KHARTOUM
MEDICAL JOURNAL
The Official Journal of the Faculty of Medicine, University of Khartoum
Published every four months

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CONTENTS

Original articles

Retrosternal goitre: diagnostic workup and surgical approach

Mohamed ElMakki Ahmed, Nasir Ahaboob Arabi,Seif Eldin Ibrahim Mahadi, Haitham Osman, Reem Mohamed ElHassan

1667 - 1672

The association of insulin and insulin resistance with the renin angiotensin aldosterone system in newly diagnosed patients with essential hypertension

Nouralsalhin A. Alaagib, Mohamed Mustafa Kardash, Mohamed Yousif Sukkar

1673 - 1680

The Mycetoma Patients' Late Presentation: The Causes and Challenges

Hussein Suliman Hussein , Sahar Mubarak Bakhiet, Ahmed Hassan Fahal

1681 - 1687

Clinical presentation and factors associated with chronic suppurative otitis media in children in Khartoum State

Nagwa Malik Hahana, Nazik Elfadil, Osama Mohamed khalid.

1688 - 1693

Measurements of the cerebral cortical thickness in healthy Sudanese subjects during third and fourth decades of age

Wegdan Ahmed, Tahir Osman, Bunyamin Sahin, Amani Elfaki

1694 - 1699

Instructions to authors

1700 - 1702

ORIGINAL ARTICLE
Retrosternal goitre: diagnostic workup and surgical approach

Mohamed ElMakki Ahmed,[1]* Nasir Ahaboob Arabi,[1] Seif Eldin Ibrahim Mahadi,[1] Haitham Osman,[2] Reem Mohamed ElHassan [3]

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ABSTRACT

Introduction The treatment of a retrosternal goitre (RSG) via cervical delivery of the goitre is achievable. This study aimed to suggest when is median sternotomy indicated and reference to a specialized unit is required.

Patients and methods A hundred patients with RSG were seen in one surgical unit in Khartoum Teaching Hospital during the period 2008 - 2014. The diagnosis was established on clinical examination, chest X-ray, thoracic inlet view and CT scan when necessary.

Results Ninety eight patients had thyroidectomy, two asymptomatic patients were conserved. In 98 patients who had thyroidectomy the mean age of the patients was 51 years, male to female ratio 1:3. All presented with pressure symptoms. Total thyroidectomy could be achieved via cervical approach in 95 patients and 3 patients needed median sternotomy.

All palpable goitres reaching maximum the lower curvature of the aortic arch on a plain thoracic inlet and chest X-ray could be delivered by cervical approach.

Five patients with radiological evidence of deep RSG below the aortic arch were considered to be possible candidates for median sternotomy. Ten patients were considered as possible candidates for sternotomy on CT scan. Only 3 patients ultimately needed sternotomy indicating that a chest X-ray can be fairly reliable in predicting median sternotomy.

Conclusion The majority of retrosternal goitres with a palpable cervical part could be delivered by cervical approach. Chest X-ray was fairly reliable to predict cervical thyroidectomy and CT scan could be reserved when the chest X-ray shows a shadow below the aortic arch.

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INTRODUCTION:

Patients with RSG usually present with pressure symptoms like dyspneoa, and nocturnal chocking. Glands extending down to the lower level of the aortic arch as shown on a plain chest X-ray can be delivered via a cervical approach[1]. Most doctors order a CT scan when the plain Chest X-ray report RSG, an expensive and not always available tool of investigation in most of the regional hospitals in developing countries. A reference of such patients to a thoracic unit where sternotomy can be done is always resolved to. The aim of this study is to clarify the role of Chest X-ray (CXR) in diagnosing RSG and when CT scan be ordered and patients be referred to a thoracic unit.

PATIENTS AND METHODS

This is a hospital based study conducted in Khartoum Teaching Hospital including 100 patients with RSG. Patients were asked about pressure symptoms namely: nocturnal choking, using 2

or more pillows during sleep, preference to sleep on a certain cervical position and dyspneoa on activity. Stridor was considered as an emergency. The size of the goitre was assessed using Perez classification.[2] The retrosternal extension was classified preoperatively according to CXR view and CT scan whether the lower limit of the gland shadow above the arch of the aorta, reaching the lower border or below the aortic arch. A gland reaching below the tracheal bifurcation was considered an indication for median sternotomy Proper preoperative assessment was made to assess fitness for surgery based on ASA score in addition to haematological, biochemical and cardiothoracic assessment. Patients were consented for median sternotomy where appropriate.

RESULTS

One hundred patients with RSG were studied; all were referred from various peripheral hospitals. The mean age ± SD was 517± years with male to female ratio 1:3. Two female patients aged 80 and 85 years with deep retrosternal goitre had been on follow up for 10 years without significant symptoms and were treated with levothyroxine 50 mcg daily.

The main presenting symptom of 98 patients was dyspnoea in 78.6% (n=77), nocturnal chocking in 65% (n=64) and 24% (n=24) of patients had disturbed sleep nocturnally. Fifty two percent (n=52) of patients used more than one pillow during sleep. Two patients presented with emergency stridor and underwent urgent thyroidectomy through cervical incision. Goitre size, assessed clinically, was Perez three in 36% (n=36), Perez two in 24% (n=24), Perez 1b in 19 % (n=19), Perez 1a in 18% (n=18), and Perez zero in 3% (n=3). The consistency of the gland was firm in 94 patients, soft in 4 and hard in 2 of the patients. On physical examination we could not go below the gland in 93 and percussion note was resonant over the upper sternum in half of the patients. The whole gland was enlarged in 69 patients; the right lobe was dominant in 15 and the left lobe in 16 patients. The majority of the patients (n=68) were euthyroid, toxic in 18 and hypothyroid in 14 patients. Congested visible neck veins were noted in 17 patients. There was no statistical significant correlation between size of the goitre (Perez) and age, dyspnoea, dysphagia, change of voice, number of pillows, and chocking at night (P value >0.05). CXR showed apical shadow in 98 patients, it was above the level of the arch of the aorta in CT scan in 79 patients, at the level of arch of the aorta in 14 (Figure 1), and below the arch in 5 patients (Figure 2). Two patients who had median sternotomy had goitre shadow below bifurcation of the trachea on both Chest X-ray and CT scan. The third patient was an 80 years old male who presented with pressure symptoms and engorged neck veins without a palpable gland. A chest X-ray showed a left soft tissue shadow at the lower level of the aortic arch which was confirmed by CT scan. A provisional diagnosis of an ectopic thyroid was made. At operation a trial of cervical delivery failed and was followed by extensive bleeding. A large gauze pack was inserted and a left hand was pushed to stop bleeding while the assistant made mini sternotomy.

The CT scan neck and thorax showed the goitre shadow above the aortic arch in 60 patients, at the aortic arch in 10 and below the arch in 10 patients. In 20 patients the chest X-Ray showed soft tissue shadow well above the arch and there was no need for CT scan.

Five patients with radiological evidence of deep RSG below the aortic arch were considered to be possible candidates for median sternotomy. When CT scan was done to those patients with goitre at the arch of the aorta, 10 patients were considered as possible candidates for sternotomy. Only 3 patients ultimately needed sternotomy indicating that a chest X-ray is more predictive of sternotomy than CT scan ($p = 0.000$ for the radiology versus $p = 0.026$ for the CT scan).

Ten patients had malignant goitre, of whom five patients had lung metastasis, and one patient had pleural effusion. The gland showed calcification in 26 patients. X-Ray showed the trachea deviated to the right in 62 patients and to the left in 20 patients.

Tracheal compression occurred in 64 in antero-posterior view and 9 on the lateral view. Ninety five patients were fit for surgery (ASA 1 or 2), and two (2.1%) patients were ASA 3 or 4. Endotracheal intubations were easy in 77 and difficult in 20 patients. The first trial of endotracheal intubation was successful in 72 patients, a second trial on 22 and a third trial or more in 4 patients. The goitre was removed through cervical approach in 95 patients and only three patients needed sternotomy. The lower part of the RSG was broad in 73 and narrow in 27 patients. The lower end of the gland was delivered intact in 80 and in pieces in 18 patients. In all patients where the gland delivery was in pieces the inferior part was broad and cystic that eased delivery after being punctured by finger manipulation and evacuated. Where malignancy was suspected this manoeuvre was not tried. The left lobe was the commonest to extend retrosternally in 60, the right lobe in 28, and the whole gland in 10 patients. The operative time was 1-3 hours in 87 patients. Postoperatively a wide bore chest tube was put in the cervical wound after being sectioned longitudinally to form zinc like shape as open drainage to avoid haematoma formation. Ten patients had tracheomalacia and postoperative stridor was managed by formal tracheostomy. Postoperative recurrent laryngeal nerve injury occurred in 3.1% (n=3); one patient had change of voice before surgery due to malignant goitre; the second patient became normal after few weeks, while the last one was not reachable. Transient hypocalcaemia occurred in 10 patients and was permanent in 2 patients. Total thyroidectomy was done in 93 patients and debulking in 7 patients for malignant goitres. The histo-pathological specimens were benign in 87 patients and malignant in 10 patients. There were 2 deaths: one was an emergency thyroidectomy for a large benign goitre followed by tracheostomy and the other was a patient with an anaplastic carcinoma who had debulking of the tumour followed by tracheostomy.

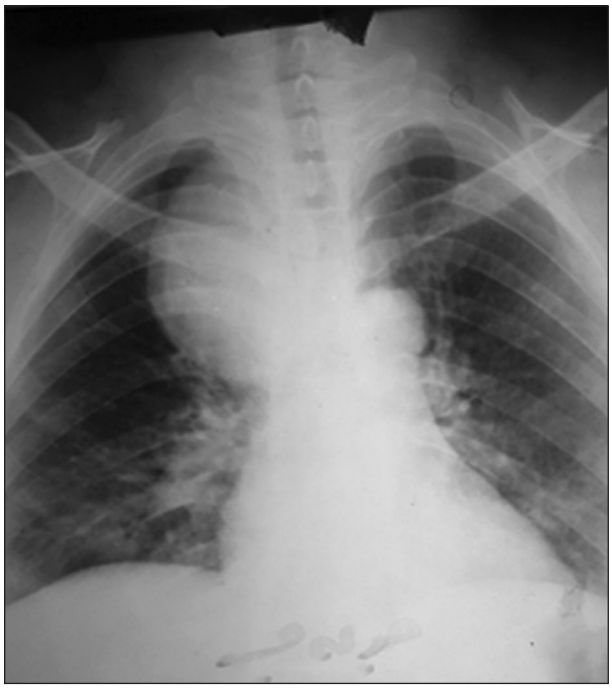

Figure 1A.

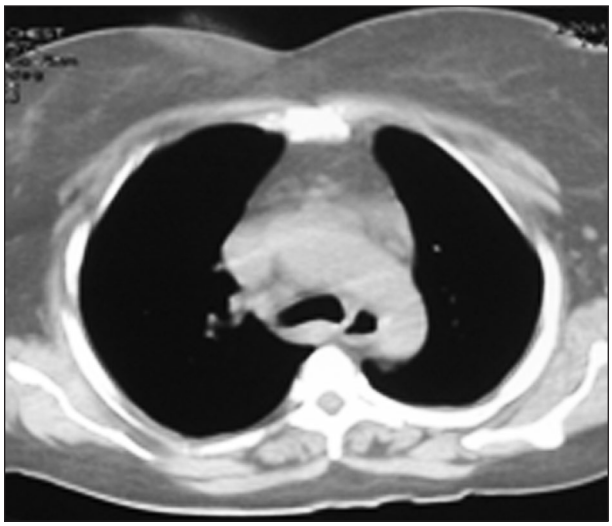

Figure 1B.

Figure 1A. Chest X-ray with retrosternal goitre extending to the lower end of the aortic arch, cervical delivery. Figure 1B. CT scan with retrosternal goitre at the aortic arch

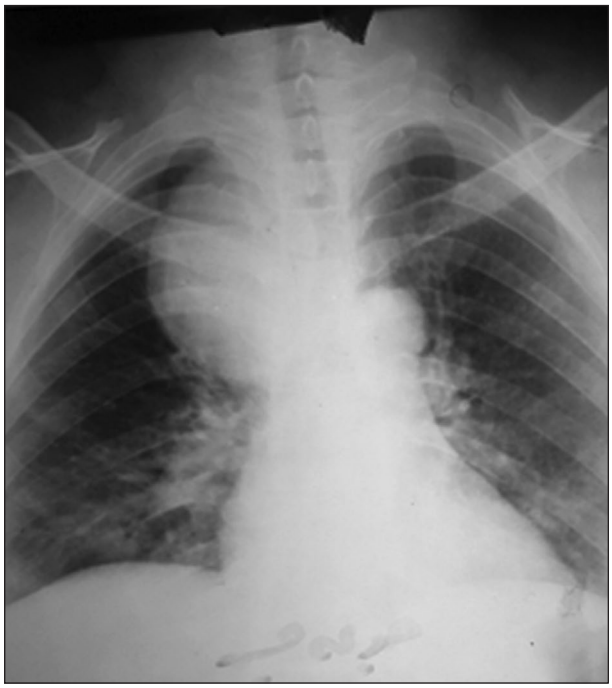

Figure 2A.

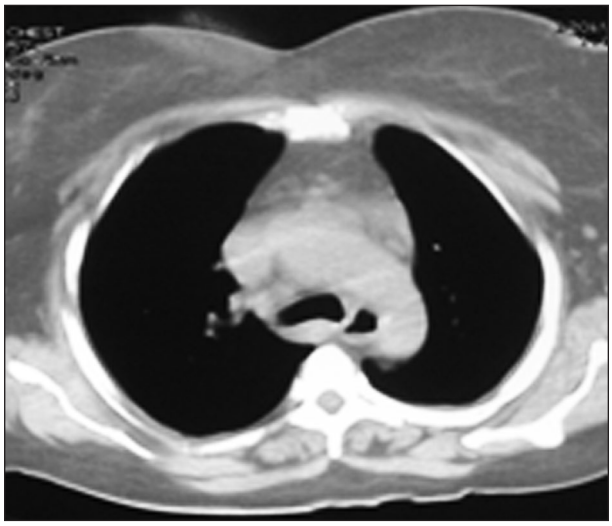

Figure 2B.

Figure 2A. Retrosternal goitre removed via median sternotomy. A chest X-ray showing retrosternal goitre below tracheal bifurcation. Figure 2B. CT scan: Retrosternal goitre below aortic bifurcation

DISCUSSION

There is no agreed definition for intrathoracic goitre and its development may be due to anatomical factors and the negative intrathoracic pressure may play a significant role.[3] It was reported that presence of substernal goitre, per se, should be an indication for surgical management.[4] However, asymptomatic elderly patients could be conserved and spared a major surgical procedure as we reported in two elderly patients. The mean age of the studied patients was 51 years (range between 26-72 years). Both age and sex ratio were similar to patients with non-retrosternal goitre.[5] The work up before surgery routinely included chest X-ray and CT scan in many centres.[6]

Thyroidectomy was the second most common elective operation in Khartoum Teaching Hospital[7] and post-thyroidectomy tracheostomy might be needed post-operatively for large and retrosternal goitres.[8] Emergency partial thyroidectomy under cervical block to relieve acute airway obstruction from thyroid cancer can be done in acute respiratory obstruction.[9]

The most common presenting pressure symptoms were nocturnal chocking in 66%. Around half (52.6%) of the patients felt comfortable to sleep on one side. The sense of dysphagia and/or changing of voice were both very subjective; no detectable change of voice was noted by the doctors and symptomatic relief was noted following surgery. The combination of the following symptoms were very indicative of pressure on the trachea: those were namely nocturnal chocking, use of more than one pillow, feeling comfortable sleep on one side and dyspneoa on waking. Good physical examination and chest X-Ray were the two main tools needed for the diagnosis of intrathoracic goitre. CT scan was reserved for those goitres where a large mediastinal tumour could be seen in an X-ray.[3] Superior vena cava obstruction with dilated upper chest wall veins is an important physical sign of retrosternal extension.[10] Calcification of the goitre is not related to malignancy, clue to dystrophic calcification is often seen in degenerating stroma of nodular goitres, and rarely, ossification is seen.[11] The main deviation of the trachea was to the right.[12] In all the patients who had RSG above the aortic knuckle in the plain X-Ray, thyroidectomy was done through a cervical incision except for the ectopic retrosternal goitre without a palpable cervical part. In those two patients where the goitre extended

to the bifurcation of the trachea a sternotomy was needed. Long-standing goitre with deep (below the aortic knuckle) mediastinal extension and tracheal space compromise can be postulated to increase the likelihood of sternotomy[1]. Other features that increase the likelihood of sternotomy were malignancy, extension to the posterior mediastinum, substernal extension to the aortic arch and lack of solid attachment between the cervical and mediastinal parts.[13] This last version is typical of our patient with ectopic retrosternal lobe where no connection was found between the cervical lobe and the mediastinal part. The broader the retrosternal component the more difficult is the cervical delivery. We opted to penetrate the capsule and deliver the gland in pieces. Colloid cyst sometimes was the main part of this broad base and that makes it easy to puncture and evacuate the fluid and enhance cervical delivery. However, malignancy must be excluded before embarking on this manoeuvre. It is important that the non retrosternal lobe to be dealt with first and the superior pole of the retrosternal lobe ligated to give space for traction.

The two patients who presented to the emergency unit with stridor due to acute tracheal obstruction in long standing RSG were admitted to ICU and both of them underwent urgent thyroidectomy through cervical incision. It was reported that obstructive symptoms are usually insidious and evolve over a period of time, however, acute respiratory infection in substernal goitre, and direct pressure on the trachea might be responsible for this sudden severe respiratory distress. This is a surgical and anaesthetic emergency and needs urgent initial endotracheal intubation.[7] Two patients with a long history of resistant bronchial asthma received bronchodilator, underwent thyroidectomy and were cured. Paul Vadasz and Lajos Kotsis reported that unrecognized mediastinal goitres can produce asthma like symptoms, which may lead to late or misdiagnosis and deficient treatment.[10] Total thyroidectomy, near total and subtotal were the main surgical options.[12] The goitre was benign in 90% in our patients; other authors reported up to 94% incidence of benign RSG.[12,13] Postoperative haematoma is a fairly common complication[12] and we used a wide bore chest tube open drainage after being sliced to form a zinc-like drain and sometimes the wound is left open and stitched 48 hours later.

There was transient hypocalcaemia in three patients and two patients had permanent hypoglycaemia. Many studies reported that transient hypocalcaemia ranged between 5-10%.[12,15,16] We reported three patients with recurrent laryngeal nerve injury; one had change of voice before the surgery due to neoplastic invasion, the second case was transient and the third one was not reachable. Median sternotomy carries a minor risk of hypoparathyroidism or recurrent laryngeal nerve injury.[16]

CONCLUSIONS

Retrosternal goitre patients usually present with pressure symptoms and can be accurately diagnosed by plain CXR and thoracic inlet. CXR is mandatory in all patients with goitre and pressure symptoms. In a CXR with a goitre shadow above the level of arch of the aorta, thyroidectomy can be done via a cervical approach. CT scan can be done to those with Chest X-Ray showing RSG shadow reaching the lower end of the aortic arch or where an ectopic thyroid is suspected. Retrosternal goitre should be suspected in patients presenting with acute respiratory obstruction or asthma like symptoms.

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The association of insulin and insulin resistance with the renin angiotensin aldosterone system in newly diagnosed patients with essential hypertension

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ABSTRACT

Objective Activation of the renin angiotensin aldosterone system (RAAS) results in increased production of reactive oxygen species and oxidative stress resulting in insulin resistance (IR) and impaired vascular function. The aim of this study is to determine the association of plasma glucose (PG), IR, angiotensin II (AngII), aldosterone and blood pressure (BP) after oral glucose with and without sodium chloride (NaCl) in patients with newly diagnosed essential hypertension.

Design and Method Twenty newly diagnosed uncomplicated untreated hypertensive patients were studied. Patients fasted overnight, then each subject took 75grams (gm) glucose with and without 3gm NaCl dissolved in 250ml water; each on a separate day. Patients were monitored for 2 hours. Half hourly BP, PG, serum Na^+, K^+, insulin, AngII, and aldosterone were measured. IR was assessed using Homeostasis Model Assessment (HOMA) index.

Results Subjects were classified into obese (BMI> 30 Kg/m2) (n=11) and nonobese (BMI< 30 Kg/m2) (n=9). In nonobese patients PG correlated positively with AngII after intake of glucose alone (P=0.05) and with NaCl (P=0.007). IR correlated positively with AngII (P=0.002) and aldosterone (P=0.02) after glucose intake. In obese hypertensive patients after glucose intake IR correlated positively with AngII (P=0.04) and with BP (P=0.001). Serum insulin showed positive association with BP (P=0.03) after intake of glucose alone, with systolic BP (P=0.03) after glucose with NaCl.

Conclusions The positive association of serum insulin and IR with BP in obese hypertensive patients and the positive correlation of AngII with IR and/or PG may indicate a possible role of AngII in impaired glucose tolerance in hypertensive patients. Reduction of sugar as well as salt may be beneficial in the control of hypertension.

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INTRODUCTION

Hypertension is a common disease and its prevalence is predicted to increase by 60% by 2025, when a total of 1.56 billion people may be affected.[1] Several mechanisms have been suggested as possible causes of obesity-induced hypertension. An activated Renin Angiotensin Aldosterone System (RAAS) might provide a pathophysiological link between obesity, insulin, and hypertension. Indeed, many studies have reported a link between plasma insulin and RAAS.[2-4] The sympathetic nervous system is known to be stimulated by RAAS, and both angiotensin II (AngII) and insulin stimulate and/or facilitate sympathetic nervous system activity; thus forming another level of interaction between these hormonal systems.[5,6] AngII and aldosterone act within the central nervous system to cause sympatho-excitation and raise the BP.[7]

Angiotensin II acting through angiotensin-1 (AT1) receptors can inhibit insulin-induced nitric oxide (NO) production. It also enhances the activity of NADPH oxidase that leads to an increased reactive oxygen species generation resulting in the degradation of NO and vascular impairment.[8] AngII was found to impair insulin-induced glucose uptake in cardiac and skeletal muscle.[9] Furthermore, Huan et al (2012) reported a significant association of aldosterone with insulin resistance (IR) in African Americans.[10] It was suggested that aldosterone may interfere with insulin signaling in various tissues.[3] Both AT1 receptor and mineralocorticoid receptor activation interfere with insulin signaling mechanisms in the heart,[11,12] vasculature,[13,14] and skeletal muscle.[15] Numerous clinical trials with Renin Angiotensin system (RAS) inhibitors, such as angiotensin converting enzyme (ACE) inhibitors and AngII receptor blockers (ARBs), showed that the inhibition of RAS results in improvement of insulin sensitivity and may prevent hypertension and end organs damage.[16-18] Lastra et al study (2010) suggested an impact of salt restriction, RAAS blockade, and mineralocorticoid receptor antagonism not only on cardiovascular and renal protection, but also on improved insulin sensitivity and glucose homeostasis.[4] Blocking AngII using ACE inhibitors and ARBs has been reported to improve insulin sensitivity, insulin-mediated glucose uptake[19,20] and enhance endothelial function.[21]

The reverse interaction of insulin on AngII activity and signaling pathways is still unclear. Unlike the effects of AngII upon insulin action, which is predominantly inhibitory, the effect of insulin upon AngII action seems to be stimulatory, but it still needs more investigation. Insulin-induced increase in the renal AT1 receptor function; which may provide a mechanism for development of hypertension in conditions associated with hyperinsulinaemia through increasing renal sodium reabsorption.[22]

We hypothesize that sodium (Na^+), glucose and insulin, at least in some patients, may play a role in the regulation of the RAAS leading to cardiovascular and electrolytes abnormalities which present themselves as essential hypertension. The aim of this study is to determine the association of plasma glucose (PG), IR, angiotensin II (AngII), aldosterone and blood pressure (BP) after oral glucose with and without sodium chloride (NaCl) in patients with essential hypertension.

MATERIALS AND METHODS

This is a short term experimental case control study including 20 newly diagnosed untreated adult essential hypertensive patients. Sample size was calculated using the formula for experimental study with serial samples:

$$n=1+2C(s/d).^2$$ Equation2 (Snedecorand Cochran1989)[23]

Subjects with BP ≥ 140/90 were considered as hypertensive patients.[24] BP was measured using mercury sphygmomanometer (Kawamoto, Japan), according to the standardized methodology.[24] Hypertensive patients with mandatory reason for immediate initiation of treatment were excluded. Patients with cardiovascular disease, renal disease, hyperlipidaemia, diabetes mellitus or subjects with random blood glucose more than 200 mg/dl, smokers and alcoholic subjects were also excluded.

Hypertensive patients were recruited from primary health care clinics. After selecting newly diagnosed subjects with essential hypertension, complete physical examination and ECG were done to exclude any abnormality. Subjects who volunteered to participate in the study signed an informed consent form approved by the ethical committee of the Faculty of Medicine, Khartoum University and completed a questionnaire including personal data and past medical history.

Weight in kilograms (Kg) and height in meters (m) were measured using standardized scale (Seca, Germany). The body mass index (BMI) in kg/m^2 was calculated as a ratio between body weight (kg) and squared height (m^2). Random blood glucose, urea, creatinine, lipid profile were measured by spectrophotometer (Biosystem, Spain) for each subject to exclude any abnormality.

Patients were advised to continue their normal dietary habits and not to restrict their usual carbohydrates or salt intake. The selected subjects were asked to fast overnight (8-10 hours), water is allowed, and to attended to the laboratory early morning. After resting for 15 minutes a baseline fasting BP and blood sample were taken. Each subject underwent a set of two experiments and drank solution of (i) 75gm glucose (ii) 75gm glucose plus three gm sodium chloride. This is the maximum level of daily nutrient intake that is likely to have no risk of adverse effects,[35] dissolved in 250 ml of water to be consumed in no more than five minutes. Each experiment was scheduled on a different day separated by at least 3 days with random sequence of experiments. All experiments were done early morning and subjects were studied in sitting position. Each subject was monitored for two hours. Half hourly BP measurements and venous blood sample were taken to measure: plasma glucose (PG) using glucose oxidase method (Biosystem, Spain) by spectrophotometer and serum Na+ and potassium (K+) by Na/K analyzer (Easy Lyte Na/K analyzer, Medica, USA), using Ion Selective Electrode (ISE) technology. Serum aldosterone by competitive ELISA using enzyme immunoassay test kit (Immunospec, USA), serum AngII levels by Sandwiched ELISA using Human Angiotensin II ELISA Kits (Wkea Med Supplies Corp, USA) and serum insulin by quantitative immunoassay test kits (Immunospec, USA) were also assessed.[26]

The estimate of IR using Homeostasis Model Assessment (HOMA) index was calculated with the following formula as described by Wallace and Matthews (2002).[27]

Fasting serum insulin (μU/ml) X Fasting plasma glucose (mg/dl)/405

The HOMA cut-off point of >2.5 is considered as insulin resistance.

The BP measurements were done in the sitting position by the same investigator in a quiet office with comfortable room temperature according to standardized method.[28] A larger cuff was used for obese patients. Systolic BP (SBP) was taken as the point of onset of the auscultated pulsation (phase 1), and diastolic BP (DBP) was the point before the disappearance of the sounds (phase 5). Three readings were taken at intervals of at least one minute, and the average of those readings was used for statistical analysis. If there is >5 mm Hg difference between readings, an additional reading was obtained, and then the average of all the readings was used.[28] Mean BP (MBP) was calculated as DBP+1/3 (SBP-DBP).

Results obtained were analysed using the Statistical Package Program for Social Sciences (SPSS) version 21. Descriptive statistic was done for all variables. The relation between BP, PG, serum electrolytes, AngII and aldosterone was tested with Spearman correlation. Comparison of the above variables between obese and nonobese hypertensive patients was done with independent student t-test. $P<0.05$ was considered significant.

RESULTS

Subjects were classified into obese (BMI> 30 Kg/m2) (n=11) and nonobese (BMI< 30 Kg/m2) (n=9). Descriptive statistics was displayed as means ± SE as shown in Table. No significant difference was found in PG and serum insulin between obese and nonobese hypertensive subjects. However, in nonobese patients, PG had positive significant correlation with AngII after intake of glucose alone ($P=0.05$) and with NaCl ($P=0.007$).

Table. The mean† plasma glucose, serum electrolytes and hormones in hypertensive patients after intake of glucose alone

Variable	Nonobese patients Mean± SE (n=9)	Obese patients Mean± SE (n=11)	t Test P value
Plasma Glucose (mg/dL)	129.7±6.2	126.7±4.8	0.70
Serum Insulin (µIU/ml)	54.2±5.8	71.7±7.8	0.08
Serum Na (mmol/L)	137.9±.6	138.5±.6	0.47
Serum K (mmol/L)	3.6±.1	3.7±.1	0.80
Serum Aldosterone (pg/ml)	234.8±17.0	200.6±9.3	0.08
Serum AngiotensinII (ng/ml)	28.1±1.2	58.1±14.3	0.04*

SE = Standard error

† The mean value is calculated from 5 samples for each patient taken 0-120 minutes after intake of glucose.

According to HOMA index, 9 patients (out of 20) showed IR; 6 of them were obese. In nonobese patients PG correlated positively with AngII after intake of glucose alone (P=0.045) and with NaCl (P=0.007). IR correlated positively with AngII (P=0.002) and aldosterone (P=0.02) after glucose intake. In obese hypertensive patients IR had significant positive association with SBP (P=0.000), DBP (P=0.04), MBP (P=0.001) and with AngII (P=0.04) after glucose intake. This association was insignificant in nonobese hypertensive patients. In obese hypertensive patients, insulin showed significant positive correlation with: SBP after intake of glucose (P=0.04) and glucose with NaCl (P=0.03) and with DBP (P=0.04) and MBP (P=0.03) after intake of glucose alone (see Figure). After intake of glucose with NaCl, insulin showed a highly significant positive correlation with serum Na (P=0.005).

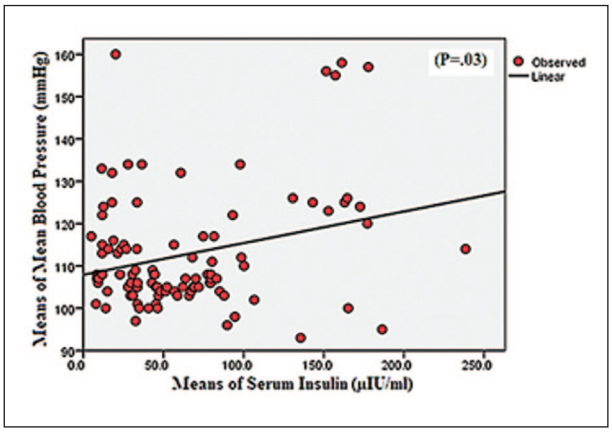

Figure. Correlation of insulin with mean blood pressure in obese hypertensive patients after intake of glucose alone

DISCUSSION

We found that IR was present in 9 patients (out of 20); 6 of them were obese. In obese hypertensive patients IR showed significant positive association with BP. This association was insignificant in nonobese hypertensive patients. Akande et al found a higher occurrence of IR in hypertensive Nigerian patients compared with normotensive subjects.[29] Lima et al studied the prevalence of IR and associated cardiovascular disease risk factors in treated and untreated patients with essential hypertension. In untreated patients the DBP and IR were significantly correlated.[30] On the other hand, Toft I et al (1998) results showed no difference in insulin sensitivity between hypertensive patients and their well-matched normotensive control persons after euglycaemic hyperinsulinaemic clamp. Increments in BMI and waist-to-hip ratio have deleterious effects on both BP and insulin sensitivity. Therefore, it was suggested that IR in hypertension is associated with body fat rather than BP.[31] Failure to detect association between BP and IR could be due to poor classification of the subjects; as obesity is one of the main factors that can be associated with IR. Moreover, including very young and old ages in one study may cause misinterpretation of the results. However, many studies support our finding that IR is related to the development of hypertension. Newer literature has clarified the possible pathophysiology of IR and

its relationship to development of hypertension.[32] A number of proposed mechanisms caused by compensatory hyperinsulinaemia associated with IR have been suggested as causes of hypertension. Insulin affects the BP through its direct cardiovascular effects as well as its systemic actions affecting the sympathetic nervous system and kidneys. Insulin increases cardiac contractility,[33] increases cardiac output,[34] stimulates secretion of the vasoconstrictor ET-1 from vascular endothelium and stimulates vascular smooth muscle cells proliferation and proinflammatory activity.[35-37] IR is associated with increased systemic and vascular inflammatory responses and oxidative stress, which may contribute to vascular dysfunction.[38] Insulin also activates the sympathetic nervous system[39] and can increase blood volume by increasing renal sodium retention.[40,41] It has been reported that salt sensitivity of BP is strongly associated with IR in lean essential hypertensive patients.[42]

It is not known till now whether IR is a cause or a result of hypertension; both of them occur together due to certain metabolic changes. IR can lead to hypertension and high BP associated with increase in AngII and aldosterone, due to disturbed RAAS, which can result in IR. However, the association of insulin and IR with BP appears in obese subjects. We suggest that adipose tissue is the underlying pathological factor responsible for the high BP through disturbed metabolic and hormonal mechanisms. Our findings support the hypothesis that obesity is the link between hypertension and IR.

We found that IR had significant positive correlation with aldosterone in nonobese patients. Similar results were reported by Colussi et al who found significant positive correlations between plasma aldosterone, plasma insulin and IR in hypertensive patients. They suggested that this relationship might contribute to maintenance of high BP in patients with hypertension.[43] A number of recent studies have shown that aldosterone production is associated with IR.[44,45] It has been found that insulin can directly stimulate aldosterone production and can increase AngII-stimulated aldosterone production.[46] Therefore, hyperinsulinaemia associated with IR and obesity may induce increase in aldosterone levels thus forming a positive feedback between aldosterone level and hyperinsulinaemia which suggest a potential mechanism for the development of hypertension in obese insulin resistant subjects.

Furthermore, Kumagai et al (2011) performed a 10-year of follow up prospective study in nondiabetic subjects showed that plasma aldosterone levels predicted the development of IR in a general population.[45] Huan et al studied the associations of Aldosterone and aldosterone: renin ratio with IR and BP in African Americans. They found that IR, estimated by HOMA, was lowest in the low aldosterone group compared with the high aldosterone group. They reported a significant association of aldosterone with IR.[10]

In this study IR had significant positive correlation with AngII in obese and nonobese hypertensive subjects. Ogihara et al (2002) found that chronic infusion of AngII into normal rats induces hypertension and IR.[47] It was found that AngII can inhibit insulin-induced NO production and enhance the activity of NADPH oxidase that leads to an increased reactive oxygen species generation resulting in the degradation of NO.[8] AngII was also found to impair insulin-induced glucose uptake in cardiac and skeletal muscle.[9] Lastra et al (2010) found that activation of RAAS results in increased production of reactive oxygen species and oxidative stress, which impaired insulin signaling resulting in IR and impaired vascular function.[4] Moreover, our finding that AngII is significantly associated with IR in obese and nonobese hypertensive patients is supported by many clinical trials which showed that RAS inhibitors, such as ACE inhibitors and ARBs improved insulin sensitivity and insulin-mediated glucose uptake and may prevent hypertension and end organs damage.[16-20]

In our study the increased insulin level stimulated by oral glucose intake in obese and nonobese hypertensive subjects was not associated with significant change in the level of AngII. Trovati

et al (1989) found that plasma renin activity and AngII level increased significantly and the concentration of aldosterone decreased in humans during euglycaemic insulin clamp. The observed changes were attributed to the decrease in plasma potassium caused by insulin infusion because these changes did not occur in a control clamp study with a potassium infusion.[48] It was reported that insulin is able to enhance AngII induced DNA synthesis.[49] up regulate AT1 receptor gene expression by post-transcriptional mechanisms[50] and induce an increase in the renal AT1 receptor function.[22] The reverse effect of insulin on AngII activity seems to be stimulatory, but it is still unclear.

CONCLUSIONS

This study points out some aspects of RAAS regulation which needs further in depth investigation. In both hypertensive groups AngII correlated positively with IR and/or plasma glucose which may indicate a possible role of AngII, possibly of adipose tissue origin, together with other adepokines in impaired glucose tolerance seen in hypertensive patients with the metabolic syndrome. The results of the present study suggest that reduction of sugar as well as salt is beneficial in the control of obesity related hypertension.

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The Mycetoma Patients' Late Presentation: The Causes and Challenges

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ABSTRACT

Late presentation of mycetoma patients to attain medical care is one of the most important prognostic factors that is strongly associated with a poor treatment outcome and high amputation rate. The present study explored the prevalence and causes of the late presentation of mycetoma patients presenting to the Mycetoma Research Centre (MRC), Soba University Hospital. It included 288 patients with confirmed mycetoma. The data were collected using a pre-designed structured questionnaire by direct personal interview.

In this study, 138 patients (48%) were less than 30 years of age at presentation, and 228 patients (79%) were males. The patients were from different parts of the country, but most of them were from El-Gezira (n=85, 29.5%) and Sennar (n=38, 13.2%) States. Most of the patients (n=180, 62.5%) had either only basic primary education or none. The study showed that 118 (40.9%) patients were severely affected by the disease, had dropped education or job and were unable to perform their routine daily activities. Most of the patients 209 (72.6%) had disease duration of more than one year at presentation while only 79 (27.4%) patients had a disease duration of less than one year. Due to the mycetoma painless nature, 198 (94.7%) patients ignored the disease initially, 83 (39.2%) of them attributed the late presentation to financial reasons, and geographical distance was a cause in 43 (20.6%) patients. One hundred and nineteen (56.9%) patients presented to their local health facilities, 53 (44.5%) of them received inappropriate treatment without being diagnosed as mycetoma, and 66 (55.5%) patients received insufficient treatment despite being diagnosed as mycetoma. The study showed a statistically significant association between the patients' age, level of education, marital status, occupation and the late presentation.

From the obtained results, it is recommended that more efforts to raise disease awareness and advocacy on early presentation, diagnosis and treatment among both the population and health care providers are needed in particularly in endemic areas. Training of health care providers on early case detection and management in mycetoma endemic areas is mandatory. Improvement of the local health and medical facilities in endemic areas is essential for early mycetoma diagnosis and treatment; and to reduce the geographical distance between the affected villages and the tertiary centres.

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INTRODUCTION

Mycetoma is an old and still neglected tropical disease.[1] It is a debilitating chronic subcutaneous granulomatous inflammatory disease which is classified into eumycetoma (caused by fungi) and actinomycetoma (caused by bacteria).[2,3] The most common bacterial causative agents are *Nocardia brasiliensis*, *Actinomadura madurae, Actinomadura pelletieri* and *Streptomyces somaliensis*.[4,5] *Madurella mycetomatis, Madurella tropicana and Madurella fahali* are the most frequent causative agents for eumycetoma.[6,7] In general, actinomycetoma is more prevalent in Mexico and South America, while eumycetoma is more frequently seen in the African continent, however, within a country, the mycetoma type distribution is variable and differs per region.[8,9]

The disease epidemiological characteristics are still not well understood. Mycetoma pathogenesis is poorly understood; probably environmental, genetic and immunogenic factors all playing a role.[10,11,12] Likewise, the actual annual incidence and prevalence of mycetoma globally are not well documented as it is badly neglected and not a reportable disease.[13,14] Still, there remain many controversies on the infection entry route, although traumatic inoculation of causative organisms from the soil into the skin and subcutaneous tissue is the popular theory.[1,2,3]

The disease is characterised by the triad of a progressive, painless subcutaneous mass, multiple sinuses and purulent or seropurulent discharge that contains grains. The grains are of various colours, sizes and consistency depending on the causative organism.[15,16] The subcutaneous mass usually spreads to involve the skin and the deep structures, resulting in destruction, deformity, and loss of function, and occasionally, it can be fatal.[17] Mycetoma frequently affects the foot and hand, and that is seen in more than 80% of patients.[1,2,3,4] Actinomycetoma lesions are more inflammatory, more destructive, and invade bone earlier. In contrast, eumycetoma has a slower presentation but ultimately can be just as destructive.[5,6]

Mycetoma frequently affects the poorest of the poor in poor, remote endemic regions of low socioeconomic status. The majority of patients are farmers, workers, and students. The disease contributes further to their poverty and community economic loss.

Figure 1. Showing massive foot eumycetoma of five years duration at presentation

Mycetoma patients tend to present late for medical treatment, and the cause of that is multifactorial.[21,22] The disease is slowly progressive and frequently painless, and these are the common causes. Other factors delaying medical help include the patients' low socio-economic status, reduced health education level, financial constraints, long distances to secondary and tertiary care facilities and the scarcity of medical and health facilities in endemic villages.[21,22,23]

The delay in the presentation of patients further complicates the management, as the patients will need to receive treatment for more prolonged periods increasing both the economic burden and the risk of developing drug-related side-effects. They will also undergo more extensive surgeries ranking up to amputation, leading to significant disease disability, which will have adverse effects on the patients, their families and the local community as a whole.[24,25]

In this study, we explored the causes of the late presentation of patients and the factors associated with it, so as to develop plans and strategies to decrease its occurrence and minimise its disabling effects.

MATERIAL AND METHODS

This hospital-based cross-sectional descriptive study was conducted at the Mycetoma Research Centre, Khartoum, Sudan, during the period September – December 2018. The study included 288 patients, and the sample size was calculated using the proportion of patients presenting after more than one year (0.751) in a study conducted at the centre that included 6,792 patients, between the period 1991-2014.[16] Systematic sampling technique was used for patients' recruitment. A pre-designed data collection questionnaire was used, and the data were collected by direct interview. In this study, late presentation is defined as disease duration of more than one year at presentation. The data were managed by the Statistical Package for Social Sciences programme (SPSS.23). Descriptive statistical analysis was conducted. The data were

summarised numerically, and the associations between numerical and categorical data were established through ANOVA. The relationship between the late presentation and its causal factors was established through regression analysis. All statistical tests were considered statistically significant when $p< 0.05$.

RESULTS

The study included 288 patients with confirmed mycetoma clinically and histologically; 228 (79%) of them were males, and 60 (21%) were females. Their ages ranged between 10 and 78 years with a mean of 3414.6 years. One hundred thirty-eight patients (48%) were below the age of 30 (Table).

In this study, 66 (22.9%) patients were freelancers labourers, 51 (17.7%) were unemployed, and 47 (16.3%) were farmers. Thirty-four (11.8%) patients were students and housewives each. One hundred fifty-nine (55.2%) patients were married, and 180 (62.5%) received only primary education or no education (Table). The patients were from different parts of the country; those from the El-Gezira State were 85 (29.5%), Sennar State 38 (13.2%), White Nile State 34 (11.8%), Northern Kordofan State 33 (11.5%) and Khartoum State were 31(10.8%) patients. There were three patients from overseas (Table). The majority of the patients were of low economic status. One hundred eleven (38.5%) patients had monthly income less than 1,000 SDG (equivalent to about 22 US dollars), 172 (59.7%) patients had an income ranging between 1,000 and 5,000 SDG, and only five (1.7%) patients had an income of more than 5,000 SDG, (Table).

The study showed, 258 (89.5%) patients presented with swelling and discharging sinuses. The pain was recorded at presentation in only 97 (33.7%) patients. The majority (n=209, 72.6%) of patients had late presentation while only 79 (27.4%) patients had disease duration of less than one year at presentation. The causes of the late presentation were numerous; the painless disease nature was the leading cause documented in 198 (94.7%) patients. The use of traditional treatment (such as traditional ointments and cautery) delayed 95 (45.5%) patients from presenting earlier. Financial constraints barred 82 (39.2%) patients from medical treatment, and the long geographical distance between patients' localities and health facilities was documented in 43 (20.6%) patients.

Figure 2. Showing the blocked roads in an endemic village during the rainy season.

Mismanagement at the local health facilities was documented in 119 (56.9%) patients; 66 (55.5%) received insufficient courses of mycetoma treatment, and 53 (44.5%) patients were misdiagnosed and hence they were mismanaged.

In this study, the patients' demographic characteristics; gender, education level, residence, marital status, occupation and monthly income, were correlated with the disease duration at presentation. The study showed, young patients presented earlier than the elderly patients, and that was statistically significant (P<0.00). There was no significant correlation between the gender and the late presentation, males tend to present earlier, but it was not statistically significant, (P=0.37). Single patients presented earlier than married ones, and that was statistically significant, (P<0.00). With regards to occupation, students tend to present earlier, (P<0.004). There was also a statistically significant association between the education level, and the late presentation, more educated patients, tend to present earlier, (P<0.045).

Patients with a higher income tended to present earlier, but the association was not statistically

significant, (P=0.11). There was also no association between the patients' residence, and the late presentation, patients from Khartoum tended to present relatively early, in contrast to those from Gadarif and West Darfur States, but that was not statistically significant, (P=0.66).

Table. The patients' demographic characteristics

Demographic Characteristic		No.	%	Disease duration at presentation	
				Early	Late
Gender	Male	228	79.2%	63	165
	Female	60	20.8%	16	44
Age in years *	>15	10	03.5%	6	4
	16-30	128	44.4%	42	86
	31-45	79	27.4%	20	59
	>45	71	24.8%	11	60
Occupation *	Free Lancer	66	22.9%	22	44
	Unemployed	51	17.7%	11	40
	Farmer	47	16.3%	10	37
	Student	34	11.8%	17	17
	Housewife	34	11.8%	4	30
	Driver	20	06.9%	8	12
	Employee	12	04.2%	2	10
	Merchant	10	03.5%	1	9
	Teacher	8	02.8%	3	5
	Police Officer	6	02.1%	1	5
Marital Status*	Married	159	55.2%	34	125
	Single	127	44.1%	44	83
	Divorced	2	00.7%	1	1
Education Level *	None	59	20.5%	13	46
	Primary	121	42.0%	33	88
	Secondary	71	24.7%	21	50
	Higher	37	12.8%	12	25
Monthly Income In SDG	<1000	111	38.5%	25	86
	1000 - 5000	172	59.7%	52	120
	>5000	5	01.7%	2	3

State Residence	El-Gezira	85	29.5%	30	55
	Sennar	38	13.2%	9	29
	White	34	11.8%	6	28
	North Kordofan	33	11.5%	9	24
	Khartoum	31	10.8%	11	20
	West Darfur	15	5.2%	0	15
	River Nile	14	4.9%	5	9
	North Darfur	11	3.8%	3	8
	Gadarif	9	3.1%	3	6
	South Kordofan	9	3.1%	2	7
	Kassala	4	1.4%	0	4
	Chad	3	01%	1	2
	Blue Nile	2	0.7%	0	2

DISCUSSION

Late presentation of mycetoma patients which is often associated with advanced tissue and bone involvement is one of the most important prognostic factors that affect the duration and outcome of treatment.[26] Patients who present late will need to receive prolonged treatment course that increases the risk of developing drug side effects and toxicity.[24,25,26] That, also inferring great economic burden on themselves, their families and the health system and will overall have a poorer outcome of treatment than those who present at early stages of the disease.[20,21]

This study explored the causes of and factors associated with late presentation of patients, as to understand the root causes of this problem to address them carefully in planning future health strategies directed towards combating mycetoma. The demographics of the patients involved in the study were in accordance with other series reported from Sudan, as most patients were young males, the majority were of low-socioeconomic status and residing in mycetoma endemic areas mainly the states of El-Gezira, Sennar, White Nile and North Kordofan.[1,2,3]

In this study, late presenters constituted about 72% of patients, which is similar to other reports from the MRC.[15,16] This was due to be various causes, some related to patients' behaviour, others were linked with the socio-economic factors and some related to poor local health facilities. Ignoring the lesion initially due to its painless nature was a factor for almost all patients who presented late, and about half of them used some traditional treatment before presenting to health facilities. The traditional medicine such as local ointments and cautery is usually available in the same village in most cases, the healers are well-respected community members, and most of them are religious leaders. The traditional treatment in the village reduces the need to travel to secondary or tertiary centres and is cheaper than a professional one. This native treatment causes numerous complications and delay of patient to seek treatment. Thus, there is a need for objective and passionate community education and health awareness, especially in endemic areas.

Training of local health providers and improving health facilities in mycetoma endemic areas is of paramount importance as about 57% of patients who presented late were mismanaged initially either by receiving insufficient mycetoma treatment such as localised surgeries, not followed by sufficient medical therapy or had an inappropriate diagnosis. That caused a significant delay for them to receive proper treatment, and had affected the treatment outcome.

The financial constraints and long geographical distance between patients' localities and the MRC are significant difficulties that face the patients in

receiving treatment and attending their regular follow up visits. They were also other significant causes of delaying the presentation of some patients such as road blocks during raining season and social obligations. Thus there is an urgent need for improving the local medical facilities at the mycetoma endemic areas to encourage earlier patients' presentation, and to reduce the financial burden on the patients and their families.

As for the association between the patients' demographic characteristics and the disease duration at presentation, the patients' age, level of education, marital status and occupation were statistically significant. The study showed young patients presented earlier than elder ones, which could be explained by the fact that younger individuals have higher financial and physical abilities to travel the distance and present themselves to the centre. Students also presented earlier than other patients of other jobs such as farmers and freelancers. That can be explained by the fact that the latter groups are more engaged in income-generating activities to support themselves and families and they cannot stop working where students can spare time in particular during holidays to seek medical advice. Furthermore, students because of their education and disease awareness are better than the other groups.

Patients with higher levels of education presented early, which further highlights the importance of health education and awareness. Single patients presented earlier than married ones, which could be related to the engagement of married women in daily household activities, and children and husbands care.

In conclusion, it is recommended that more efforts are needed to raise disease awareness and advocacy on the early presentation for diagnosis and treatment among both population and health care providers, particularly in endemic areas. Training of health care providers in mycetoma endemic areas is necessary for early case detection and management. Improvement of the local health and medical facilities in endemic areas is essential for early diagnosis and proper treatment.

ETHICAL CONSIDERATION

The study was approved by the Ethical Committee, the Faculty of Medicine, University of Medical Sciences and Technology. Informed verbal consent from the patients was obtained whereas their privacy and confidentiality were maintained.

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Clinical presentation and factors associated with chronic suppurative otitis media in children in Khartoum State

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ABSTRACT

Introduction Chronic suppurative otitis media is a potentially disabling health problem. Not only is it an important cause of preventable hearing loss, but it is the most common cause of hearing impairment in low recourse countries.

Objectives To study incidence and factors associated with chronic suppurative otitis media (CSOM) in children in Khartoum State.

Methodology This is a cross sectional prospective facility-based study conducted in paediatric patients who presented with chronic otitis media without otitis externa in selected hospital outpatients' clinics in Khartoum State during the period October 2017 - February 2018.

Results A total number of 76 patients were enrolled: males were 53% and females were 47%. The mean ± SD age was 9.9±0.98 years; a peak incidence of 32.9% was seen in the age group 5-9 years. All the patients presented with ear discharge which was unilateral in 60.5% and bilateral in 39.5%: it was mucopurulent and profuse in 77.6% (n=59); hearing impairment was found in 66 (86.8%) patients and ear pain (otalgia) was present in 24 (31.6%) patients. Factors associated with CSOM included previous upper respiratory tract infections (88.2%), poor hygiene (86.8%), passive smoking (80.2%), bottle feeding (77.9%), recent history of acute otitis media (AOM) 77.6%, poorly-educated mothers (76.3%), malnutrition (73.7%) and inadequate breast feeding (73.6%). Low socioeconomic conditions, overcrowding and in-availability of healthcare facilities were prevalent in 72.4%, 56.5% and 57.9% of patients, respectively.

Conclusions The study revealed that most of the factors associated with CSOM are preventable.

Recommendations Raising health awareness of mothers on hygiene, breast feeding and seeking prompt medical care for their children as well as educating medical personnel about CSOM, its presentation, risk factors early diagnosis, treatment and early referral will contribute to prevention of CSOM and hearing impairment in children.

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INTRODUCTION

Chronic suppurative otitis media (CSOM) is defined as recurrent ear discharge for more than six weeks due to permanent ear drum perforation which does not heal spontaneously. Not only is it an important cause of preventable hearing loss, but it is the most common cause of hearing impairment in low recourse countries with subsequent sequel on language, speech, behaviour development and school performance of children. The aim of this study is to look at the clinical presentation and factors associated with CSOM among Sudanese children in Khartoum State.

MATERIAL AND METHOD

This is a cross sectional prospective facility-based study done in paediatric patients who presented

with CSOM without otitis externa in three Khartoum Ear None and Throat (ENT) hospitals, namely Omdurman, Ibn Sina, and Suba University Hospital in the period from October 2017 to February 2018. Children with CSOM were selected on one-clinic-day per week basis. Data were collected via questionnaire after explaining and obtaining consent of the caregiver/child; general and local ENT examinations were done for all patients. Data were analysed using SPSS v23.

RESULTS

A total of 76 patients: 40 (53%) males and 36 (47%) females in the age range 2-17 years were enrolled. The mean ± SD age was 9.9±0.98 years; 65 (85.5%) were aged between 5 and 14 years and 11 (14.5%) were more than 15 years (Figure); 44 (57.9%) were from rural and 32 (42.1%) patients were from urban areas.

In this study all the patients with CSOM presented with ear discharge (otorrhoea), it was unilateral in 60.5% and bilateral in 39.5%. Ear pain (otalgia) was present in 24 (31.6%) patients. The discharge was odourless in 55 (72.4%) and had foul smell in 21 (27.6 %); it was mucopurulent and profuse in 59 (77.6%) and scanty in 17 (22.4%) patients. Hearing impairment was found in 66 (86.8%) patients; vertigo and ear itching was present in three (3.9%), and one patient (1.3%), respectively.

Other relevant symptoms seen in the patients, in this study, included: nasal discharge, nasal obstruction, sneezing, post nasal drip, snoring and facial pain. These were reported in 39 (51.3%), 28 (36.8%), 25 (32.9%), 22 (28.9%), 22 (28.9%) and 14 (18.4%) patients, respectively.

The mothers of 58 (76.3%) and 18 (23.7%) patients received primary and post primary school education, respectively and the difference was statistically significant (p=0.01). Other associated factors investigated included: low socioeconomic status found in 55 (72.4%) patients while 21 (17.6%) patients were of moderate and high social class, the difference was statistically significant (p=0.04); overcrowding (number of children in the household <3 (n=10, 13.2%), 3-6 (n=23, 30.3%) and >6 children (n=43, 56.5%)) was found to be marginally significant (p=0.05), poor hygiene in 66 (86.8%) (p=0.008) and passive smoking in the household that was found in 80.2% of patients (p=0.009) as shown in Table.

Inadequate breast feeding, and poor positioning was observed in 48 (63.2%) patients compared to 28 (36.8%) patients who were adequately breast fed and the difference was statistically significant (p=0.005**)**; bottle feeding was practiced in 77.9% of the patients and this was also statistically significant (p=0.006). Poor nutrition was observed in 56 (73.7%) compared to 21 (26.3%) patients with good nutrition (p=0.04). Previous history of recurrent upper respiratory tract infection was seen in 88.3% of the patients (p=0.008). History of acute otitis media (AOM) was observed in 59 patients (77.6%), which is statistically significant (p=0.02): out of these 48 (63.1%) patients had more than 6 episodes while 12 (15.8%) patients had a minimum of 3 episodes of AOM. Other factors which are found to be insignificant included gender, history of systemic disease, swimming, ear cleaning habit, family history of otitis media, and craniofacial malformation (Table).

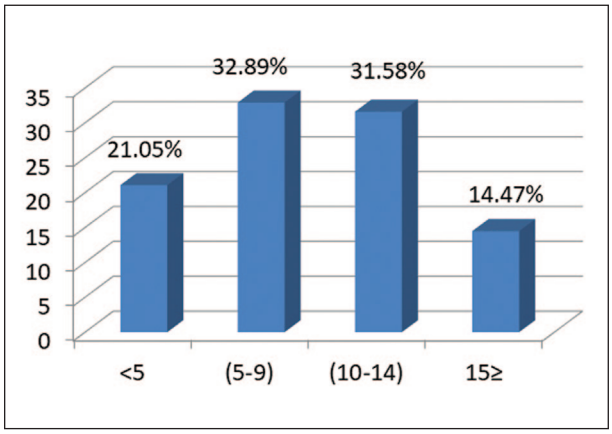

Figure. Age distribution of patients with chronic suppurative otitis media

Table. Factors associated with chronic suppurative otitis media (CSOM)

Factor	Frequency (n)	Percent	P value
Mother education (primary school or less)	58	76.3	0.01
Low Socioeconomic conditions	55	73.4	0.04
Overcrowding (number of children in the household => 3)	66	86.8	0.05
Poor hygiene	66	86.8	0.008
Passive smoking	61	80.2	0.009
Inadequate breast feeding (usually infant lain flat)	56	73.6	0.03
Bottle feeding	59	77.9	0.006
Poor nutrition	56	73.7	0.04
Previous history of upper respiratory tract infections	67	88.2	0 008
History of acute otitis media	59	77.6	0.02
History of tonsillo-adenoid infections	48	63.2	0.055
Family history of CSOM	32	42.1	0.92
Swimming	16	22,1	0.32
Ear cleaning habits	15	19,7	0.556

DISCUSSION

This study showed that males and females were equally affected in agreement with studies done by Garud[9] and Osuji.[13] However male to female ratio of 1.25:1.00 was described in a study done by Khader et al[1] and a similar male predominance was described in other studies.[1,8,21] In this study the mean age of presentation was 9.9±0.98 years and the peak incidence was observed in 25 (32.9%) patients aged between 5-9 years. This is in disagreement with many other studies. Nnebe et al[10] reported that the peak incidence (i.e. 72.3%) was noted in those below 5 years; Adoga A et al[11] showed that children mostly affected were those under-fives; Anggraeni R et al [6] found that 50% of their series were in their first 3 years of life; Amutta SB et al[8] reported that the age group 1-5 years had the highest number of cases although the mean age being 8.2±3.2 years; SubtilJ et al.[12] reported that 79.0% of cases were between 3 and 6 years old. On the other hand, in agreement with the results in this study, Basavaraj MC, Jyothi P[4] observed that the highest frequency (34%) was in the age group of 1-10 years. Moreover Onotai LO, Osuji AE[13] reported higher proportion of CSOM among the age group >12 years; while the study done by Garud S et al[9] reported that no significant difference was observed in the ages of children.

In this study the incidence of CSOM observed in patient coming from rural areas (58%) was greater than in those from urban areas (42%). This is in agreement with a study done by Anggraeni R et al[6] who reported a prevalence of 27 per 1000 of CSOM in rural areas compared to 7 per 1000 children in urban areas. Similar findings were observed by Garud S et al.[9]

In this study the presentation with ear discharge (otorrhoea) as the commonest symptom in patients with CSOM, is in agreement with most studies.[15] Unilateral ear discharge was observed in almost two-thirds of the patients in this series and is also in agreement with the reports of Maharjan[14] and Nnebe[10] but contradicts that of Amutta S Bet al[8] who found that bilateral CSOM was predominant. The fact that more than three-quarters of the patients presented with profuse purulent to mucopurulent ear discharge reflects that the majority of these patients had a tubo-tympanic type of CSOM i.e active mucosal perforation with otorrhoea. The remainder 17 patients (22.4%) who presented with scanty ear discharge were in the age group 10-14 years; scanty discharge is a sign of osteitis and indicative of chronicity.

The second common presenting symptom in this study i.e. hearing impairment was observed in 66 (87%) patients is equally reported by many authors (Maharjan M et al,[14] GarudSet al.[9]) Ear

pain which was present in one-third of this series was also reported in 40% of the cases studied by Alabbasi AM et al.[15] The pain could be attributed to attacks of acute infection of the middle ear cleft on top of a chronically discharging ear or a persistent perforation.

Vertigo was present in one-third of the patients in this study but none of them complained of tinnitus; this disagrees with a study done by Alabbasi AM et al [15] who observed tinnitus in 60% of the cases. Similarly no reports of systemic diseases especially immune-difficiecy was observed and this may be related to the small sample size. A significant number of our series had symptoms suggestive of allergy and this might explain the high frequency of nasal obstruction and discharge, postnasal drip, sneezing and snoring.

In this study previous history of upper respiratory tract infection (URTI). AOM and tonsillo-adenoid infections was present in 88%, 78% and 63% of the patients, respectively, in agreement with many other studies [3,4,5,8,10,11,16,17,20,21,22,] However Verhoeff M et al.[16] and Bakhshaee Metal [24] did not establish an association between CSOM and recurrent upper respiratory infections or AOM.

In this study three-quarters of the mothers of the patients with CSOM were poorly educated; this agrees with other study done by van der veen EL et al[3] who concluded that educational level of the parents is a risk factor of CSOM. But this result disagrees with study done by Parvez Aet al [19] where no significant association was observed with respect to mothers' education.

In the present study passive smoking, observed in four-fifth of the patients, was one of the strongly identified associated factors and this is in line with many other studies[3,21,17,19] but disagrees with a study done by Verhoeff M et al.[16] They found no association between CSOM and passive smoking.

Inadequate breast feeding was observed in two-thirds of the patients while bottle feeding was adopted in three quarters - a risk factor that had been identified before in epidemiologic studies.[3,21,22] in association with CSOM. However, Verhoeff M et al [16] reported no association between CSOM and breast feeding.

low socioeconomic status and overcrowding i.e. three or more children living in the household which were observed in more than three-quarters of patients in this study were also reported as risk factors of CSOM in many other studies.[16,11,6,17,18,8,19]

CONCLUSION

In this study the most commonly affected age group was 5-9 years. The most common symptoms of presentation were ear discharge (otorrhoea), hearing impairment, ear pain, and vertigo. Symptoms associated with CSOM include nasal obstruction, nasal discharge, sneezing, headache\facial pain, snoring and postnasal drip. CSOM is a multi factorial disease associated with many factors namely passive smoking, previous upper respiratory tract infections, AOM or tonsillo-adenoid infection; bottle feeding, inadequate breast feeding, poor nutrition, low socioeconomic status, poor hygiene and inadequate healthcare facilities.

RECOMMENDATIONS

Education and raising awareness of medical assistants in primary health centres and doctors at all levels about CSOM, its presentation, risk factors, preventive measures, early diagnosis, treatment and prompt referral of non-responding patients to specialized ENT centres will reduce the incidence of CSOM and hearing impairment. Not to mention the importance of increasing awareness of mothers about benefits of breast feeding, better nutrition of their children, good hygiene and seeking early medical treatment.

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Measurements of the cerebral cortical thickness in healthy Sudanese subjects during third and fourth decades of age

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ABSTRACT

Introduction The cortex is the outer covering of cerebrum that contains the functional areas including motor, sensory, visual, auditory, and speech. Measuring the cortical thickness of the cerebral hemisphere has greater importance because it supports the neuroscientists in their investigations of normal and abnormal changes in the cortical thickness. The aim of the present study was to measure cortical thickness of the cerebral hemisphere, frontal lobe, and frontal lobe gyri in young adult Sudanese in the third and fourth decade and to determine the effect of sex and age on the cortical thickness of cerebral hemisphere and its gyri.

Material and methods The study included 139 healthy Sudanese subjects (80 males and 59 females) ranging between 20-39 years of age; they were assigned into the third and fourth decades. T1-weighted MR brain images with thickness 1mm were obtained. MR images of the subjects were analysed using the automatic segmentation software (BrainSuite). Cerebral cortical thickness (CCT) of the cerebral hemispheres, frontal lobes, and frontal lobe gyri were estimated using the output data of process of the software.

Results The CCT of the cerebral hemispheres (3.810.21±mm) (3.840.16±mm) and frontal lobes (4.26±0.22mm) (4.240.22±mm) during third and fourth decade, respectively was not different between genders ($P>0.05$). Within third decade, there was no gender difference in CCT of frontal lobe gyri, except for the left precentral gyrus. While within fourth decade, the gender difference was reported in the middle frontal, pars opercularis, pars triangularis, precentral and paracentral, and subcallosal gyri ($P<0.05$). CCT of the cerebral hemisphere and frontal lobe did not change from third to fourth decade ($P>0.05$). Changes in CCT from third to fourth decade were noticed in the precentral, paracentral gyri, and pars opercularis.

Conclusion Cortical thickness of the cerebral hemisphere and frontal lobe were not different between genders and was not changed by age; so they are independent values from sex and age. However, gender differences and change by age were reported in some frontal lobe gyri. This data can serve as normative database and reference data for both researchers and clinicians.

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INTRODUCTION

The cerebral cortex composes of grey matter and contains more than 10 billion neurons. The cerebral cortex is thicker over the gyri (4.5mm) than sulci (1.5mm).[1] The thickness of the cortex provides information about the size and number of neuronal cell bodies; synaptic connections, and the myelination of fibers. It was reported that cortical thickness of the frontal lobe may be affected by normal aging and some disease such as Alzheimer, Huntington, and Schizophrenia diseases.[3] Measuring the cortical thickness of the frontal lobe has greater importance, because it

supports the neuroscientists in their investigations of normal and abnormal change in the cortical thickness. Measuring the cortical thickness from magnetic resonance (MR) images can be done by applying the manual and automated methods. The manual methods were used to estimate the cortical thickness from Brain MR images; but are time consuming even by expert anatomist, subjective, and the natural of the cortex, which is highly folded may lead to errors in measurements.[4] Therefore, there is strong demand to perform reliable and accurate automated methods to measure the cortical thickness.

In the present study cortical thicknesses of the cerebral hemisphere, frontal lobe, and frontal lobe gyri were measured from T1 weighted brain MR images by applying automatic segmentation tool called BrainSuite, which is a collection of software tools that automatically calculate cortical thickness of regions of interest from brain MR image.

MATERIAL AND METHODS

The current study includes 139 normal young adult Sudanese subjects ranging between 20-40 years of age. The subjects were assigned into two groups depending on their age decade: third decade (20-29) and fourth decade (30-39) aiming to examine the sex differences with each age decade and structural change between third and fourth decade. The numbers of subjects in the third and fourth decades were 84 and 55, respectively. Matching for age, sex and body mass index (BMI) was performed. Age and BMI of males and females were (28±5.72) and (28±6.00) years; and (23.93±3.6) and (24.89±5.07) kg/cm^2, respectively. The participants were excluded if they are drug abuse, or had head trauma, neurological diseases, psychiatric illnesses, or congenital malformation related to the brain. The study was approved by the Ethical Committee of the National Ribat University.

The sample size was calculated using the following formula, keeping the confidence level equals to 95% and the margin of error equals to 5%.:

$$n = (Z^2)_{(1-\alpha/2)} P (1-P))/d^{(2)}$$

where $(Z^2)_{(1-\alpha/2)}$ = for 95% confidence level = 1.96

P = Anticipated proportion of infant mortality =10% (cite reference).

d = Margin of error = 5%.

n = Sample Size = 140.

(Ref: Sample size determination in health studies version 2.0.21. WHO)

Magnetic resonance (MR) imaging

Structural MR imaging was done in the radiology department, Doctors' Clinic, Khartoum. MR imaging was performed on 1.5 Tesla Philips scanners, Version: 3.2.1. T1-weighted MR brain images obtained using three-dimensional acquisition by Magnetization Prepared Rapid Acquisition (MP-RAGE), acquisition time (5 minutes and 18 seconds), Slice distance was 1.0mm, the field of view was 250 read, 192mm phase, TR=1657ms, TE=2.95ms, bandwidth 180Hz/pixel, flip angle 15°, ECHO spacing=7.5ms, phase resolution=100%, and slice resolution=50%.

MR images analysis

MR images of the subjects were analyzed using automatic segmentation software (BrainSuite 13a), performed on a Toshiba computer Core i3, 2.10 GHz, 6GB. The software analyzed each MR image in two stages: the first stage is cortical surface extraction sequence, which took 30 minutes to run; while the second stage was long and lasted for 2 hours and 15 minute, which was surface and volume registration.

Cortical surface extraction sequence (CSE)

The first step in the CSE was removing of the skull and scalp from MR image. The next steps included classifying the tissue into cerebrospinal fluid (CSF), grey and white matter; and labelling the brain volume into cerebrum, cerebellum, and brainstem. After that the BrainSuite running cortex masked

selection and topology correction: that included extraction of the cerebral cortex and correction of any errors that might occur during that process. The last stages in the cortical surface extraction included the generation of the pial surface and separation of the cortical surface into left and right hemispheres and displayed them with different colour (Figure 1)

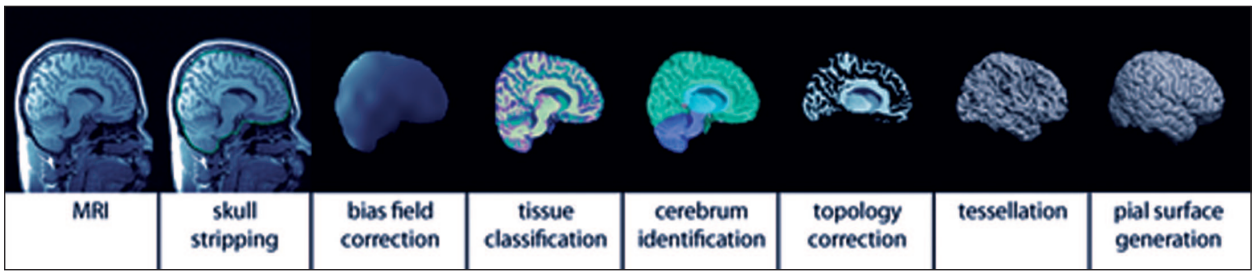

Figure 1. Steps of cortical surface extraction sequence (www.Brainsuite.org)

Surface and volume registration (SVReg)

The SVReg is a programme that registers the results of cortical thickness extraction sequence, which includes the volumes and surfaces to the brain atlas created by expert neuroanatomist. Registering images allows for automatic labelling and analysis of cortical and subcortical structures. (www.Brainsuite.org). Results of SVReg were: labelled inner, pial and mid cortical surfaces of cerebrum; labelled brain volume; and spread sheets of statistics include measurements of the cortical and subcortical structures (Figure 2).

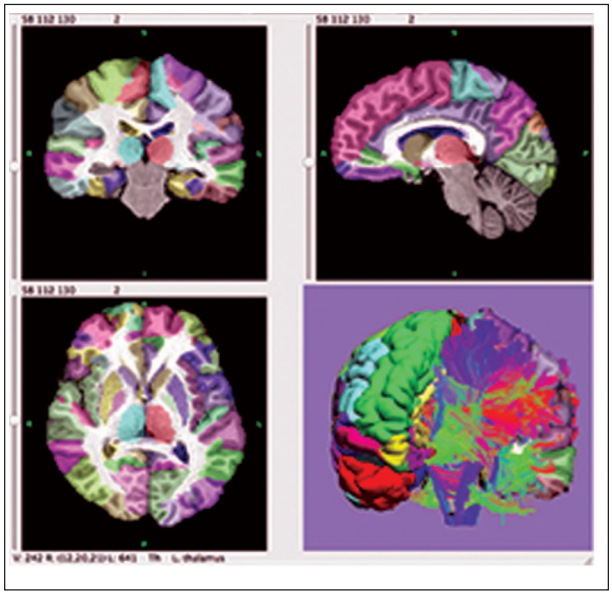

Figure 2. MR image analyzed by BrainSuite (www.Brainsuite.org)

BrainSuite automatically calculate cortical thickness of gyri of the cerebral hemispheres. To calculate cortical thickness of cerebral hemisphere and frontal lobe the following formulae were used in microsoft excel worksheet:

Cortical thickness of the cerebral hemisphere= ∑ cortical thickness of cerebral gyri (1)

Cortical thickness of the frontal lobe= ∑ cortical thickness of frontal lobe (1)

Statistical Analysis

Data were analysed using Statistical Package of Social Science (SPSS) version 21.0; independent sample t.test was performed to compare mean values of cortical thickness between males and females as well as between third and fourth decades. P value equals or less than 0.05 is considered statistically significant.

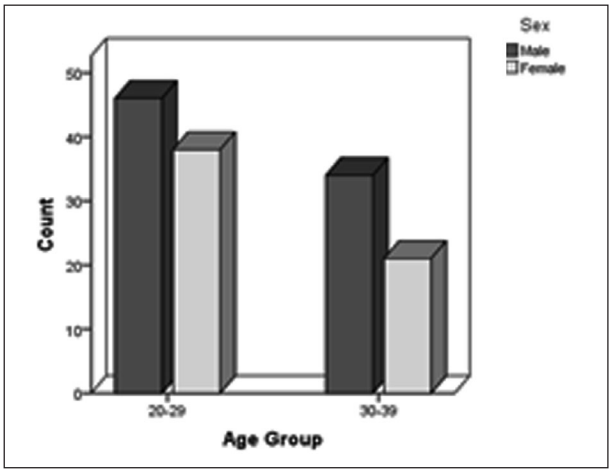

Fig.3: Distributions of subjects according to gender and age decades

RESULTS

Figure 3 shows the number of male and female subjects in the two age group decades.

Sex differences in the cerebral cortical thickness (CCT) depending on Age decade

To determine the gender differences, mean CCT of region of interest was compared between males and females in the third and fourth decades. Within the third decade, there were no differences between genders in the CCT of the hemispheres, frontal lobe, and frontal lobe gyri (P>0.05); with exception of CCT of the total precentral gyri which was larger in females (P<0.05). Within the fourth decade, males had larger CCT in the right middle frontal gyrus, pars opercularis, pars triangularis; in addition to the left and total precentral and paracentral gyri. Conversely, females had larger CCT in the total subcallosal area (P<0.05). There were no differences between genders in the hemispheres, frontal lobe and other frontal lobe gyri (P>0.05). Details of the data of CCT of regions of interest are given in Table.

Change by decade in the cerebral cortical thickness (CCT)

To determine the change by decade, cortical thickness of regions of interest was compared between males during third and fourth decades; and between females during third and fourth decades. Cortical thickness of the hemispheres, frontal lobes, and most of frontal lobe gyri did not change from third to fourth decade in males or females. The change by decades in CCT was demonstrated in the precentral, paracentral and pars opercularis gyri, which was not homogeneous neither in males nor females. In males, from third to fourth decade: CCT of the right precentral and paracentral gyri decreased; conversely, CCT of the left and total precentral; and total paracentral gyri increased. In females, from third to fourth decade: CCT of the left and total precentral; the right and left paracentral gyri and the right pars opercularis decreased. Details of the data of cortical thickness of regions of interest are given in Table.

Table. Cortical thickness of regions of interest

	Cortical Thickness			
	20-29 Years		30-39 Years	
Region of Interest	Males	Females	Males	Females
Rt. Cerebral Hemisphere	3.85±0.14	3.82±0.22	3.81±0.15	3.75±0.17
Lt. Cerebral Hemisphere	3.80±0.18	3.79±0.15	3.84±0.21	3.79±0.12
T. Cerebral Hemisphere	3.80±0.17	3.80±0.15	3.84±0.19	3.80±0.14
Rt. Frontal Lobe	4.28±0.18	4.26±0.29	4.24±0.19	4.19±0.21
Lt. Frontal Lobe	4.27±0.20	4.25±0.26	4.23±0.23	4.30±0.26
T. Frontal Lobe	4.27±0.18	4.26±0.26	4.23±0.20	4.25±0.20
Rt. Superior Frontal	4.70±0.20	4.68±0.26	4.61±0.19	4.66±0.19
Lt. Superior Frontal	4.55±0.27	4.52±0.28	4.56±0.27	4.44±0.22
T. Superior Frontal	4.61±0.25	4.58±0.24	4.63±0.22	4.54±0.16
Rt. Middle Frontal	4.22±0.22	4.20±0.31	4.26±0.21	4.13±0.16C
Lt. Middle Frontal	4.22±0.24	4.22±0.25	4.22±0.22	4.15±0.18
T. Middle Frontal	4.21±0.22	4.21±0.23	4.23±0.21	4.17±0.16
Rt. Pars Opercularis	4.62±0.28	4.52±0.29	4.58±0.37	4.36±0.18BC
Lt. Pars Opercularis	4.48±0.25	4.46±0.24	4.46±0.30	4.41±0.19
T. Pars Opercularis	4.50±0.23	4.49±0.23	4.53±0.24	4.50±0.18
Rt. Pars Triangularis	4.25±0.22	4.15±0.34	4.20±0.27	3.99±0.32C
Lt. Pars Triangularis	4.35±0.25	4.29±0.26	4.33±0.28	4.33±0.23

T. Pars Triangularis	4.26±0.21	4.23±0.22	4.26±0.26	4.23±0.19
Rt. Pars Orbitalis	4.26±0.35	4.20±0.32	4.22±0.30	4.10±0.47
Lt. Pars Orbitalis	4.24±0.40	4.17±0.29	4.35±0.38	4.21±0.40
T. Pars Orbitalis	4.21±0.25	4.20±0.22	4.29±0.28	4.22±0.27
Rt. Precentral	3.52±0.22	3.52±0.23	3.38±0.19A	3.45±0.22
Lt. Precentral	3.26±0.23	3.34±0.23	3.38±0.28A	3.19±0.29BC
T. Precentral	3.34±0.20	3.43±0.18C	3.47±0.23A	3.29±0.22BC
Rt. Paracentral	3.88±0.32	3.95±0.30	3.66±0.24A	3.76±0.29B
Lt. Paracentral	3.66±0.31	3.76±0.30	3.78±0.33	3.61±0.20BC
T. Paracentral	3.71±0.29	3.80±0.25	3.85±0.30A	3.71±0.19C
Rt. Transverse Frontal	4.36±0.66	4.27±0.69	4.43±0.43	4.33±0.43
Lt. Transverse Frontal	4.26±0.56	4.22±0.57	4.23±0.57	4.32±0.46
T. Transverse Frontal	4.32±0.50	4.25±0.53	4.31±0.50	4.32±0.34
Rt. Cingulate	4.08±0.22	4.05±0.24	4.02±0.18	4.03±0.30
Lt. Cingulate	3.99±0.23	4.01±0.23	4.06±0.28	4.02±0.16
T. Cingulate	4.01±0.21	4.02±0.21	4.08±0.23	4.03±0.17
Rt. Subcallosal	3.56±0.89	3.75±0.84	3.42±0.84	3.59±0.82
Lt. Subcallosal	4.47±1.16	4.34±0.99	4.36±0.76	3.95±0.68C
T. Subcallosal	4.03±0.86	3.98±0.68	3.96±0.65	3.72±0.81
Rt. Orbito-Frontal	4.54±0.28	4.51±0.42	4.57±0.31	4.44±0.36
Lt. Orbito-Frontal	4.51±0.36	4.44±0.32	4.58±0.38	4.47±0.31
T. Orbito-Frontal	4.52±0.34	4.47±0.28	4.56±0.32	4.49±0.28

(Mean±SD), A: P ≤0.05 in comparison between males, B: P ≤0.05 in comparison between females C: P ≤0.05 in comparison between sex

DISCUSSION

Sex Differences in the Cerebral Cortical Thickness (CCT) Depend on Age Decade

The present study found that cortical thickness of frontal lobe gyri was ranging from 3.30 to 4.66mm and 3.29 to 4.67mm in males and females, respectively. The lowest cortical thickness of the frontal lobe gyri located in the right superior frontal gyrus and highest cortical thickness of the frontal located in the left precentral gyrus in males and females. The findings of the present study demonstrated that gender differences in CCT depend on age decade; during third decade there were no significant differences in cortical thickness of the hemispheres, frontal lobes, and frontal lobe gyri; with exception of cortical thickness of the total precentral gyrus which were larger in females. During fourth decade gender differences in CT have been reported in the right middle frontal gyrus, pars opercularis, pars triangularis; in addition to the left and total precentral and paracentral gyri; and the total Subcallosal area.

One possible reason for gender differences in CCT includes differences in the rate of maturation and/ or thinning of the cortex at specific age.[2] The findings of the present study confirm this concept; as cortical thickness of precentral and paracentral decrease with age in males but increase with age in females. Other reason for the gender differences in the cortical thickness could be due to differences in the cells numbers, degree of myelination of the white matter and/ or size of the cells.[5]

Change by decade in the cerebral cortical thickness (CCT)

The result of this study found the changes by decades in cortical thickness of the precentral, paracentral

gyri, and pars opercularis. The decrease in CCT from third to fourth decade has been reported in males and females: in males, in the right precentral and paracentral gyri; in females, in the left and total precentral, the right and left paracentral gyri and the right pars opercularis. This decrease in CCT can be explained by the following: shrinkage of neurons,[6] reduction in synaptic density,[7] reduction in spines of dendrites,[8] losing of presynaptic terminals,[9] and alteration of microvasculature.[10] The increase in CCT from third to fourth decade has been reported merely in males in the left and total precentral, and total paracentral gyri. This increase in thickness could be explained by neuronal plasticity induced by learning at an age where functional connectivity maturation is still in progress with the refinement of neuronal connections.[11]

CONCLUSIONS

Cortical thickness of the cerebral hemisphere and frontal lobe were not different between genders in the third and fourth decade; however, gender differences in cortical thickness was reported in some gyri of frontal lobe. Males had larger cortical thickness of the right middle frontal gyrus, pars opercularis, pars triangularis; the left and total precentral and paracentral gyri in the fourth decade and females had larger cortical thickness of the total precentral gyri and subcallosal area with the third and fourth decades, respectively. Cortical thickness of the cerebral hemisphere and frontal lobe showed no change from third and fourth decade, however some gyri of frontal lobe changed with age. From third to fourth decade: cortical thickness of the right precentral and paracentral gyri decreased; but cortical thickness of the left and total precentral; and total paracentral gyri increased in males; cortical thickness of the left and total precentral; the right and left paracentral gyri; and the right pars opercularis decreased in females.

Acknowledgement

This study was supported by Organization for Women in Science for Developing World (OWSD)

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