6±2.1	0.714
Gender			
Men	13 (13.4%)	90 (72.6%)	**0.011***
Women	34 (27.4%)	84 (86.6%)	
Mean BMI (kg/m^2)	22.53±3.5	22.5±4.1	0.977
Smokers (n)	3 (6.4%)	29 (16.7%)	0.075
Alcohol consumers (n)	12 (25.5%)	41 (23.5%)	0.779
Mean daily fluid intake (ml)	2031.91±11.30	1849.42±802.07	0.180
Intake of fizzy drinks (n)			
Never	5 (10.6%)	14 (8.1%)	0.109
Seldom	34 (72.3%)	103 (59.2%)	
Frequent	8 (17.1%)	57 (32.7%)	
Mean length of sleep (hours)	7.8±1.02	7.5±1.1	0.262
History of a systemic illness (n)	8 (17.02%)	26 (14.9%)	0.820
Daily use of a drug (n)	7 (14.8%)	20 (11.4%)	0.528
Mean frequency of daytime voiding (n)	4.69±1.87	4.69±1.77	0.997
Urgency	5 (10.6%)	8 (4.6%)	0.156
Incontinence	1 (2.1%)	1 (0.6%)	0.381
PMR	5 (10.6%)	6 (3.4%)	0.59
Mean BAI score	10.29±8.26	10.44±9.9	0.266

BMI=body mass index, BAI=Beck anxiety inventory, *p<0.05

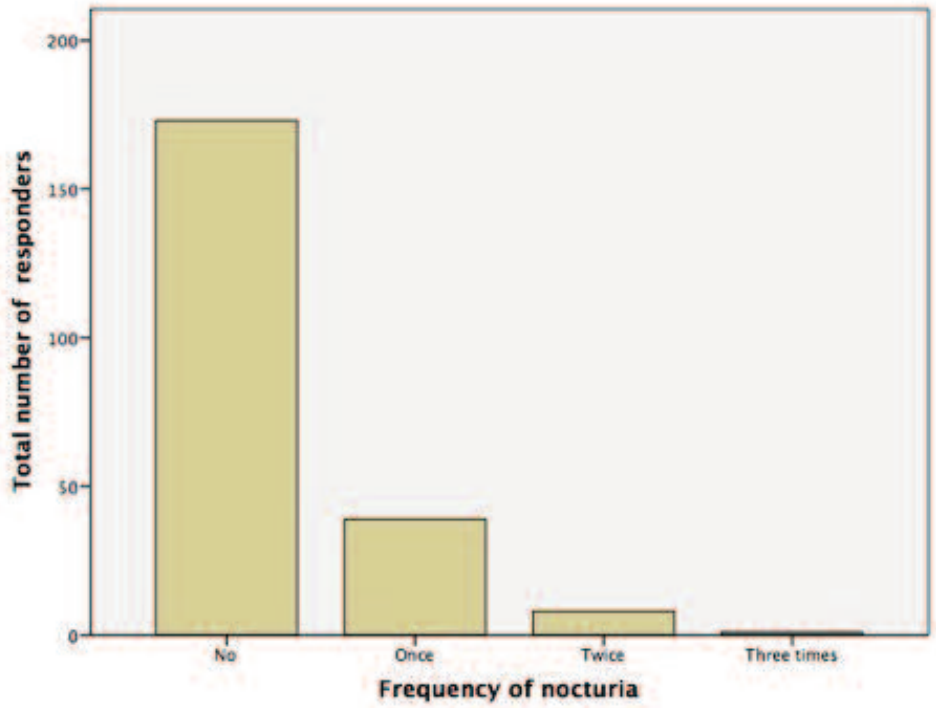

Figure 1. The distribution of the responders with or without nocturia.

obstruction), iii) global polyuria (primary polydipsia, diabetes) [9, 10]. Not surprisingly these associated comorbidities are common in the aging population. Therefore, nocturia is recognized as a common lower urinary tract symptom of these individuals. Most of the research regarding nocturia has been developed on middle aged or elderly people though it is not a rare symptom in young adult population. Moreover, the bother of nocturia has not been widely investigated in this group. To best of our knowledge this is the first

Table 2. Comparison of the bother scores with nocturia in women and men.

Bother Score	Women	Men
0	14 (41.17%)	7 (53.84%)
1	7 (20.58%)	1 (7.69%)
2	2 (5.58%)	3 (23.07%)
3	3 (8.82%)	0 (0%)
4	2 (5.58%)	0 (0%)
5	2 (5.58%)	1 (7.69%)
6	1 (2.94%)	0 (0%)
7	1 (2.94%)	0 (0%)
8	2 (5.58%)	0 (0%)
9	1 (2.94%)	0 (0%)
10	0 (0 %)	1 (7.69)

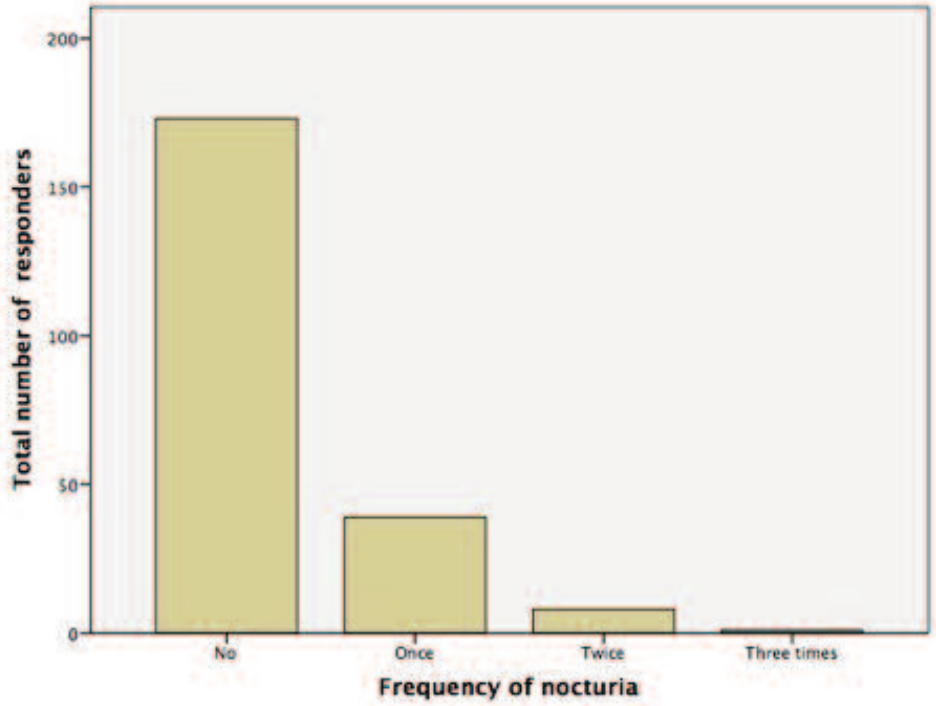

Figure 2. The bother scores of the responders according to frequency of nocturia episodes.

study with a focus on nocturia in medical students in Turkey.

Sleep is an important aspect of human life which is crucial for mental and physical health. Sleep deprivation due to nocturia is more important in younger population than elderly people. Young individuals particularly college students are prone to stressful conditions such as examinations. According to the results from this survey approximately one medical student in five had symptoms of nocturia according to the current definition of ICS. The rate of nocturia was 28.2% and 13.4% in women and men, respectively. Similarly, Bosch and Weis [11] reported a nocturia prevalence of 35% and 11% aged between 20 and 40 for women and men, respectively. The exact pathophysiology of female predominance is not clearly understood. Taking care of a child or baby was suggested as a related factor by Bosch and Weiss [11]. However, in our population none of the medical students had a baby. Also, increased rates of insomnia was speculated as a predisposition factor younger women [11].

The level of bother was related with frequency of nocturia episodes in most of the studies [12, 13]. Therefore, in some studies nocturia is defined with a criterion of at least two voids at night [13]. In the present study, approximately 80% of the patients reported a nocturia frequency of one and there was a

correlation with nocturia episodes and bother. However, the level of the bother can change in individual basis. For example, in the present study while one man with two episodes of nocturia reported the maximum bother score; another man with three episodes replied a moderate score. This phenomenon was also reported by Kupelian *et al.*[4].

In most of the epidemiological studies, smoking, BMI, alcohol and soft drinks were found to be a prognostic factor for nocturia[4, 14]. Smoking may cause storage symptoms on the other hand increased levels of arginine-vasopressin may counter balance this negative effects [14]. In our survey we did not find any relation with any of these parameters. The longer periods of sleep and increased fluid intake may result in nocturia. However, these parameters were not found to be related with nocturia.

Depression and anxiety disorders may be important risk factors for nocturia. These disorders may be more relevant with nocturia for young population. An impairment in circadian rhythm of anti-diuretic hormone can explain pathophysiology of nocturia in these disorders [15]. In a study, risk of having nocturia was found to be 6 and 3 times higher in men and women with depression. We hypothesized anxiety scores will be higher in medical students with nocturia. However, BAI scores were not different across the students with or without nocturia.

There are some studies reporting a link between nocturia and survival. This may be clinically important in elderly population [4]. The importance of this phenomenon is still elusive in young population.

The Limitations of the Study

The major limitation of the study was the small sample size and lack of voiding frequency charts or bladder diaries to determine exact pathology of nocturia.

Conclusions

In conclusion, nocturia is a frequent symptom among medical students especially in women. In most of the cases the bother is related with the frequency of nocturia. The results from the current study suggest no role for anxiety in development of nocturia.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Traumatic superior orbital fissure syndrome: a rare case report

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ABSTRACT

Superior orbital fissure syndrome is a severe clinical entity characterized by injuries of neurovascular structures passing through the superior orbital fissure. A 38-year-old male patient admitted to outpatient clinic with left upper eyelid ptosis, ecchymosis, mydriasis, hypoesthesia in upper eyelid and frontal region, blepharoptosis, restriction of ocular movements in all directions, loss of accommodation reflex and absence of direct pupillary reflex. Three-dimensional computed tomography scans demonstrated left-sided orbital fractures resulting in obliteration of the superior orbital fissure. He underwent surgical decompression. The patient had intravenous methylprednisolone administration at preoperative and postoperative periods during hospitalization. He was discharged on the postoperative day 5. At the 9th postoperative month, the cranial nerve functions were almost completely recovered. We consider that the decompressive surgery in conjunction with perioperative steroid therapy may be effective for the traumatic superior orbital fissure syndrome.

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Keywords: Superior orbital fissure syndrome; cranial nerve; ophthalmoplegia; orbital trauma; steroid; surgical decompression

Introduction

Superior orbital fissure syndrome (SOFS) is a rare and severe clinical entity characterized by traumatic or non-traumatic injuries to the cranial nerves (CN III, IV, V1 and VI) along with the autonomic nerves and vascular structures passing through the superior orbital fissure [1, 2].

The etiological factors associated with the SOFS can be divided into three categories: traumas, tumors and infections [3]. Numerous etiological factors including carotid-cavernous sinus fistula [1], maxillofacial traumas [1, 3-5], pseudoaneurysm of the internal carotid artery [6], orbital metastatic hepatocellular carcinoma [7], aspergillus sinusitis [8], etc., were noted as the possible causes of the SOFS. Regardless of the underlying etiological factors, the clinical symptoms of the syndrome are primarily the results of the inflammation and the compression of the neurovascular structures in the superior orbital fissure [4].

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In this report, we aimed to share our clinical experience regarding the treatment and the follow-up of a patient with traumatic SOFS and to draw attention of the clinicians to the importance of its association with the maxillofacial traumas.

Case Presentation

A 38-year-old male patient, who had a motor vehicle accident 10 days previously, admitted to the outpatient clinic of plastic and reconstructive surgery with the complaint of being unable to open his left upper eyelid. As a result of blunt chest trauma, he had developed a left-sided pneumothorax, treated with chest tube drainage, and had been followed-up in another hospital's intensive care unit for 7 days. The patient stated that, although he had a concomitant head trauma. Neither physical examination nor imaging studies were performed during the follow-up period for this situation.

Physical examination of the left eye revealed ecchymosis, subconjunctival hemorrhage, mydriasis, hypoesthesia in the upper eyelid and the frontal region, blepharoptosis, restriction of the ocular movements in all directions and loss of accommodation reflex, loss of corneal reflex and absence of direct pupillary reflex. Due to the fractures of the left frontozygomatic region, the patient had tenderness on palpation and step deformities were palpated. Ophthalmological examination did not reveal any signs of optic neuropathy, bruit, chemosis or displacement of the globe (Figure 1).

Three-dimensional computed tomography scans demonstrated left-sided fracture lines involving the frontozygomatic region and greater wing of the sphenoid bone resulting in en-bloc displacement of the lateral orbital wall into the orbital cavity and obliteration of the superior orbital fissure (Figure 2). Magnetic resonance imaging of the left orbita did not reveal any pathological findings of the globe or the optic nerve.

For surgical decompression, the patient was operated under general anesthesia. A subgaleal bicoronal flap was raised, extending laterally to the supraauricular areas and anteriorly to the frontal

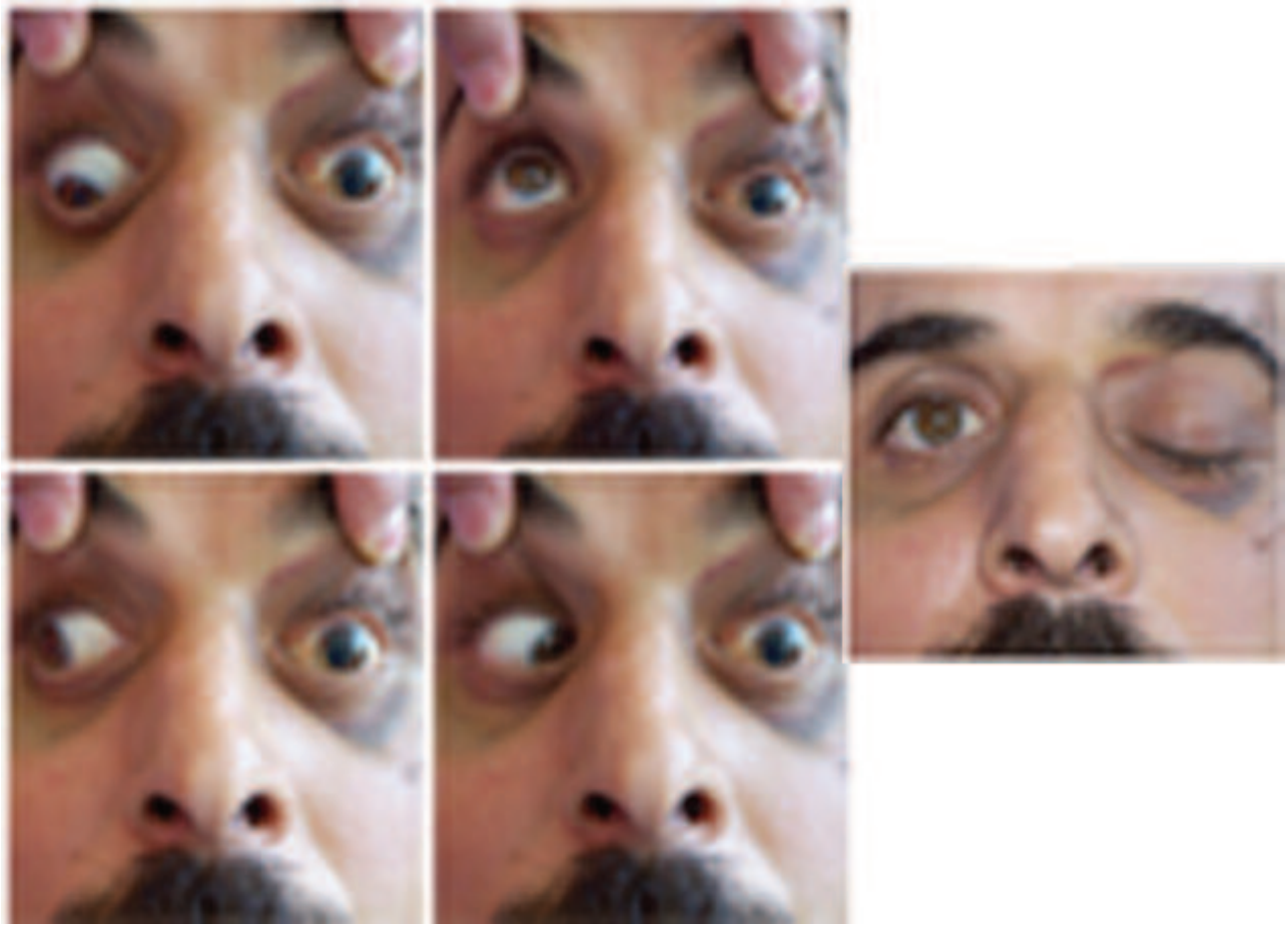

Figure 1. Due to total ophthalmoplegia of the left eye, the patients had blepharoptosis, mydriasis and restriction of the left-eye movements in all directions.

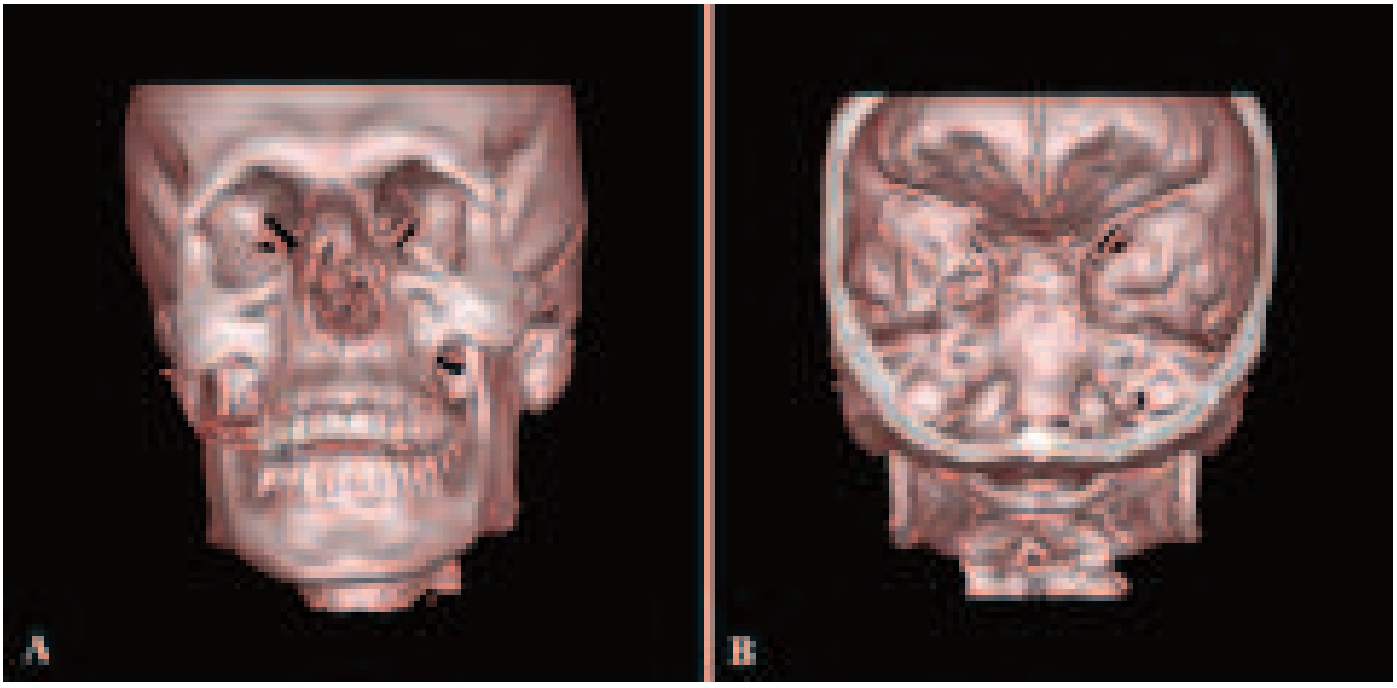

Figure 2. Preoperative 3D CT scans of the skull. (A) An anterior view demonstrates the obliterated superior orbital fissure (arrow) as a result of a complex fractures displacing the lateral orbital wall medially and (B) posterior view of the obliterated superior orbital fissure (arrow). 3D CT=three-dimensional computed tomography.

region. Through a periostal incision located superiorly to the left supraorbital bar, the subperiostal plane was reached and dissected till the lateral orbital wall and the zygomatic arc were exposed. A neurosurgeon then performed a left frontal craniotomy and lateralized the medially displaced lateral orbital wall to expose the orbital cavity. The medially impacted greater wing of the sphenoid bone was thereby lateralized and the superior orbital fissure was decompressed. The rigid fixation of the craniotomy flap was then subsequently performed, along with the rigid fixation of the fracture of the frontozygomatic suture line. After surgical hemostasis, a Jackson-Pratt drain was placed, the bicoronal flap was sutured and the procedure was successfully completed without any complication. The patient had intravenous methylprednisolone administration (1 mg/kg once daily) at pre-operative and post-operative periods till discharge from the

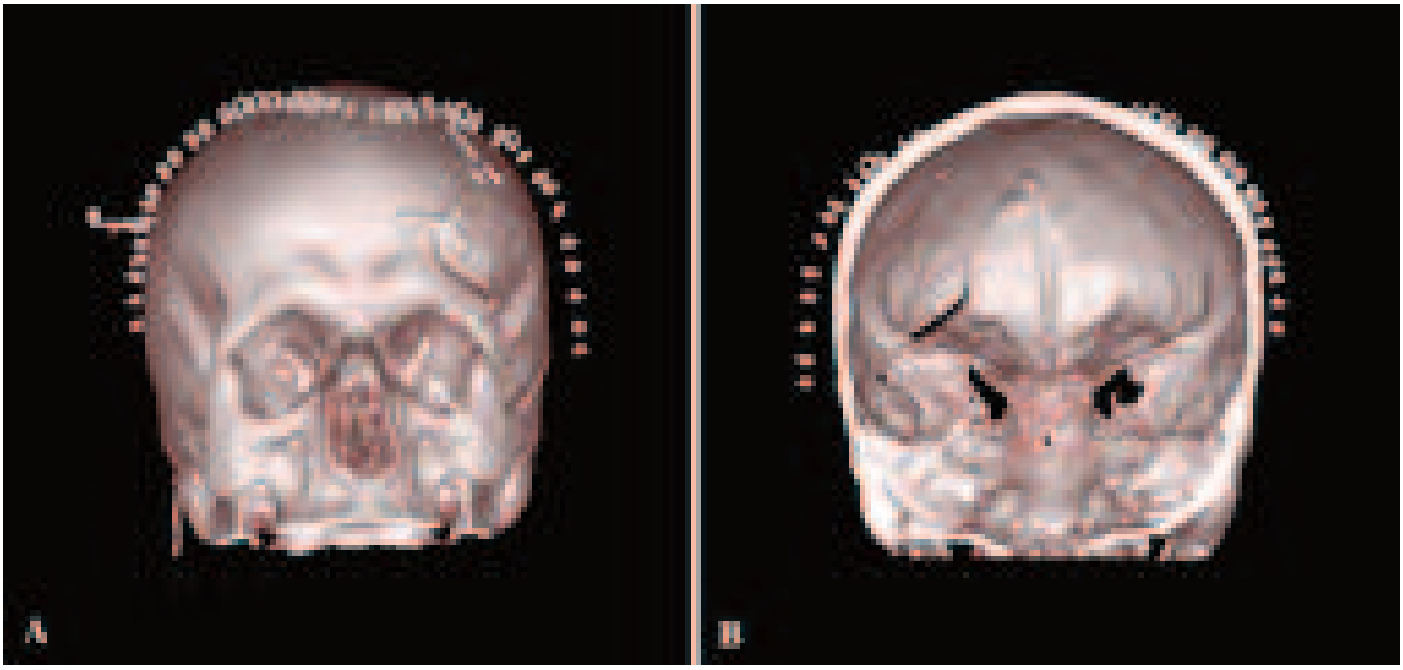

Figure 3. Postoperative 3D CT scans. A. Anterior (arrow) and B. posterior view of the reduced fracture lines and decompressed superior orbital fissure (arrow). 3D CT=three-dimensional computed tomography.

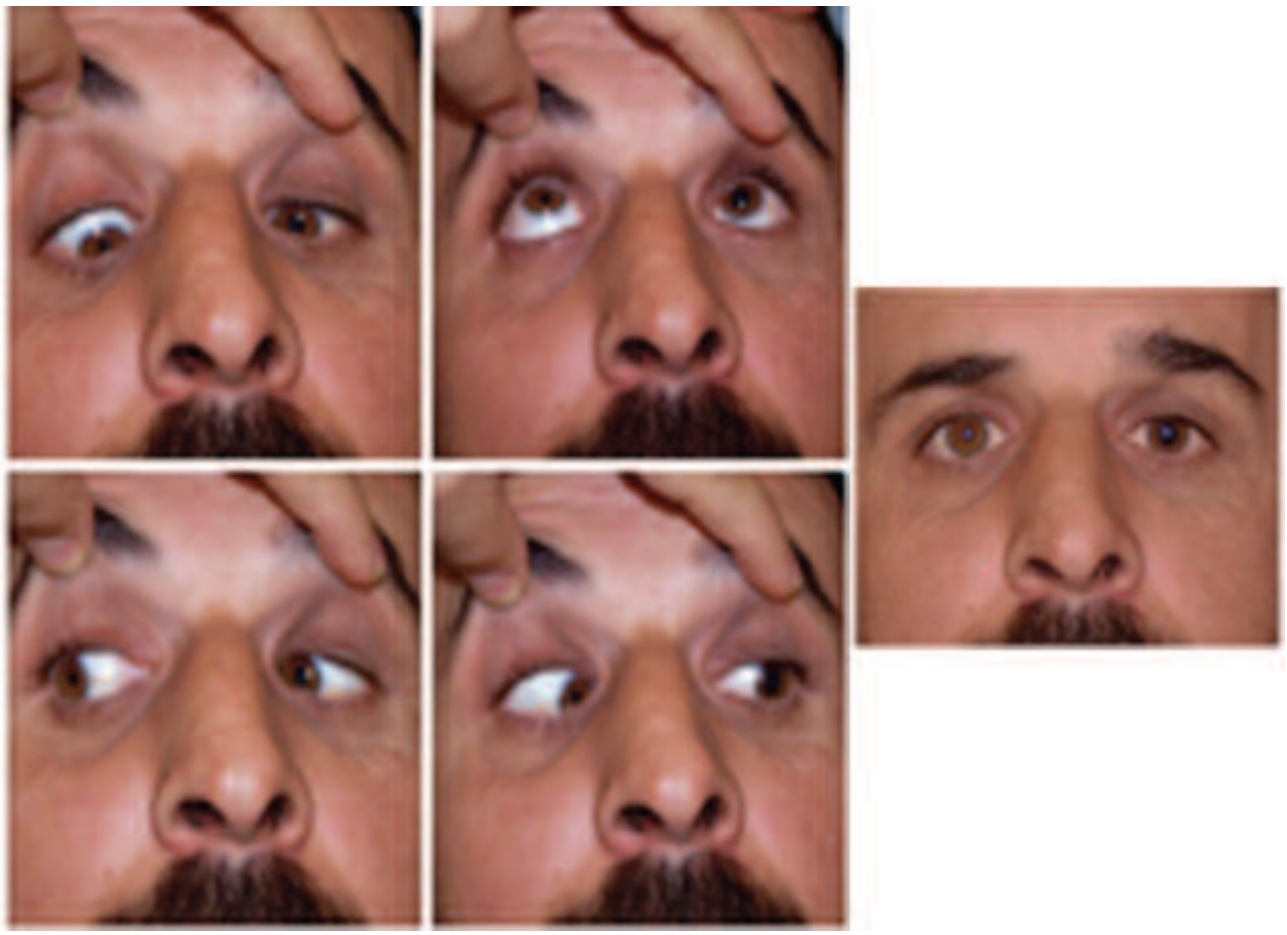

Figure 4. Postoperative examination on the 2nd month demonstrating minimal restriction in elevation and depression movements of the left eye with minimal mydriasis.

hospital. On the 1st post-operative day, three-dimensional computed tomography scans demonstrated that the former fracture lines were reduced and the superior orbital fissure was larger in size (Figure 3). The patient was discharged on the 5th post-operative day on medication regimen included artificial eye drop, analgesic, antibiotic and reduced dosage of oral methylprednisolone.

Physical examination performed at the 2nd postoperative month revealed partial recovery of the sensory and motor functions of the cranial nerves; elevation and depression movements of the left eye were minimally restricted and minimal mydriasis was still present (Figure 4).

At the 9th post-operative month, the cranial nerve functions were almost completely recovered with the only pathological findings being 2-mm restriction of the elevation movement of the left eye and persistent minimal mydriasis (Figure 5).

Discussion

Superior orbital fissure is an important anatomic structure that lies between the superior and lateral orbital walls and serves as a conduit between the orbital cavity and the middle cranial fossa. Oculomotor nerve (CN III), abducens nerve (CN VI), nasociliary branch of the ophthalmic nerve (CN V1) and sympathetic-parasympathetic nerve fibers together reach the orbital cavity by passing through the intra-conal compartment of the superior orbital fissure, which was firmly bounded by the annulus of Zinn. Also, lacrimal and frontal branches of the ophthalmic nerve (CN V1), trochlear nerve (CN IV) and superior ophthalmic vein are the main neurovascular structures of the extra-conal compartment of the superior orbital fissure (Figure 6) [9, 10].

SOFS is a rarely described symptom complex due to compression of the compartments of the superior orbital fissure. Clinical presentation may vary from

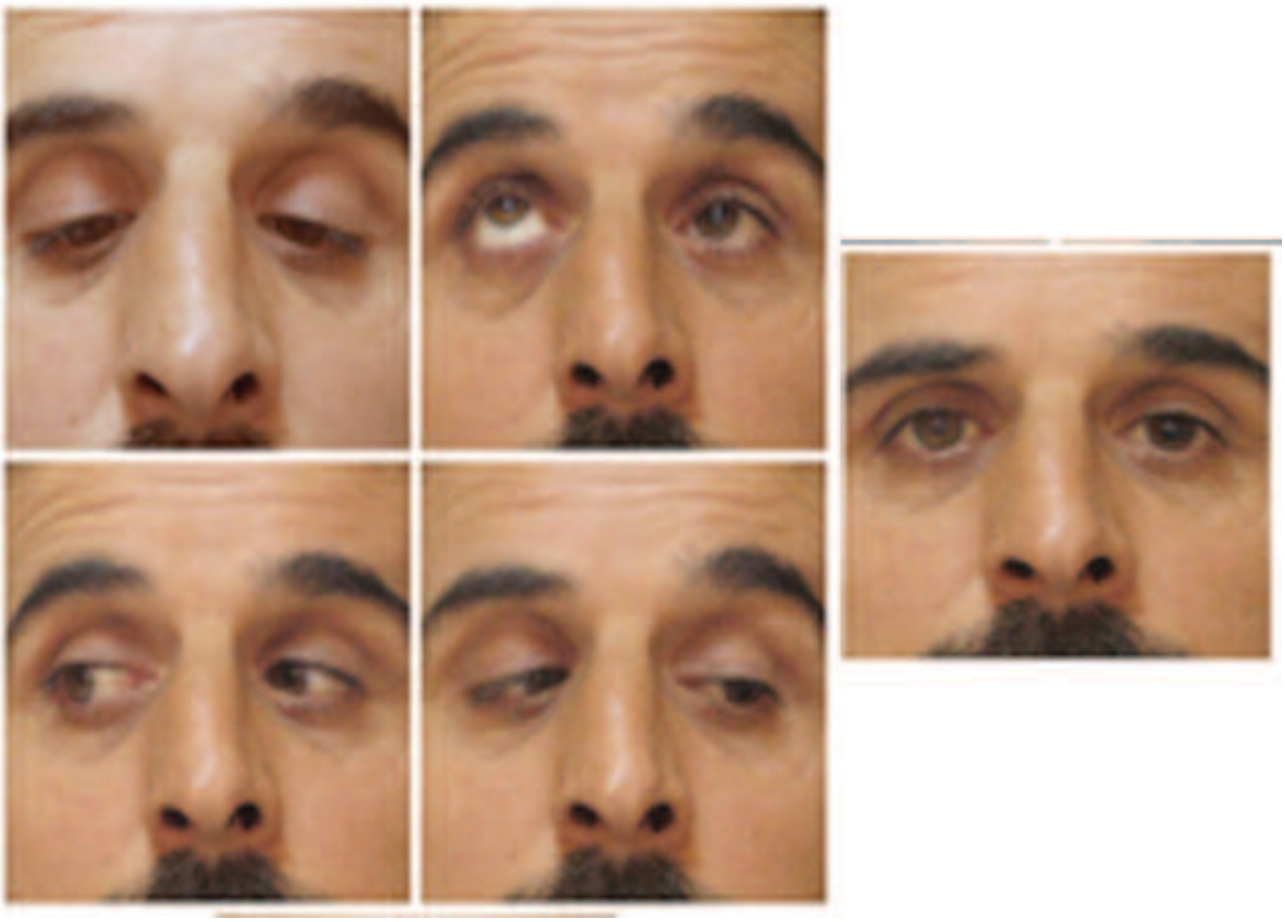

Figure 5. Postoperative examination on the 9th month demonstrating 2-mm restriction of the elevation movement of the left eye and persistent minimal mydriasis.

partial to complete neurologic sequelae depending on the degree of the injury. The clinical findings of the syndrome may include upper eyelid ptosis (due to sympathetic denervation of the Mueller muscle or involvement of the CN III resulting in paralysis of the levator palpebrae superioris muscle); ophthalmoplegia (due to paralysis of the CN III, IV and VI); mydriasis, loss of accomodation reflex, loss of direct pupillary reflex (due to involvement of the CN III and its accompanying parasympathetic fibers resulting in

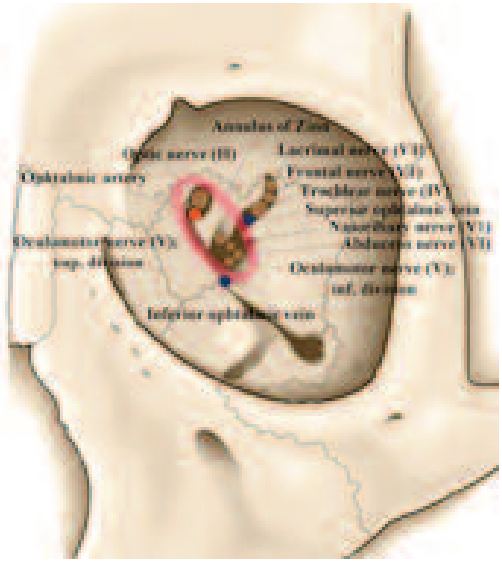

Figure 6. An illustration of the left superior orbital fissure, along with the anatomic structures passing through it.

ciliary muscle paralysis); loss of sensation in the region of the globe, upper eyelid and forehead region and loss of corneal reflex (due to CN V1 paralysis) and proptosis (due to loss of extraocular muscle tone) [1, 4, 9].

Approximately 0.3% of the maxillofacial fractures were reported to be associated with the traumatic SOFS and the most common fractures were described as Le Fort II-III, orbital and zygomaticomaxillary complex fractures [1, 3-5].

The most important clinical consideration in differential diagnosis of the SOFS is the orbital apex syndrome which presents with the findings of the SOFS and varying degrees of visual loss due to optic neuropathy [2]. Also, carotid-cavernous sinus fistula, an abnormal communication between the cavernous sinuses and the carotid arterial system, may mimic the presentation of the SOFS with additional signs and symptoms such as orbital or frontal bruit, chemosis, pulsating exophtalmus, loss of visual acuity, etc [11]. Therefore, in cases of suspected SOFS, it is crucial to perform a proper ophthalmologic examination to rule out the orbital apex syndrome and carotid-cavernous sinus fistula. In the presented case here, there was no evidence of optic involvement, orbital/frontal bruit, chemosis or exophtalmus, excluding orbital apex syndrome and carotid-cavernous sinus fistula.

In the traumatic SOFS, two mechanisms are responsible for the compression of the neurovascular structures of the superior orbital fissure; (1) an indirect mechanism, occurs due to presence of intraorbital edema and hemorrhage resulting in increased intraorbital pressure (indirect traumatic SOFS), (2) a direct mechanism, occurs due to displacement of the bone fragments resulting in narrowing of the superior orbital fissure (direct traumatic SOFS) [1]. Due to the previously reported cases of the traumatic SOFS, a consensus on the treatment algorithm does not currently exist. However, in our opinion, treatment may be effective if targeted to the mentioned pathophysiologic mechanisms of the syndrome.

In the literature, some authors suggest the possibility of recovery with observation or steroid therapy alone and some advocate the use of surgical decompression in cases with displaced sphenoid bone fragments obliterating the superior orbital fissure. In a clinical study of 33 cases [1], clinical observation (n=22) or mega-dose methylprednisolone administration (n=5) were the treatments for indirect traumatic SOFS. Of the cases that treated with steroid administration, 2 had complete recovery of the cranial nerve functions. Also, 6 cases, which were treated surgically for displaced sphenoid bone fragments, demonstrated similar recovery at the follow-ups. The authors stated that the role of the steroids is unclear for the treatment of the SOFS and surgical decompression may be beneficial to those cases with evidence of displaced sphenoid bone fragments.

In another clinical study by Acarturk *et al* [5], 11 cases with SOFS or orbital apex syndrome were completely recovered by intravenous administration of mega-dose methylprednisolone. None of these cases had displaced bone fragments in the superior orbital fissure and 8 had undergone surgery for the treatment of the concomitant maxillofacial fractures. Reduction of the fractures may have a positive effect regarding decompression of the superior orbital fissure and disappearance of the clinical signs and symptoms. Therefore, despite authors' suggestions, the effect of the mega-dose methylprednisolone treatment in the management of the SOFS does not seem obvious in this article.

Conclusion

SOFS is an important entity to recognize clinically and it is characterized by the presence of the signs and symptoms including ophthalmoplegia, ptosis, proptosis, mydriasis, hypoesthesia at the upper eyelid and forehead region, etc. In the presented case, the presence of severe craniofacial trauma had been over-looked during the case's follow-up period in another hospital; illustrating the importance of the careful evaluation of the multi-trauma cases for any concomitant maxillofacial traumas. In the light of our experience with this rare case, we consider that the decompressive surgery in conjunction with the perioperative steroid therapy may be the treatment modality for the direct traumatic SOFS. Future case reports and series of SOFS may aid in developing a consensus on the treatment of this syndrome and we wish that the case presented will contribute to this aim.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential

conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Post-catheterization giant pseudoaneurysm of the femoral artery: an delayed clinical presentation

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ABSTRACT

Post-catheterization pseudoaneurysm is most common vascular complications of cardiac and peripheral angiographic procedures. We report a 67-year-old female patient with giant (25 cmx25 cm) femoral artery pseudoaneurysm which gradually enlarged without rupture developed after catheterization in the periods of three years. She electively underwent to operation. Pseudoaneurysm pouch was evacuated and the bleeding focus from possible catheterization site was primarily repaired with polypropylene suture. Intraoperative or postoperative course was uncomplicated. The patient was discharged on postoperative day 5. The interesting aspect of the presented case is that despite a wide pseudoaneurysm, it remains unruptured for several years.

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Keywords: Post-catheterization pseudoaneurysm, femoral artery, vascular complication, angiographic procedure, surgery

Introduction

Incidence of femoral artery pseudoaneurysm depending on catheterization is less than 0.5% in some cases; on the other hand it is shown more than 5% in other cases. Using of larger-sized cannulas, multiple attempts and long procedures are main reasons for development of femoral pseudoaneurysm [1].

Arterial thrombosis, arterial embolism, hemorrhagia and pseudoaneurysm can be seen as complications of interventional catheterization. Furthermore pseudoaneurysm can cause pain, tenderness and local skin ischemias depending on pressure [2]. Rupture is the most severe complication of pseudoaneurysm. Risk of rupture increases in big hematomas, larger than 3 cm pseudoaneuryms and permanently growing pouches [3].

In this case, we would like to present a giant femoral artery pseudoaneurysm which gradually enlarged without rupture developed after catheterization in the periods of three years.

Case Presentation

A 67-year-old women underwent a diagnostic coronary angiography from right femoral artery about 3 years ago and was discharged in healthy condition.

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But after a short time of discharge, a pulsatile groin mass have occurred in the procedure area and grew day by day. A surgical procedure was offered for her hematoma but the patient didn't accept operation. After the 3 years from catheterization, the patient admitted to our clinic because of severe pain and difficulty on walking. Her vital signs were close to normal on our physical examination. There was a big pulsatile mass (25x25 cm) on her right inguinal area (Figure 1a). There were no neurological symptoms on her related extremity. Furthermore, angiographic and echocardiographic examination showed that she had atherosclerotic coronary artery disease and mild mitral regurgitation. Duplex ultrasonography and conventional peripheral angiography confirmed the diagnosis (Figure 1b). The patient was operated on elective condition (Figures 1c and d). After general anesthesia, an ilioinguinal groin incision was made, the right iliac artery, common, deep, and superficial femoral arteries were explored in the retroperitoneal and femoral regions, encircled with elastic loops and controlled. Heparinization was performed by maintaining the activated clotting time of over 200 seconds in the case when it is necessary to clamp the artery in order to repair the arterial defect. Pseudoaneurysm pouch was accessed through a place close to the possible intervention site, and the bleeding focus was detected. Intervention site on the artery was primarily repaired with 6/0 polypropylene suture. After bleeding control and a small Hemovac drain was placed, tissues were closed in layers and the procedure was ended. No intra operative or postoperative complication was observed. The patient was discharged on postoperative day 5 in healthy condition.

Discussion

Most common symptoms of post-catheterization pseudoaneurysm are inguinal pain, tenderness and protuberance. Rupture is the most severe complication of post-catheterization pseudoaneurysm. Furthermore, neuropathy, venous thrombosis, local skin ischemia,

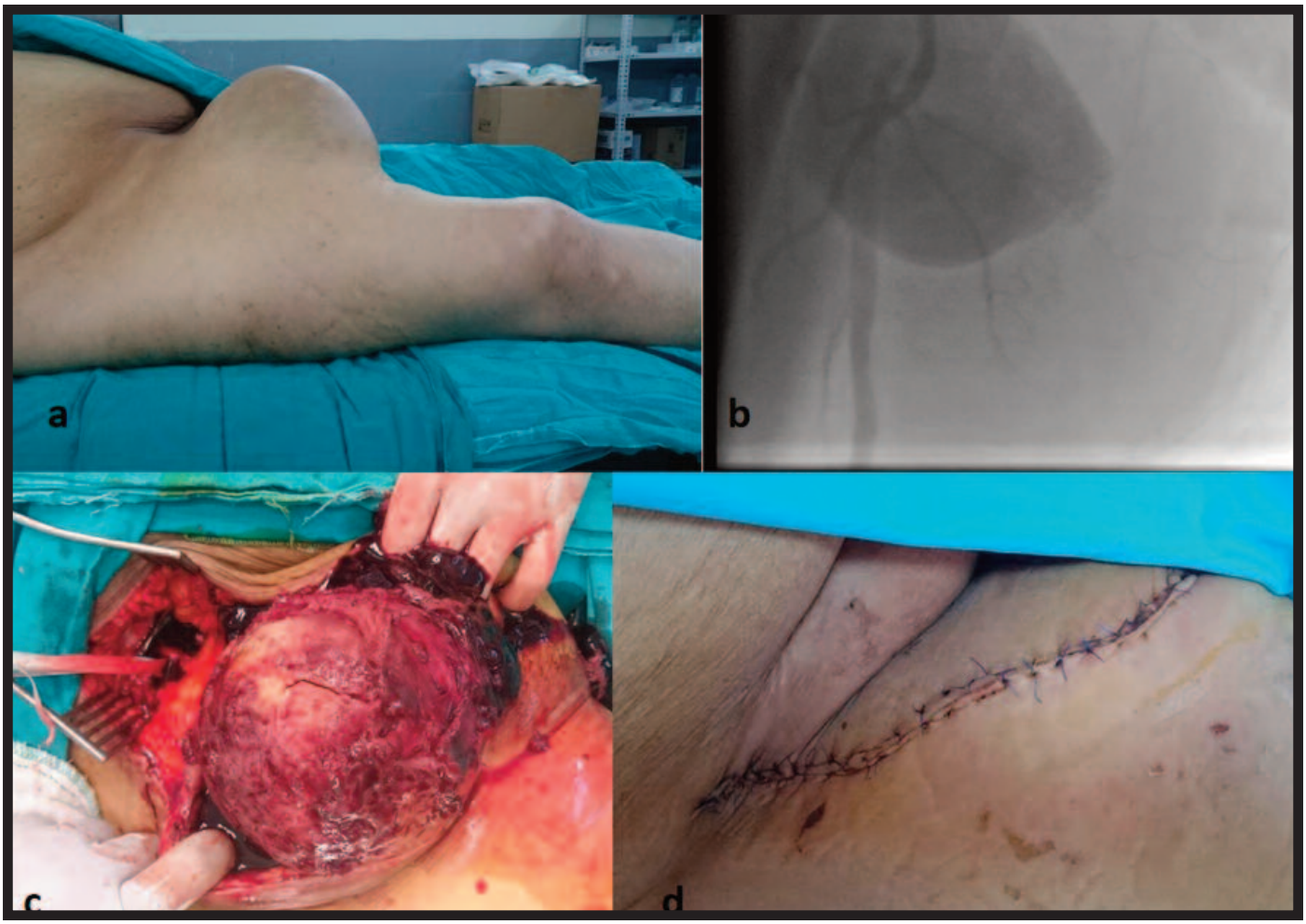

Figure 1. Preoperative picture of the femoral pseudoaneurysm in the right groin of the patient (a), angiographic imaging (b), intraoperative appearance of the lesion (c), and completed surgery (d)

infection and rarely critical extremity ischemia depending on pressure of post-catheterization pseudoaneurysm are other complications. Post-catheterization pseudoaneurysm can be detected incidentally on radiologic examinations and can stay asymptomatic [4].

Post-catheterization pseudoaneurysms usually develop 5-6 days after catheterization with symptoms of severe pain, pulsatile hematoma and new thrill on intervention site. But there are a few cases in the literature which is shown that post-catheterization pseudoaneurysms can develop after 12 days from intervention [5].

Angiography is the gold standard method in peripheral vascular diseases. In addition to angiography, Duplex Doppler ultrasonography has high sensivity and specifity for diagnosis [6]. There are some cases on literature which is urgently operated with Duplex Doppler ultrasonography without performing an angiography [7].

There are a lot of studies in literature that shows surgical treatment is more effective in big aneurysms [8]. In presented case, a diagnostic angiography had been performed to the patient from right femoral artery 3 years ago. A small hematoma after intervention progressed a giant post-catheterization pseudoaneurysm after years and became a life threatening lesion. Because of patient's surgery fear; the patient lived a long time nearly 3 years with a post-catheterization pseudoaneurysm. Patient applied our clinic because of severe leg pain and discomfort in walking. It was not appropriate to use minimal invasive methods because the size of post-catheterization pseudoaneurysm.

We were able to find a case report series of a delayed stage post-catheterization pseudoaneurysm which is diagnosed and treated after 60 days in our literature scan. And the diameter of post-catheterization pseudoaneurysm average size was 4.4 cm in this case series [9]. We found that there were 2 cases that which are termed as giant and the diameters were 55x30 mm and 45x30x50 mm, respectively in literature [10, 11].

In our case, pseudoaneurysm developed after cardiac catheterization. But because of patient's surgical fear, pseudoaneurysm became giant as 25x25 cm within three years. The interesting parts of our case were there were no severe complications even though the post-catheterization pseudoaneurysm was really big and post-catheterization pseudoaneurysm was treated surgically after 3 years.

Conclusion

Post-catheterization pseudoaneurysm is one of the most common vascular complications of cardiac and peripheral angiographic procedures. In these patients, early diagnosis and treatment prevents the development of many complications. Surgical aneurysmectomy and primary repair is a suitable approach as an effective treatment for giant sized and delayed post-catheterization pseudoaneurysms.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Class I pentalogy of Cantrell: a rare case report

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ABSTRACT

Pentalogy of Cantrell is characterized by the presence of five major congenital defects involving the abdominal wall, pericardium, diaphragm, lower sternum and various cardiac abnormalities. This rare syndrome was described by Cantrell in 1958 and it has poor prognosis. We report here a case of class I Cantrell syndrome and our aim is to share difficulties experienced and review the related literature.

Eur Res J 2017;3(1):83-86

Keywords: Cantrell syndrome, ectopia cordis, omphalocele, ventricular diverticulum

Introduction

Cantrell syndrome is a quite rare congenital defect resulting from the defective development of the septum transversum [1]. The syndrome, which is also called the pentalogy of Cantrell, has five main components: various congenital heart defects, sternum anomalies, developmental disorders of the anterior diaphragm, pericardial anomalies, and abdominal wall defects [2]. The syndrome was firstly described by Cantrell in 1958 and it progresses lethally [3]. Although it is rarely diagnosed in the early postnatal period, this case report focuses on the difficulties encountered during management of the case.

Case Presentation

A term newborn girl delivered with cesarean section from a 28-year-old mother from her second pregnancy as the first living child was admitted to the newborn intensive care unit because of the omphalocele. Her APGAR scores were 7 and 8 at 5th and 10th minutes, respectively. Antenatal history revealed abdominal wall defect, supraumbilical omphalocele and ventricular septal defect (VSD) at 24th week of the pregnancy. There was no family history suggestive of birth defects. Her birth weight was 3,620 g (50th percentiles), height 50 cm (50th percentiles), and head circumference 34.5 cm (50-90th percentiles). Physical exam revealed supraumbilical omphalocele and a neighboring pulsatile structure compatible with cardiac heart-beats (ectopia cordis) (Figure 1). Evaluation of other systems revealed no pathology. The abdominal ultrasound showed bowel loops and left lobe of the liver in the omphalocele sac, otherwise normal findings. Echocardiography showed

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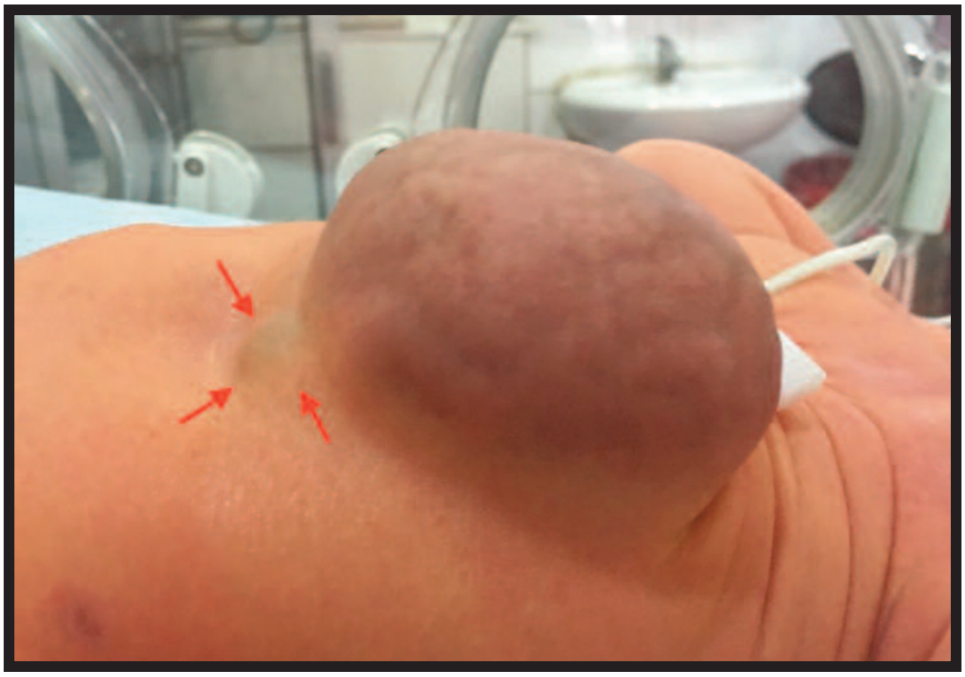

Figure 1. Preoperative photograph of omphalocele sac and ectopia cordis (red arrows)

perimembranous VSD and a diverticulum extending from the left ventricle into the abdomen adjacent the omphalocele sac. Radiograms of the skeletal system were normal. Cardiac diverticulum and omphalocele sac filled with left liver lobe and bowel loops were visualized on CT and CT angiography (Figures 2 and 3). Chromosomal analysis showed a normal female karyotype. On the 8th day of life, the patient was operated. The omphalocele sac and the diaphragmatic defect were repaired primarily and the cardiac diverticulum was excised. During the operation, it was realized that the anterior diaphragm, diaphragmatic pericardium and the inferior end of the sternum were undeveloped. With these findings, the complete pentalogy of Cantrell was considered. During postoperative follow-up period the patient needed 16 days of mechanical ventilation – 14 of which intubated and 2 noninvasive. On the first 5 days of this period, she was monitored with high-frequency oscillatory ventilation and was given inotropes (dobutamine 5 mcg/kg/day). On the 12th day after the operation, the patient was started enteral nutrition, on the 19th day she tolerated full enteral feeding. There were not any cardiac and respiratory complications during the follow-up and the patient was discharged on the 29th day with no need to oxygen support. The patient does not have any problems and is 5 months old at the present day.

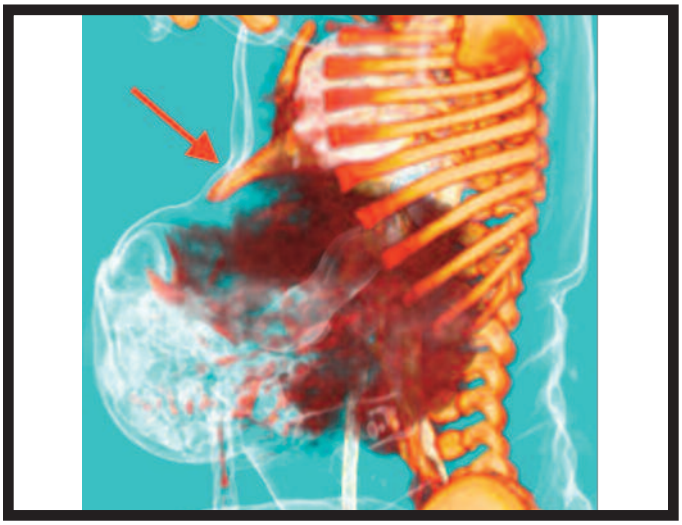

Figure 2. Volume Rendering 3D CT image (left oblique view) showing omphalocele sac and ectopia cordis (red arrow)

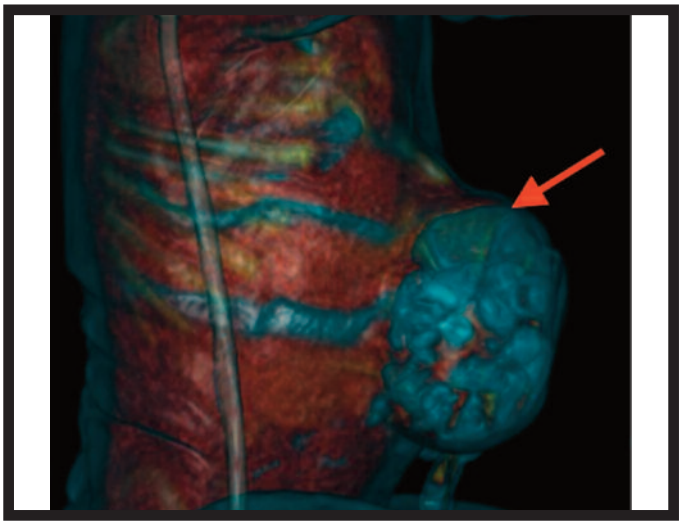

Figure 3. Volume Rendering 3D CT image (right oblique view) showing omphalocele sac and ectopia cordis (red arrow)

Discussion

The pentalogy of Cantrell results from the ventral migration defect of the septum transversum which originates from the mesoderm on the 3rd week of embryonic life [1]. The thoracic diaphragm, anterior abdominal wall and front bowel develop from the septum transversum. The incidence is 5.5-7.9 per 1 million live births [1]. It is considered to be X-linked and deletion on the Xq25-26.1 locus is detected [4]. Some sporadic cases have also been reported. Steiner *et al.* [5] have detected duplication of the ALDH1A2 gene on the long arm of the 15th chromosome with the chromosomal microarray analysis. Our case has normal female karyotype (46, XX) but microarray analysis could not be done.

The cardinal findings are cardiac and sternal anomalies, diaphragm and pericardium development disorders and abdominal wall defects. Toyama [6] suggested a classification for the pentalogy of Cantrell based on the expression of these five findings: definite diagnosis with all 5 defects (class I), probable diagnosis with four defects (including intracardiac and ventral wall abnormalities) (class II), and incomplete expression with varying combinations of defects including a sternal abnormality (class III). Our patient has all the five findings, and was diagnosis as class I pentalogy of Cantrell. The most important finding, which also determines the prognosis, is the cardiac anomaly. The most common ones are VSD (72-100%) and ASD (34-53%) [3, 4]. Our patient had VSD and diverticulum, of which the incidence is 20-32%. Other reported cardiac anomalies are pulmonary stenosis, pulmonary atresia, the tetralogy of Fallot, transposition of the great arteries, dextrocardia and double outlet right ventricle [1, 4]. The most common abdominal wall defect is omphalocele (62%) [7]. Epigastric or umbilical hernia, and diastasis recti might also be seen [8]. Ninety-one percent of patients have ventral diaphragmatic hernia. During the operation, we detected that the anterior diaphragm and diaphragmatic pericardium were underdeveloped and the cardiac diverticulum was extending through these defects into the abdomen. Incidence of the absence of the pericardium is reported as 75% in the literature [9]. Sternum anomalies constitute bifid sternum (26%) or the absence of the lower 2/3 part of the sternum and 10% of patients do not have the xyphoid bone, like the case in our patient [9]. Besides these five cardinal anomalies, central nervous system anomalies such as cleft lip and palate, hydrocephaly, encephalocele or skeletal anomalies such as clubfoot and the absence of ulnae or radius, urinary system anomalies such as polysplenia have been reported in the publications as malformations accompanying the syndrome [10]. Our patient did not have any of these anomalies. Chromosomal anomalies such as trisomy 13 or 18 and Turner syndrome have been reported to accompany the syndrome, so a chromosomal analysis should always be done [4]. Our patient did not have any chromosomal anomalies.

Treatment is always surgical but the timing of the operation is controversial. While an early operation is suggested for abdominal and thoracic wall defects, a later time is suitable for cardiac anomalies. Thoracoabdominal ectopia cordis which is closely neighboring the omphalocele can be treated during the abdominal operation at early days. Mendaluk *et al.* [10] have reported discharging a patient on the 35th day after operating the omphalocele and thoracoabdominal ectopia cordis on the 2nd day of life. As patients with intracardiac diverticulum are at risk of complications such as rupture, tachyarrhythmia and thrombosis, early excision is recommended [8]. Our patient was operated on the 8th day of life; diverticulum resection, diaphragm, and omphalocele sac reparations were done during the same operation by two different teams. No postoperative complication was seen.

Although general tendency is towards treating cardiac diverticulum surgically, there are some publications reporting asymptomatic patients with diverticulum. Jia and Yinbing [11] reported a case having pentalogy of Cantrell with a left ventricular diverticulum, who was asymptomatic until age 4 and operated at that age. Yang *et al.* [4] reported a case who had a VSD, cardiac reposition and omphalocele and operated at 3 months old. The patient had cardiac diverticulum, it was not excised and no complication was observed during the one-year follow-up [4]. In our facility, tendency is towards treating cardiac diverticula surgically.

Prognosis usually depends on the severity of the cardiac anomaly. Even under the best circumstances, the mortality rate is over 50% and patients are lost because of complications like diverticulum rupture, hypotension, bradycardia, tachyarrhythmia or heart failure [4]. De Rubens Figueroa *et al.* [7] have analyzed 21 patients with pentalogy of Cantrell on their retrospective observational study and reported that 17 patients died in the first 5 months and 4 cases having ectopia cordis were among them. Causes of death are septic shock, sepsis, cardiogenic shock,

cardiac failure and organ failure [7].

During the 5 months follow-up our patient did not develop any complications and there was no cardiac dysfunction on control echocardiographies.

Conclusion

The pentalogy of Cantrell is a quite rare syndrome and most of patients do not have a high chance of survival despite proper surgical interventions and the prognosis depends mostly on the severity of cardiac anomalies. Cantrell syndrome must always be considered in patients with prenatal diagnosis of omphalocele and cardiac anomalies and chromosomal analysis should be done. Birth should be made at a medical center where pediatric surgeon teams, pediatric cardiovascular surgeons and newborn intensive care unit are present in order to increase the chances of survival.

Informed consent

Written informed consent and photography release forms were obtained from the parents of the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Complete intraventricular migration of the ventriculoperitoneal shunt

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ABSTRACT

Intracranial migration of the ventriculoperitoneal shunt is an extremely rare situation. A 2-month-old infant who had undergone ventriculoperitoneal shunt for hydrocephalus in the neonatal period presented with feeding problems and increasing head circumference. There was intracranial migration on cranial computed tomography and shunt survey images. Endoscopically the shunt was removed and a new shunt was applied. The patient was discharged with cure. This extremely rare shunt complication and its surgery both have serious complications. Therefore, the surgical technique, proper fixation of the shunt and the use of the right shunting material are significantly important.

Eur Res J 2017;3(1):87-89

Keywords: Shunt complication, intraventricular migration, endoscopic procedures

Introduction

The frequency of intracranial migration of the ventriculoperitoneal shunt is reported to be 0.1-0.4% in the literature [1]. Direction of the migration is determined by the pressure gradient between the cranial and the peritoneal cavities. The case being reported is an example for the intracranial migration of the ventriculoperitoneal shunt which is extremely rare.

Case Presentation

A 2-month-old infant who had undergone ventriculoperitoneal shunt for hydrocephalus in the neonatal period presented with feeding difficulty and increasing head circumference. She was hospitalized. The shunt catheter was not palpable on the cranium, the cervical region or the anterior chest wall. On cranial computed tomography (CT), the shunt was completely in the ventricle and acute hydrocephalus was seen. Also the parenchyma was extremely thinned. On shunt survey images, there was no continuity of the shunt catheter, so an external ventricular drain (EVD) catheter was introduced immediately and a clear cerebrospinal fluid (CSF) leak was observed (Figure 1 a, b, c). The patient was reoperated since there was no bacterial growth in the CSF culture and there was no fever. The EVD catheter

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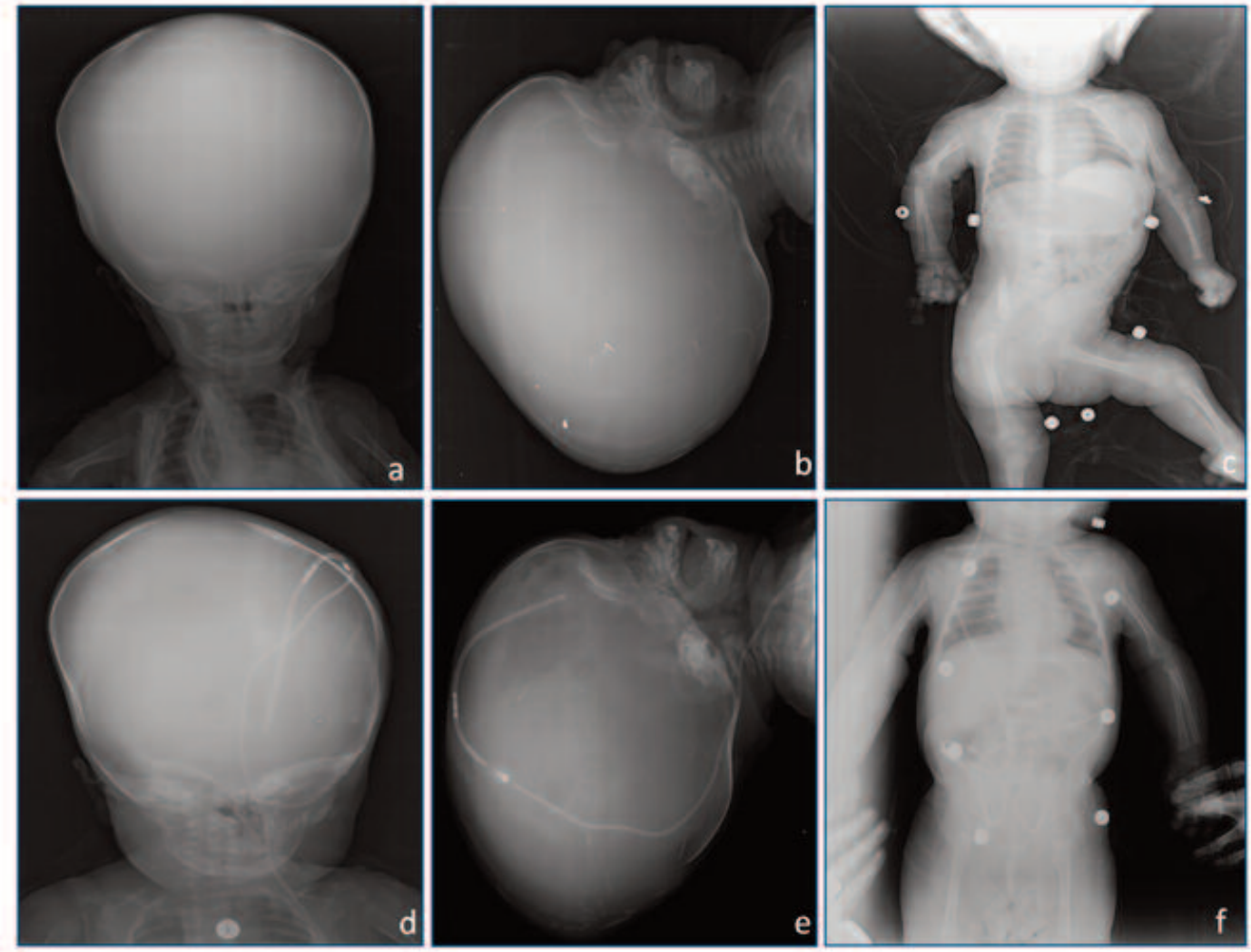

Figure1. Preoperative (a, b, c) and postoperative (d, e, f) x-rays images of ventriculoperitoneal shunt.

was removed, and the new shunt catheter was inserted endoscopically. After inserting the new shunt catheter, the old catheter was removed from the right frontal region (Figure 1 d, e, f). The patient was discharged with cure.

Discussion

Complications of the ventriculoperitoneal shunt are frequently reported for patients with hydrocephalus in the literature. Although migration of the distal edge of the ventriculoperitoneal shunt is common, intracranial migration is a rare complication and it has been reported in 0.1-0.4% of the cases [1]. Despite continuously developing shunting technology, 33% of the patients who had undergone shunt experience dysfunction of the shunt at the end of the first year, 50% after 2 years and 70% after 10 years [2].

In migration of cranial edge of the shunt, lower pressure and mechanical factor providing continuation of the shunt catheter within cranium have been considered as responsible [3, 4]. In other words, if the cranial pressure is high, the catheter will move towards the abdomen, and if the abdominal pressure is high, the catheter will move towards the cranium [3, 5]. As Ceran-Rous *et al.* [6] have reported, underlying diseases (porencephaly), dynamic causes such as abdominal peristaltic movements, dynamic translocation factors such as cervical movements, dynamic attraction factors such as increased CSF reabsorption may cause migration of the shunt. Flexion and extension movements of the neck in childhood can play a role in upward migration of the shunt catheter. In children, since the distance between the ventricular and the peritoneal edges of the catheter is shorter than that in adults, proximal migration more readily occurs. Having seizures and constipation play roles in proximal migration of the shunt catheter [4, 7]. Yilmaz *et al.* [8] suggested that, detachment of the shunt from its attachment sites due to development of

the child, as well as abdominal peristaltic movements, cervical flexion and extension movements, and the history of seizures might be responsible for migration of the ventricular catheter.

The second most common cause of shunt migration in pediatric patients is interruption and detachment of the shunt. Predisposing factors are shunt design, the material used and the surgical technique. Any fixation point can cause interruption by causing tension of the shunt. In addition, immune reaction can cause calcification and dissolution of the shunt material [9, 10]. During surgical procedure, a loose binding or use of absorbable suture material on connection part can lead to detachment in the shunt system by causing tension. Metal instruments can cause small erosions or even full-thickness tears leading to detachments. Risk for shunt detachment occurs only if a connection part is present in the shunt system. For one-piece shunts there is no such problem [11, 12]. Within shunt material, a catheter whose distal tube is stuck with valve and other wall is coated with pure silicone (to prevent calcification) is the best choice when ventricular edges are bound appropriately [13].

When complete intraventricular shunt migration was searched in the PubMed, 10 cases were encountered. Although this situation is extremely uncommon, both the case itself and the surgical procedure are quite risky. In cases in which the shunt is migrated towards the ventricle; anemia, sepsis and hydrocephalus cause cortical atrophy [14]. Situations such as presence of adhesions to the choroid plexus can lead to intraventricular hemorrhage while the shunt is being extracted [15]. To prevent this, avoiding burr holes and wide dural incisions, and attention to proper fixation of the shunt are critical [16, 17].

Conclusion

Complete intraventricular shunt migration is an extremely rare case. The situation itself and its surgery both have extremely severe complications. To prevent this, the surgical technique, proper fixation of the shunt and the use of the right shunting material are significantly important.

Informed consent

Written informed consent and photography release forms were obtained from the parents of the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Acute monoplegia secondary to herpes zoster infection: a case report

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ABSTRACT

Brachial plexopathy with motor involvement secondary to herpes zoster infection is very rare. Also known as shingles, herpes zoster occurs as a result of reactivation of varicella zoster virus in the dorsal root ganglia. We present a 69-year-old male patient with right upper extremity monoplegia secondary to herpes zoster infection. Physical examination showed scars from rash on his right antecubital fossa. Electroneuromyography showed a low amplitude motor response of the right median nerve, while having no sensation response at digits 1 and 3. Right ulnar and radial nerve sensation responses were lower in amplitude compared to the left side. Herpes zoster should be considered in the differential diagnosis of acute monoparesis. It is very important in avoiding unnecessary tests and treatments.

Eur Res J 2017;3(1):90-93

Keywords: Herpes zoster infection, acute monoplegia, brachial plexopathy

Introduction

Also known as shingles, herpes zoster occurs as a result of reactivation of varicella zoster virus in the dorsal root ganglia [1]. Postherpetic neuralgia is the most common complication of herpes zoster. The neurological complications of herpes zoster include aseptic meningitis, myelitis, encephalitis, Guillain-Barre syndrome, development of stroke, and peripheral neuropathy [1, 2]. Brachial plexopathy with motor involvement secondary to herpes zoster infection is very rare [2]. It is believed that motor involvement may develop due to dermatomes involved by extension of the inflammation from the dorsal root ganglia to the ventral roots. However, the exact pathology is unknown [3]. We present a case of right upper extremity monoplegia secondary to herpes zoster infection.

Case Presentation

A 69-year-old male patient presented to our clinic with a complaint of pain and weakness in the right upper extremity that started 3 months ago. It was a burning pain, and the patient described discomfort in daily activities when using his right upper extremity and right hand. He had no history of trauma. During

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anamnesis, he described a vesicular itchy rash on the antecubital fossa in the right arm, which started 3 days before the onset of pain and weakness. He had presented to our dermatology department for his complaint of rash, and received antiviral treatment. He had diagnosis of diabetes mellitus and hypertension in his history. He had no specific features in his family. Physical examination showed scars from rash on his right antecubital fossa (Figure 1).

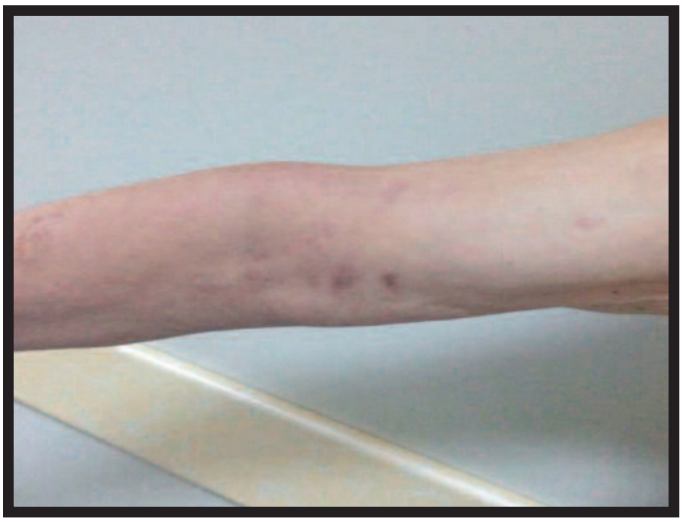

Figure 1. Appearance of scars from rash on right antecubital fossa.

There was no atrophy in the muscles of the right upper extremity (Figure 2). The cervical range of motion (ROM) was full active, and painless. No sign of spurling's was found. The passive and active ROM of the shoulder, elbow, wrist and fingers were full and painless.

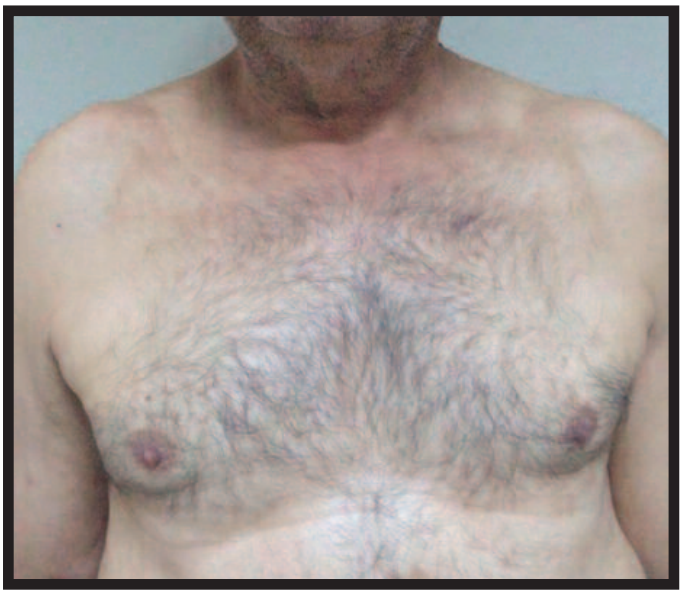

Figure 2. There is no atrophy in the muscles of the right upper extremity of the patient.

Neurological examination revealed muscle strength of 4/5 in the shoulder flexion, extension, and abduction; of -3/5 in the elbow flexion and extension; of -3/5 in the wrist flexion and extension; and -3/5 in the finger abduction and adduction. Biceps, brachioradialis and triceps reflexes were hyperactive. There was no pathological reflex. Sensation examination showed hyperalgesia in all dermatome areas in the right upper extremity.

Laboratory tests (hemogram, sedimentation, CRP, biochemical tests) were normal. Cervical magnetic resonance imaging (MRI) showed no feature except diffuse bulging at the 65 levels C3-C4, C4-C5, C5-C6, and C6-C7. There was no root pressure. Brachial plexus MRI 66 showed no space-occupying lesion with a pressure on the brachial plexus. Electroneuromyography (ENMG) showed a low amplitude motor response of the right median nerve, while having no sensation response at digits 1 and 3. Right ulnar and radial nerve sensation responses were lower in amplitude compared to the left side. Needle electromyograhic analysis showed subacute-chronic neurogenic involvement along with spontaneous denervation potentials in all muscles, with innervated upper-middle-lower truncus (pan-plexopathy), remarkably in muscles innervated by upper and middle truncus in the right brachial plexus. The patient received physical treatment and underwent a rehabilitation program with a hotpack on the right shoulder, transcutaneous electrical nerve stimulation (TENS) on the right upper extremity trace, and neuromuscular electrical stimulation (NMES) on the biceps brachii, extensor carpi radialis longus and brevis muscles. A therapeutic exercise program was given including ROM, stretching, strengthening, improving hand skills. After 20 sessions of this therapeutic program, the patient was re-evaluated. A 50% reduction was found in visual analogue scale (VAS) score. Neurological examination showed a 1/5 increase in the muscle strength. Increased muscle strength was more remarkable during the follow-up at month 1, with shoulder flexion, extension, and abduction 5/5; elbow flexion and extension 4/5; wrist flexion and extension 4/5; and finger abduction and adduction 4/5.

Discussion

Differential diagnosis of unilateral acute weakness of the upper extremity may have many etiologies,

including traumatic injuries (damage to brachial plexus etc.), infectious diseases (polio etc.), allergic collagen autoimmune disorders (acute disseminated encephalomyelitis etc.), biochemical disorders (periodic paralysis etc.), degenerative disorders (multiple sklerosis etc.), anatomical, structural disorders (thoracic outlet syndrome, spinal stenosis etc.) and arteriosclerotic vascular venous disorders (cerebral ischemic attacks etc.) [4]. Approximately 0.5% to 3% of patients with herpes zoster infection develops peripheral motor paresis that is a very rare complication [1]. A literature review revealed that in 1991, Ohtake *et al.* [5] reported a 73-year-old female patient, who developed weakness in the right upper extremity with an axonal degeneration of the proximal portion at level C4-6 following brachial plexus involvement secondary to herpes zoster.

Fabian *et al.* [3] performed a post-mortem pathological examination after a 78-year-old female patient with monoplegia who developed brachial plexus involvement secondary to herpes zoster died from heart attack, and they detected lymphocytic infiltration and myelin breakdown, but found that axons were preserved. They found perivascular lymphocytic cuffing in the cervical spinal cord, but no anterior horn necrosis. Based on these results, motor paralysis might have been related with an inflammatory process. In 2005, Yoleri *et al.* [6] reported a case who developed muscle weakness in the shoulder girdle associated with involvement of the C5-7 motor roots and upper truncus of the brachial plexus secondary to herpes zoster. In 2006, Eyigor *et al.* [7] described a 54-year-old male patient with monoparesis, hyperalgesia, allodynia, edema, and both color and skin-temperature changes, who was diagnosed with complex regional pain syndrome and brachial plexopathy secondary to herpes zoster. Cervical MRI and brachial plexus MRI showed no pathology. Electrophysiological analysis revealed partial degeneration of the superior, medial and inferior truncus in the brachial plexus similar to our case. In 2010 [8], MRI images of a patient with weakness, sensory loss and atrophy due to brachial plexus involvement secondary to herpes zoster showed inflammatory changes in the brachial plexus. Brachial MRI showed no involvement in our patient. In 2011, Alshekhlee *et al.* [9] described various neuropathic findings, multiple neuropathies, radiculopathy and brachial plexopathy in 3 patients with herpes zoster infection of the upper extremity, and found that weakness and electrophysiological changes were not related with dermatomes. Also in our case no relation was found with dermatomes.

In a study which evaluated 49 patients with zoster associated limb paralysis in 2014, Jones *et al.* [10] reported that the mean age of onset was 71 years; the duration between rash and weakness was approximately 5.8 days; and 11% of patients had diabetes mellitus. The mean duration of paralysis was days. Of 22 patients with upper limb paralysis, 4 had multiple cervical level involvement at C5, 6, and 2 at C8, T1, 12, while 2 had ulnar level, and 2 median level involvement. The diagnosis is typically made with ENMG evaluation based on clinical findings. MRI is important for excluding space-occupying lesions involving the brachial plexus and spinal cord, and other pathologies. Imaging is beneficial in eliminating other diagnoses. Often no pathology is determined by imaging methods [2, 10]. In our case, brachial plexus MRI and cervical MRI also failed to show any pathology to explain the monoparesis.

Our patient developed weakness 3 days after rash, however the duration between skin lesions and development of weakness is variable. In some cases, weakness seems to have developed a few months after the rash. The probability of peripheral axonal damage secondary to sensory and motor involvement and development of complications is often increased in elderly patients and immunocompromised patients [1].

Our case was a 69-year-old patient, and he had concomitant diseases such as hypertension and diabetes mellitus. Functional improvement occurs between 1 and 2 years in most cases [10]. Our patient showed a remarkable improvement pattern 4 months after the onset. Literature shows that use of antivirals at appropriate doses can prevent motor involvement, and use of steroids can also be effective in such cases. Some publications recommend use of iv acyclovir and iv steroids in case of paresis [1, 6]. We didn't prefer iv steroids due to presence of diabetes mellitus in our patient. Although he received antiviral treatment in early period, he still developed paresis, but it is likely that he might have had more prominent manifestations if he didn't receive such treatment. The patient benefited from the physical treatment, and strengthening rehabilitation program. While he had difficulty in using his hand upper extremity at his presentation, he was able to use it for daily activities very easily during the follow-up.

Conclusion

Herpes zoster should be considered in the differential diagnosis of acute monoparesis. It is very important in avoiding unnecessary tests and treatments.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Primary squamous cell carcinoma of the thyroid: a rare type of thyroid cancer

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ABSTRACT

Primary squamous cell carcinoma of the thyroid is rare but aggressive malignancy. Primary treatment is complete surgical resection of the tumor. If surgical eradication of the tumor is not successful, it has poor prognosis although multimodality treatment. We report a case with multiple thyroid nodules of which fine needle aspiration cytology was suspicious for malignancy. After total thyroidectomy, well differentiated squamous cell carcinoma was observed in histopathological examination. Postoperative investigation ruled out metastasis of the other sites and recurrence has not been observed for 25 months. Early and accurate diagnosis is crucial to achieve complete cure with surgery and long-term survival.

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Keywords: Squamous cell carcinoma, thyroid, cancer

Introduction

Primary squamous cell carcinoma (PSCC) of thyroid is a rare type of thyroid malignancy because thyroid gland lacks squamous epithelium. It is seen in less than 1% among all thyroid malignancies. To our knowledge, during the last 30 years, only about 90 cases were published [1]. The median age is fifth and sixth decade, but PSCC can be seen at any age. It manifests as enlarging mass, pain, and hoarseness. The diagnosis of PSCC should include clinical, endoscopic, radiological, and histological evidence. Metastatic squamous cell carcinoma (SCC) should always be excluded. In the cases in which direct extension from SCC of adjacent structures to thyroid is observed, exact diagnosis may be difficult. As well as clinical characteristics, optimal treatment strategy of PSCC is poorly defined because of its rarity. PSCC is an aggressive tumor and has poor prognosis although multimodality treatment including surgery, radiotherapy and chemotherapy. It generally has a fatal course within one year of initial diagnosis.

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Case Presentation

A 60-year-old female patient was admitted to our outpatient clinic for multiple nodules. She had no complaint of dyspnea, dysphagia, hoarseness, weight loss or neck mass. She was asked for malignant risk factors such as radiation, hereditary conditions, thyroiditis, diet, smoking but her past medical and family histories were unremarkable. Her serum free thyroxine (fT4), free triiodothyronine (fT3) and thyroid-stimulating hormone (TSH) levels were 0.9 ng/dl, 1.8 pg/ml, and 3.8 μiu/ml, respectively. Other laboratory findings were within normal ranges. Ultrasound revealed one 10x7.5 mm solid nodule in the right lobe of thyroid, and one 7x5.5 mm solid nodule in the left lobe. These lesions were oval-shaped and had hypoechoic heterogeneous microstructures (Figure 1 a, b). There was no mass and palpable lymph nodes in neck examination. From both nodules, we performed fine needle aspiration biopsy and cytology (FNAC). Pathological examination was benign for the right nodule and was suspicious for malignancy for the left one. Total thyroidectomy was planned. Preoperative calcitonin level was within normal range. Total thyroidectomy was carried out with no complication. During surgery, infiltration of adjacent structures was not observed. In the histopathological examination of the specimen, well-differentiated squamous cell carcinoma was revealed. The specimen of the right lobe measured 4.5×2.2 cm. There were two benign colloidal nodules in the right lobe. The specimen belonging to the left lobe measured 5.5×4.0 cm. Tumor was 0.7x0.6 cm in size. The hematoxylin and eosin (H&E) stained sections showed invasive, well differentiated squamous cell carcinoma. The neoplastic cells were disposed in sheets, nests and anastomosing cords. Tumoral cells showed marked pleomorphism polygonal-shaped, it consisted of abundant eosinophilic cytoplasm. The tumor had a well-defined capsule formation around. It had extracapsuler extension, but lymphovascular invasion was not observed (Figure 2). By immunohistochemistry, the tumor cells were positive for cytokeratin 5/6. Stains for synaptophysin, chromogranin, and calcitonin were negative. In further immunohistochemical examination, the tumor cells were negative for thyroglobulin and positive for epithelial membrane antigen (EMA), cytokeratin 7 and cytokeratin 19. Ki67 proliferation index was found as increased.

Postoperative examinations of nose, throat and neck by otorhinolaringist and imaging studies (CT and MRI scan of head and neck and F-18-fluorodeoxyglucose positron emission tomography) was performed for possible primary malignant lesion of squamous origin causing metastasis to thyroid (Figure 3). Investigations ruled out the possibility of other primary sites. Our case was diagnosed with

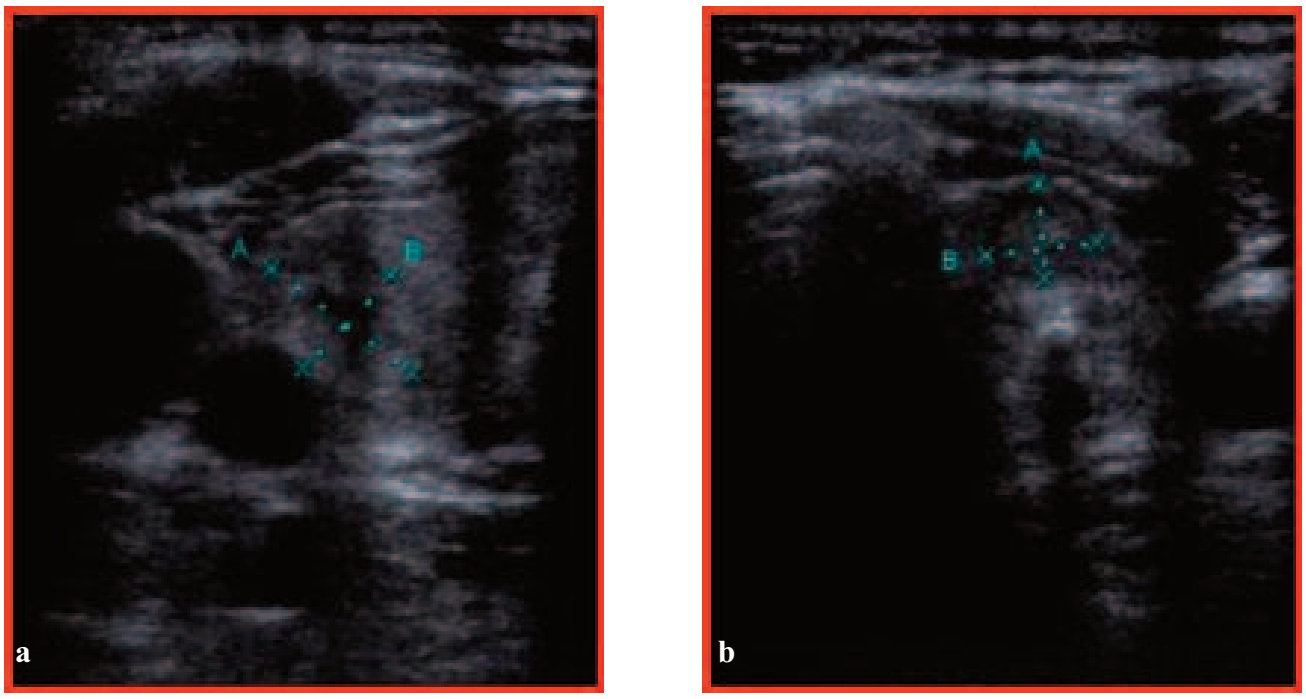

Figure 1. Ultrasound revealed one 10x7.5 mm solid nodule in the right lobe of thyroid (a), and one 7x5.5 mm solid nodule in the left lobe (b). These lesions were oval-shaped and had hypoechoic heterogeneous microstructures.

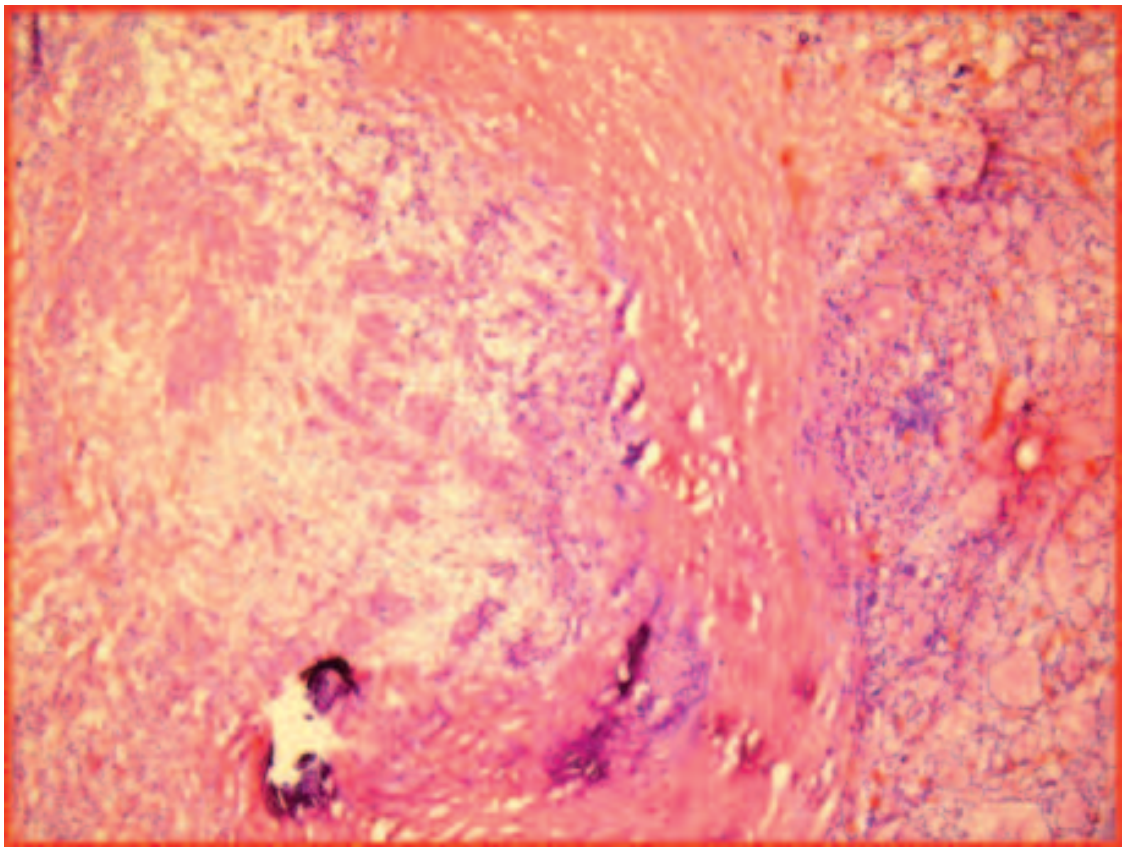

Figure 2. The tumor had a well-defined capsule formation around. It had extracapsuler extension, but lymphovascular invasion was not observed.

PSCC of thyroid by exclusion of metastasis and features of histopathological and immunohistochemical examinations. Because the tumor was locally limited, adjuvant chemoradiotherapy was not considered. Forty-three months have passed after surgery. In CT imaging of neck, chest and abdomen, recurrence has not been observed till now and she has no complaint. She attends her regular outpatient clinic follow-ups.

Discussion

PSCC of thyroid is a rare malignancy when compared with other thyroid cancers. The reported incidence ranges from 0.7% to 3.4% [2-4]. In a systemic review of literature, Cho JK et al. reported that mean age was 63.0 (range; 24-90) and female to male ratio was 2 to 1 [1]. Our patient was a 60-year-old female in accordance with the literature.

The origin of PSCC of thyroid still remains unclear. There are two theories regarding the pathophysiology of PSCC. The embryonic rest cell theory depends on squamous cell derivation from remnants of the thyroglossal duct and thymic epithelium [5, 6]. According to the second "metaplasia" theory, the source of squamous cells is from follicular, papillary or anaplastic cells [7]. In our patient, Hashimoto's Thyroiditis was not observed in surgical specimen.

Clinical presentation of PSCC of thyroid varies according to tumor's aggressiveness. It may manifest as neck mass, hoarse voice, weight loss, neck pain, dysphagia, dyspnea, stridor [5]. Clinical presentation depends on invasion of tumor to the adjacent structures such as esophagus, trachea etc. Rapidly enlarging neck mass and weight loss should be suggestive for PSCC of the thyroid. The patients may also be asymptomatic as our case, possibly be due to early detection of cancer.

In the diagnosis of PSCC of the thyroid, physical examination, endoscopic, radiological and histopathological studies are crucial. Metastatic SCC of other sites should be excluded. Kidney, lung, head and neck cancers are common sites for thyroid metastasis [8]. So exclusion of metastatic SCC can be provided with endoscopic and radiological imaging. For diagnosis, FNAC is reliable [5]. Kumar *et al.* [9]

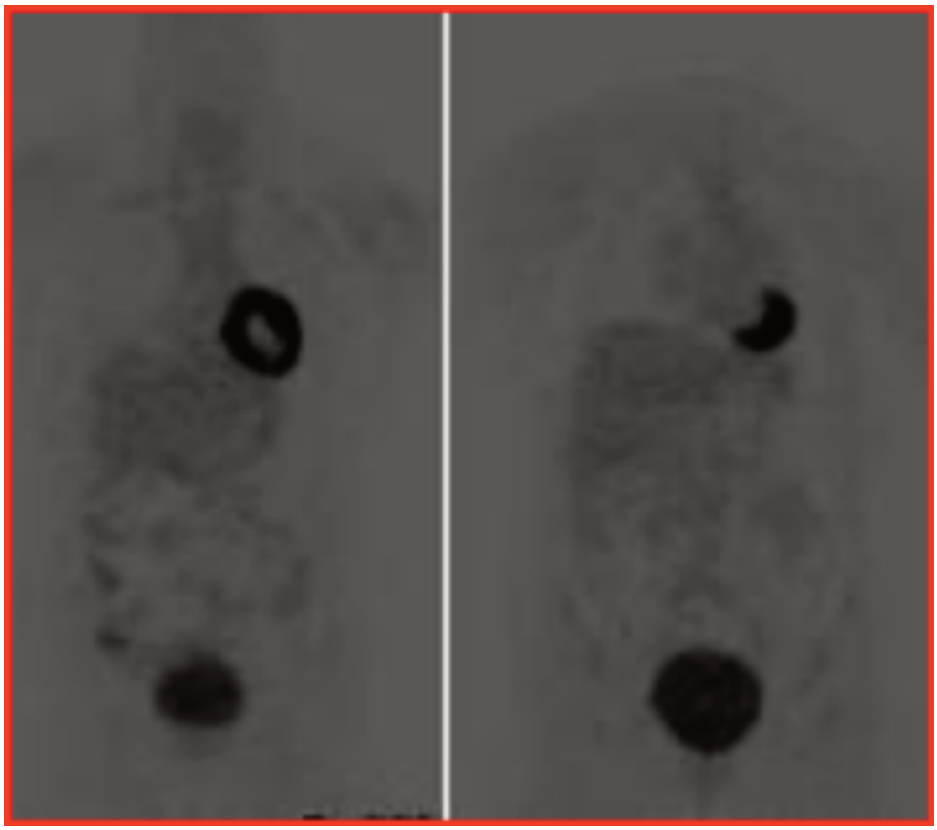

Figure 3. Postoperative positron emission tomography scan was performed for possible primary malignant lesion of squamous origin causing metastasis to the thyroid.

reported that the presence of dyskeratotic, spindle cells and eosinophilic granular keratin material were essential to diagnose SCC in FNAC. Suspicious of high-grade malignancy in cytology combined with clinical, radiological, endoscopic findings can be the most important diagnostic clue for PSCC of the thyroid [10].

Due to rarity of PSCC of the thyroid, treatment modality is not clear. There was no consensus of the extent of surgery, chemotherapeutic agents and radiotherapy. In systemic reviews, treatment with surgery, radiotherapy and chemotherapy alone has been found to be effective and it has extremely poor prognosis [3, 5]. In the treatment of patients with locally advanced and metastatic disease, combined and aggressive treatments should be considered, but they may not be effective. So, for a long survival, as our patient, early diagnosis and curative surgery with clear margins seem to be crucial.

Conclusion

In conclusion, PSCC of thyroid is a rare but very aggressive malignancy among thyroid cancers. FNAC is reliable for the diagnosis, but metastatic SCC should be excluded. Complete surgical eradication of tumor is the primary treatment in early stages of the PSCC of thyroid. In locally advanced and metastatic cases, treatment with surgery, radiation therapy and chemotherapy alone has been found ineffective in recent publications. So, early and accurate diagnosis is crucial to achieve complete cure with surgery. For that reason, though rarity, PSCC of thyroid should be kept in mind in patients with thyroid nodules. Evaluation of the specimens by experienced pathologist and excision of the nodules by experienced surgeon are very important in terms of early diagnosis and effective treatment of PSCC of thyroid.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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