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EDITORIAL

HEPATITIS D IN CHILDREN AND ADOLESCENTS – AN UPSURGE?

Sina Aziz

Pediatric liver disease due to viruses capable of sustained infection includes Hepatitis B virus (HBV) and Hepatitis C virus (HCV). HBV is a DNA virus and is transmitted through contamination with infected blood or body fluids and also mother to infant transmission. Seroprevalence of HBV is low in general pediatric population.¹ Recent data from Sarwar Zuberi Liver Centre (SZLC) shows an upsurge of HDV co infection with HBV in some areas of Sindh. However, the possibility exists that patients with HBV were not being screened for HDV, previously and now due to awareness among physicians HDV screening is also being done prior to starting treatment for HBV. Spontaneous rate of mother to infant transmission, so called vertical transmission for HBV is 85-90% which is much greater than other viruses such as HCV (4-6%).²³ This rate is in the absence of co-infection with HIV.

Hepatitis D virus or delta virus (HDV), the smallest known animal virus, is a defective RNA virus because it cannot produce infection without a concurrent HBV infection. The 36-nm-diameter virus is incapable of making its own coat protein; its outer coat is composed of excess HBsAg from HBV. Hence, the virion is a hybrid consisting of a nucleocapsid core, comprising HDV RNA genome and HDV antigen, and a lipid envelope containing HBsAg, and thus HDV infection occurs only in chronic HBV carriers.

HDV can cause an infection at the same time as the initial HBV infection (co infection), or HDV can infect a person who is already infected with HBV (super infection). The route of transmission is mainly parenteral: infection may occur at the same time or subsequent to HBV acquisition. Transmission usually occurs by intrafamilial or intimate contact in areas of high prevalence, which are primarily developing countries. HDV was assumed to be rare in the developing world. Very little data is available regarding the prevalence of HBV and HDV co infection in Pakistan. However, recently it has been documented as a co-infection with HBV in adult, and pediatric population from this part of the world also.⁴⁵ Patients’ follow up at SZLC has shown that 50% of the patients presenting with HBV infection had a co infection of HBV and HDV. Treatment of HBV and HDV co infection requires a minimum, one year of expensive treatment which is not always possible in our group of low socio-economic patient population. This data is alarming as major risk factors in this study group were lack of HBV immunization and unsafe injection use. HDV genotype I was seen in our patients similar to other studies.⁷ However; this aspect is being further explored. In areas of low prevalence, such as the United States, the percutaneous route of infection is far more common. HDV infections are uncommon in children in the United States but must be considered when fulminant hepatitis occurs. In the United States, HDV infection is found most frequently in parenteral drug abusers, developmentally disabled, patients with hemophilia and persons emigrating from areas that include southern Italy, parts of Eastern Europe, South America, Africa and the Middle East.⁸

HDV has diminished in Europe, since 1970-80s. However, HDV remains an important health problem outside Europe, with new foci of infection being identified in developing countries.⁹ The incubation period for HDV super infection is about 2-8 weeks; with co-infection, the incubation period is similar to that of HBV infection.¹⁰

Liver pathology in HDV hepatitis has no distinguishing features except that damage is usually more severe.¹¹ In contrast to HBV, HDV causes injury directly by cytopathic mechanisms. Many of the more severe cases of HBV infection appear to be a result of co infection of HBV and HDV. HDV super infection of a person who has chronic HBV infection is more common in developed countries. Clinical presentation of HDV infection in HBV carriers may be asymptomatic with complete resolution of infection, develop acute hepatitis or fulminant hepatic failure, and develop rapid progression of chronic hepatitis. Symptoms
of HDV are similar to but usually more severe than those of other hepatotropic viruses. Clinical outcome of HDV infection depends upon the mechanism of infection. In acute hepatitis, which is more severe than for HBV alone, is common but the risk of developing chronic hepatitis is low. In super infection, acute illness is rare and chronic hepatitis is common. However, the risk of fulminant hepatitis is highest in super infection. HDV should be considered in any who experiences acute hepatic failure. HBV/HDV co infection develop cirrhosis, hepatic decompensation, and HCC (hepatocellular carcinoma) compared to those with HBV alone.\textsuperscript{12,13}

HDV infection can be detected by HDV antigen in hepatocyte by immunofluorescence or immunoperoxidase stains. HDV has not been isolated, and no circulating antigen has been identified. The diagnosis is made by detecting IgM antibody to HDV; the antibodies to HDV develop about 2-4 weeks after co infection and about 10 weeks after super infection. A test for anti-HDV antibody is commercially available. PCR assays for viral RNA are available.\textsuperscript{12}

The prevention of HBV infection and eradication of chronic HBV carriage will prevent the disease associated with HDV infection. Treatment of HDV is not as yet optimum or satisfactory. However, RCT (randomized control trials) using IFN (interferon) monotherapy (dose from 3 to 9 million units (MU) ) show a limited and variable response depending upon schedule of treatment.\textsuperscript{14} However, therapeutic efficacy increases when high doses of IFN-á (5 MU daily or 9-10 MU three times weekly) are given for 12 to 24 months.\textsuperscript{15}

In children the dose of alpha interferon is 6 MU/m\textsuperscript{2} thrice weekly with a maximum dose of 10MU. Lamividine has been evaluated in a small number of patients and found to be in effective in inhibiting HDV replication.\textsuperscript{16} At present no new therapies are available other than INF-á in the pediatric population. In very young children, less than 5 years of age, it is not advisable to use INF-á for HDV, due to side effects. Some trials are being done on PEG interferon.\textsuperscript{12,17}

There is no vaccine for HDV. However, because HDV replication cannot occur without HBV co infection, immunization against HBV also prevents HDV infection. Hepatitis B vaccines and HBig are used for the same indications as for Hepatitis B alone. Also, screening of HDV should be kept in mind for HBsAg positive patients especially before starting treatment for HBV. This is especially important as at SZLC, very young patients (7-10 years of age) have been seen to be co infected with HBV and HDV.

**REFERENCES**


ORIGINAL ARTICLE

HEART FAILURE PATIENTS ARE PRONE TO DEVELOP MAGNESIUM DEFICIENCY AS A RESULT OF DIURETIC/DIGOXIN THERAPY

Surraiyah Shaikh¹, Muhammad Saeed Talpur², Mohammad Shakeel³, Hasina Thawerani², Nadeem Alam¹ and Khemomal A. Karira⁴

ABSTRACT
Objective: To evaluate serum magnesium level in chronic heart failure (CHF) patients receiving diuretic and digoxin therapy.

Study Design: A case-control study.

Patients and Methods: The study was conducted at the Basic Medical Sciences Institute (BMSI), Jinnah postgraduate Medical Centre (JPMC), Karachi with collaboration of National Institute of Cardiovascular Diseases (NICVD), Karachi from April to December 2003. Serum magnesium levels were evaluated in 65 subjects including 45 patients of heart failure admitted in the NICVD, Karachi. Twenty subjects were healthy, age and gender matched controls (group-I). Patients were divided into two groups (groups-II and III) according to treatment with diuretics or combination of diuretic and digoxin. Other electrolytes including sodium, potassium, chloride and calcium were also evaluated. Student’s t test at ranging p-values of (<0.05, <0.01, <0.001) were used to determine the statistical significance.

Results: The cardiac failure patients showed lower (1.72±0.07 mg/dl) level of serum magnesium when compared with normal (0.53±0.19 mg/dl) control subjects and even more significantly lowered (1.65±0.09 mg/dl) in patients who were receiving diuretics and digoxin as compared to patients (1.80±0.10 mg/dl) who were on diuretics only (p<0.001).

Conclusion: Patients with chronic heart failure were characteristically prone to develop magnesium deficiency along with other electrolytes (potassium, calcium, and chloride) due to administration of diuretics and digoxin.

Keywords: Chronic heart failure, Magnesium, Electrolytes, Diuretic, Digoxin

INTRODUCTION
Magnesium, a biologically essential cation, has recently received considerable attention in clinical medicine, especially with regard to the role of its depletion in cardiovascular pathophysiology.¹ After calcium, it is the second most abundant divalent cation present in serum.² Heart failure patients are prone to develop magnesium deficiency as a result of diuretic and digoxin administration.³ Diuretic therapy increases urinary magnesium losses and may cause depletion of total body and regional magnesium stores when administered on a long term basis.¹ Two types of diuretics known as loop (such as furosemide) and thiazide (including hydrochlorothiazide) can deplete magnesium level. For this reason, doctors who prescribe diuretics may consider recommending magnesium supplements as well.⁴ The diuretics in common use promote cation excretion almost exclusively in association with chloride.⁵
It is important that normal levels of magnesium be maintained while taking digoxin (lanoxin) because low blood levels of magnesium can increase adverse effects from this drug. In addition, digoxin can lead to increased loss of magnesium in the urine. Information on magnesium concentration in serum is important in treating cardiac arrhythmias, given the documented increases in incidence of supraventricular and ventricular arrhythmias in patients with hypomagnesemia.

Because altered magnesium homeostasis, particularly a deficiency, can cause alterations in metabolic functions that result in clinically recognizable events require better understanding of the magnesium status. The aim of this study was to evaluate serum magnesium level in a representative cases of CHF patients receiving diuretic and digoxin as a treatment to compare magnesium level with normal control subjects.

**PATIENTS AND METHODS**

This case control study was conducted at department of Biochemistry, BMSI, JPMC, Karachi, with collaboration of NICVD Karachi from April to December 2003.

A total of 65 subjects, 45 cases of CHF selected from NICVD, Karachi and 20 healthy normal age and gender matched subjects were selected as controls. Diagnosed cases of chronic heart failure with ischemic heart disease, valvular heart disease, rhythm disturbances, cardiomyopathy and miscellaneous (pericarditis, pleural effusain, pulmonary oedema) group of cases were included in this study. Patients were excluded if they had liver diseases, thyroid diseases or history of alcohol consumption. Prior to collection of blood samples, the personal history, physical examination and clinical status were assessed and recorded on specially designed proforma. Blood samples of all subjects were collected under aseptic measures. To minimize the variability of the analytical method, all samples were processed at one time. Serum Magnesium was determined by colorimetric method using kit (Cat No 0137) supplied by Stanbio Laboratory with microlab-200 analyzer. Sodium, potassium, and chloride were measured by ion selective electrode (ISE) technology using Easylyte analyzer.

All results were expressed as means and ± standard errors of means (± s.e.m) with inter-group comparisons performed by ‘t’-tests. A p-value of <0.05, <0.01, and <0.001 was used to indicate statistical significance.

**RESULTS**

The demographic distribution of the study subjects, is shown in Table-1. Thirty nine (60%) were males and 26 (40%) were females. All selected subjects were distributed into three groups. Group-I comprised of 20 healthy normal control subjects including 15 (70%) males and 5 (30%) females. Group-II consisted of 24 patients of CHF receiving (diuretics and digoxin) 14 (58.3%) males and 10 (41.7%) females. In group-III receiving (diuretics) 21 patients, 10 (47.6%) were males and 11 (52.4%) females were studied. Age range in this study was 35-65 years. Mean age of total study subjects was 52.95±1.11 years.

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of Subjects</th>
<th>Age (years) Mean±s.e.m</th>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Normal (Control)</td>
<td>20</td>
<td>51.10±1.60</td>
<td>15 (70)</td>
<td>5 (30)</td>
<td></td>
</tr>
<tr>
<td>II CHF (Diuretics + Digoxin)</td>
<td>24</td>
<td>52.62±2.09</td>
<td>14 (58.3)</td>
<td>10 (41.7)</td>
<td></td>
</tr>
<tr>
<td>III CHF (Diuretics)</td>
<td>21</td>
<td>55.09±1.93</td>
<td>10 (47.6)</td>
<td>11 (52.4)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>52.95±1.11</td>
<td>39 (60%)</td>
<td>26 (40%)</td>
<td></td>
</tr>
</tbody>
</table>

The mean values of serum magnesium of CHF patients was 1.72±0.07 mg/dl while in healthy controls, it was 2.53±0.19 mg/dl. The differences in serum magnesium between CHF patients and control was highly significant (p<0.001). The mean values of serum magnesium were also observed to be lower (1.60±0.09 and 1.80±0.10 mg/dl) respectively when total of groups-II and III of CHF patients respectively were compared with group-I normal (control) subjects the observations are shown in Figure-1, a and b.

The mean values of serum magnesium observed were significantly lower, in males of group-II (p<0.001)
and group-III (p<0.01) of CHF patients when compared with males of group-I normal control subjects. The mean values of serum magnesium were also observed to be similarly significantly lower respectively in females of group-II and group-III of patients when compared with group-I normal (control) subjects. These findings are depicted in Figure-2.

Figure-3 shows the comparison of mean values (±s.e.m) of serum electrolytes that include magnesium, sodium, potassium chloride and calcium. Magnesium, calcium, potassium and chloride were observed significantly lower (p<0.001, p<0.01, p<0.001, p<0.001) respectively in patients of group-II and group-III of CHF when compared with group-I (control) subjects.

**DISCUSSION**

Magnesium deficit is one of the most frequent electrolyte abnormalities in current clinical practice. There is growing evidence that magnesium status is important in pathogenesis and treatment of cardiovascular disease. Despite its importance, physicians frequently fail to consider magnesium status when managing a patient. Gottlieb et al. indicated that abnormalities of the serum magnesium concentration are not merely laboratory curiosities but have important clinical implications.

Recent advances in the analytic methods for serum magnesium determination have made the rapid and accurate measurement of this ion a useful clinical tool in a variety of disease states. This case control...
study demonstrated hypomagnesemia in chronic heart failure patients receiving digitalis glycoside. Bloom stated digoxin, an inhibitor of Na, K-ATPase, increases both the abundance and size of myocardial lesions due to magnesium deficiency. Magnesium depletion also was observed because of diuretic agents. Pronounced diuresis by diuretics and increased renal excretion of magnesium was the cause of magnesium deficiency in 55% of patients in a study carried out by Purvis and Movahed. Patients on traditional non-potassium-magnesium sparing diuretics tend to have a potentially dangerous deficiency.

In the present study the age range was 35 years to 65 years, the mean was 52.95±1.11. However, men comprised 60%, whereas women comprised 40%. When compared to this study, some other studies showed no significant difference in age and gender. Shechter noted hypomagnesemia was common in hospitalized patients, especially in elderly patients with coronary artery disease and those with chronic heart failure.

Co-existent magnesium and potassium deficiency was also observed in this study. Chakraborti et al showed that hypomagnesemia was commonly associated with an imbalance of electrolytes such as sodium, potassium and calcium.

Ceremuzynski et al assessed the role of electrolyte imbalance in cardiac arrhythmias associated with congestive heart failure. They concluded that hypomagnesemia was probably related to increased magnesium excretion is an essential feature of heart failure associated with complex ventricular arrhythmias. Strickberger et al found multifocal atrial tachycardia associated with hypokalemia and hypomagnesemia.

It is also clear from the observation of Gettes that in certain groups of patients, particularly those with hypertension and congestive heart failure treated with thiazide and loop diuretics, the presence of ventricular arrhythmias is due to hypopotassemia and possibly also due to hypomagnesemia.

A study done by Berkelhammer and Bear showed that hypocalcemia was prominent manifestation of magnesium deficiency. Seelig found that diuretics and digitalis can intensify an underlying magnesium deficiency, leading to cardiac arrhythmias that are refractory unless magnesium is added to the regimen. Magnesium has been found to be necessary for intracellular potassium repletion in these patients. Because patients with congestive heart failure and others receiving diuretic therapy are also prone to chloride loss leading to metabolic alkalosis that also interferes with potassium repletion, the addition of magnesium and chloride supplements in addition to the potassium seems prudent. In our study the chloride was also significantly low.

Chipperfield and Chipperfield proved that normal men have a significant lower concentration of magnesium in their heart muscle than women, this correlates well with the higher incidence of male ischemic heart disease. They also had good evidence that diuretics can cause magnesium deficiency which makes the heart susceptible to the development of arrhythmias, particularly during digitalis therapy.

In accordance to this study, the diuretics and digitalis causing the electrolyte disturbances were also observed by Nichols noting that loop and thiazide diuretics can induce deficits of sodium, potassium and magnesium in patients with heart failure.

Cohen et al showed that various pathophysiological factors as well as pharmacological agents, mainly furosemide (frusemide) present in the setting of congestive heart failure may enhance magnesium loss and thus produce magnesium deficiency.

Hypomagnesemia and depletion of intracellular magnesium stores have been held responsible for a variety of cardiovascular and other functional abnormalities including various arrhythmias, a few clinical studies have reported a significant association of serum magnesium levels with ventricular arrhythmias, impairment of cardiac contractility, and vasoconstriction.

Magnesium should be employed as first line therapy in digitalis intoxication and drug related arrhythmias, and should also be considered an important adjuvant
therapy in diuretic treated patients. Study of Admopoulous showed that less serum magnesium level was associated with increased cardiovascular mortality.\textsuperscript{24}

Hypomagnesemia increases potassium excretion, and hypokalemia is difficult to remedy with concurrent hypomagnesemia because the sodium-potassium-ATPase pump requires the presence of magnesium ions-potassium-sparing diuretics prevent urinary magnesium wasting.\textsuperscript{25}

Magnesium deficiency may play a critical role in the pathogenesis of ischemic heart disease, cardiomyopathy and certain arrhythmias.

The present study is limited to the serum magnesium to demonstrate the clinically diagnostic importance of serum magnesium measurement in patients with CHF, taking diuretics and digoxin. Future investigations are needed to determine urinary excretion of magnesium along with serum magnesium measurement.

CONCLUSION

It is concluded that patients with chronic heart failure were characteristically prone to develop magnesium deficiency along with other electrolytes potassium, calcium, and chloride. In already diagnosed cardiac failure patients treated with loop diuretics and digoxin, the presence of further cardiac signs should trigger a search for underlying electrolyte abnormalities particularly hypomagnesemia.

REFERENCES


ORIGINAL ARTICLE

DETERMINANTS OF ACUTE OTITIS MEDIA IN INFANTS

Yasmeen Mumtaz1, Farida Habib2, Ashraf Jahangeer2 and Adnan Habib3

ABSTRACT

Objectives: To describe the relationship of acute otitis media with mode of feeding (bottle-or breast-fed) and with different positions of infant during feeding.

Study design: Case control study

Subjects and methods: Babies aged up to 24 months (62 cases, 66 controls) were selected from the OPD of Abbasi Shaheed Hospital and the Aga Khan Hospital, Karachi. The variables considered were the gender of the infant, mother’s educational level and occupation, mode of feeding and the different positions during feeding. SPSS version 11.5 was used for descriptive and inferential analysis.

Results: There was a significant association of otitis media with lying position of baby during feeding (OR 37.7, 95% CI 13.34-106.43, p<0.001), bottle feeding (OR 3.0, 95% CI 1.43-6.25, p = 0.003), working mother (OR 3.8, 95% CI 1.38-10.34, p = 0.007) and education of mother (OR 2.1, 95% CI 1.01-4.24, p = 0.044).

Conclusion: Babies with acute otitis media were more likely to be bottle fed and having a lying posture during the feeding than babies without having acute otitis media.

Keywords: Acute Otitis Media, Bottle feed, Breast feed, infants.

INTRODUCTION

Acute otitis media (AOM) is common in young children in fact it is the number one reason that children under one year are taken to the doctor.1 Despite advances in treatments, the percentage of children who developed otitis media has remained quite steady over time. After first infection the affected children are at higher risk of developing repeated infections later in childhood.1 Treatment of such infections could have implications to the economy.2 Bland found increase incidence of otitis media in bottle-fed as compared to breast-fed infants and speculated this to be due to transfer of IgA in breast milk.3 Haemophilus influenzae is the major cause of otitis media and lower respiratory tract infection in childhood. Human milk contains numerous host defense factors which may inhibit adherence of Haemophilus H. Influenzae to pharyngeal cells and its colonization. The incidence of H. influenzae in breast-fed infants and formula-fed infants was 0 and 7.0% respectively. It is suggested that the colonization of H. influenzae in the throat was inhibited by the presence of breast milk.4

Previous studies showed that breast feeding decreases the incidence of gastrointestinal and urinary tract infection, lower respiratory tract illnesses, otitis media and meningitis. Common reasons for which breast and bottle fed infants are brought in well baby clinics include otitis media, respiratory tract infection, viral infections and gastroenteritis.5 There is evidence that breast-feeding has decreased the rate of gastrointestinal infections as compared to exclusive or supplementary bottle feeding.6-7 Exclusive breast feeding for four months or more prevents against both acute and recurrent otitis media.8-10

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The disease is more common in boys than girls. It is more common in children born with a cleft palate or other structural problems of the face or skull. Infants who were not being breast-fed had increase risk of middle ear infection. Pharyngeal mucosal immunity may develop against respiratory infection in breast fed infants.

The objective of this study was to describe the relationship of acute otitis media with mode of feeding (bottle-fed or breast-fed) and with different positions of infant during feeding, apart from some maternal factors.

SUBJECTS AND METHODS

It was a case control study conducted from April to September 2007 in Pediatric and Oto-rhino-laryngology (ENT) O.P.D of Abbasi Shaheed Hospital and Aga Khan Hospital, Karachi.

Inclusion criteria were infants with earache, fever, discharge, and irritability for the last six days or less, further supported by otoscopic findings of pussy discharge from middle ear, bulging and redness of tympanic membrane accompanied by ear pain. Infants with cranio-facial abnormalities, genetic disorders, immune deficiency, babies with recurrent AOM, chronic otitis media and permanent deafness were excluded.

A closed ended questionnaire was administered consisting of the variables regarding the gender of the infant, mother’s educational level and occupation, type of feeding (bottle vs. breast fed) and the different positions of infant during feeding (lap, lying or sitting). Data was collected and entered by the fourth year medical college students after getting formal training by the principal investigator. SPSS version 11.5 was used for descriptive and inferential analysis. Cross tabulations were performed for selected variables for bi-variable analysis against the outcome of acute otitis media and p value of less than 0.05 was considered significant.

The variables having multiple categories were compressed to meaningful dichotomized variable and relationship of different factors were observed among cases and controls through cross tabulation using chi square test of proportion. Odds ratio was calculated for each bi-variable analysis.

RESULTS

A total of 128 babies were selected and data was entered on SPSS version 11.5. Before conducting final analysis missing information in the fields were checked and corrected. Most of the mothers were house wives (82%). Data on educational status of the mothers, proportion of different age groups and duration of breast feeding to the baby is presented in Table 1. Most babies were male (72.7%). A substantial proportion (95.3%) had updated vaccination status and only seven percent had history of similar disease in his/her sibling. The reported bottle feeding was (11%) and bottle plus breast feeding was 48.4%. Only 40.6% reported exclusive breast feeding. Regarding posture of the baby during breast feeding mothers preferred lap position (57%) followed by lying (38%) and sitting (5%).

| Table 1: Baseline characteristics of the babies and their mothers selected from the pediatric outpatient department of tertiary care hospitals in Karachi. (n=128) |
|-----------------------------|-----------------|
| **Characteristics**         | **Proportions %** |
| Age (months)                |                 |
| <6                          | 21.9%           |
| 6 to <12                    | 40.6%           |
| 12 to <18                   | 28.9%           |
| 18 to <24                   | 8.6%            |
| Duration of feeding         |                 |
| <6m                         | 26.6            |
| 6 to <12                    | 32.8            |
| 12 to <18                   | 25.8            |
| 18 to <24                   | 14.8            |
| Education of the mother     |                 |
| Primary                     | 32.8            |
| Secondary                   | 24.2            |
| Higher secondary            | 30.5            |
| Graduate                    | 12.5            |

In the bivariate analysis there was no significant relationship of gender with acute otitis media. Education of the mother was significantly associated with otitis media and cases of otitis media were twice as likely from a mother having educational status less than higher secondary level than controls. Lying position of the baby during feeding was positively associated with acute otitis media. Babies with otitis media were 38 times more likely to be fed in lying position than babies without otitis media, (Table 2).
Determinants Of Acute Otitis Media In Infants

Table 2: Risk factors for otitis media among the children aged up to two years (n=128)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Otitis media (Cases n=62) Frequency</th>
<th>Otitis media (Cases n=62) Frequency</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender of the baby</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>45</td>
<td>1.007</td>
<td>0.046-2.19</td>
<td>0.98</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation of the mother</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>House wife</td>
<td>60</td>
<td>45</td>
<td>3.8</td>
<td>1.38-10.34</td>
<td>0.007</td>
</tr>
<tr>
<td>Working women</td>
<td>6</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education of the mother</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>=Higher Secondary</td>
<td>34</td>
<td>21</td>
<td>2.1</td>
<td>1.01-4.24</td>
<td>0.044</td>
</tr>
<tr>
<td>&lt;Higher Secondary</td>
<td>32</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby’s position in relation to mother during feeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the Lap</td>
<td>60</td>
<td>13</td>
<td>37.7</td>
<td>13.34-106.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lying on bed/floor</td>
<td>6</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of feeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>35</td>
<td>17</td>
<td>3.0</td>
<td>1.43-6.25</td>
<td>0.003</td>
</tr>
<tr>
<td>Breast and bottle</td>
<td>31</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

The proportion of females who exclusively breast fed their babies in this study was 41% (52/128). An earlier multi center hospital based study done in Karachi found even a lower proportion of females who exclusively breast fed their babies. Despite the fact that breast feeding is strongly recommended in our religion, well supported by culture and endorsed by the government this pattern of breast feeding exhibits the complex nature of the issue.

This study did not find any statistically significant relationship of gender with acute otitis media. However many other studies have reported male gender vulnerability for acute otitis media. The non significant results in this study could be ascribed to small sample size and low representation of female babies in the sample.

Studies have reported a positive relationship of acute otitis media with lower educational status of the mothers. This study also found that babies with AOM belong to the mothers who had educational level less than higher secondary. The reason might be educated women are generally in better position to promote health and prevent diseases in their babies. Education imparts a decision making status to the women that is usually required for prompt action during an episode of children illness.

This study showed a direct relationship of acute otitis media and employed mothers. However the available literature presents a divided opinion on the relationship of otitis media and employed mothers, Laphear and colleagues in a large study based on National Health Interview Surveys, also found that recurrent otitis media is more common among children of employed mothers. One explanation of this phenomenon is that working mothers are busy or stressed in their schedules and don’t find time to promptly act upon when the initial symptoms of respiratory tract infections develop. Another hypothesis is that working women may be supplementing breast feeding with bottle feed. Besides mothers employment, day care/out of home care (except mother’s employment) are considered independent predictors of recurrent otitis media. Presumably, use of day care is more common among employed mothers and hence could serve as a proxy variable for mother’s employment.

Despite small sample size, this study demonstrates positive relationship of bottle feeding with AOM. These results are supported by other international studies as well. Earlier studies have established the association of breast feeding with disease development in the children through demonstrating dose response relationship of breast feeding with respiratory infections. Resler et al. elaborated that most of the infants who were fully breast fed had lower odds ratio of cough and wheeze. Another birth cohort study of 2602 children concluded that breast feeding to one year may reduce the prevalence and subsequent morbidity of respiratory illness and infection in infancy.

Another study describing effect of feeding methods on respiratory illnesses, found protective effect of breast feeding on respiratory illnesses. The effect persisted even after adjustment for age of the infant, socioeconomic class, maternal age, and cigarette consumption.

Kathryn revealed another favorable effect of breast feeding by concluding that in the first year of life the percentage with any otitis media was 19% lower and with prolonged episode (>10 days) was 80% lower in breast fed compared with bottle fed infant. Similar results were given by Milosavljevic and Virijevic in a study where healthy infants enrolled at birth were followed for the occurrence of acute otitis media during the first year of life. Infants who were exclusively breast fed had 0.72 odds for developing acute otitis media as compared to those who were exclusively bottle fed. Chung et al recollected the current evidence through a
meta analysis on the effect of breast feeding on short and long term infant and maternal health outcome in developed countries. This review found that history of breast feeding was associated with a reduction in the risk of acute otitis media, severe lower respiratory tract infection and asthma. These results indicate that the reduction in morbidity associated with breast feeding is of sufficient magnitude to be of public health significance. The favorable effects of breast feeding are so profound and universal that health organizations around the world endorse breastfeeding as an important public health concern.27-33

This study also revealed an association of otitis media with positional differences of babies during feeding. The anatomy of Eustachian tube in babies allow entry of milk in to middle ear when fed in supine position. This concept of positional otitis has also been stated in earlier researches of different national and international studies.34,35

Another study demonstrated that supine posture of the baby during feeding predisposes them to abnormal post-feeding tympanographic results compared with infants fed in the semiupright position. This is the reason for recommending feeding in lap or semi upright positions.36

CONCLUSION

Babies with acute otitis media were more likely to be bottle fed, had lying posture during feeding, and belonged to mothers who are less educated and employed, where as babies without acute otitis media had opposite findings.

ACKNOWLEDGEMENT

We acknowledge the work of 4th year MBBS students (Amir Hussain, Asif Iqbal, Israr Hassan and Mohammed Babar) of Karachi Medical and Dental College who helped in the data collection.

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SURVEYING PHYSICAL FITNESS OF THE ADOLESCENT MALE TAEKWONDO ATHLETES OF IRAN NATIONAL TEAM

Zar Abdossaleh

ABSTRACT
Objectives: To survey the physical fitness (anthropometrics and physiological characteristics) of the adolescent male Taekwondo athletes of Iran national team during 2002-2005 years.
Study design: Descriptive study.
Subjects and Methods: Members of adolescent national team during 2002-2005 were examined as a static society composed of 10 members each year. Different factors of physical fitness and anthropometric characteristics (i.e. age, weight, height, vertical jump, sit ups, agility, flexibility and reaction time) were experimented. All the results were written on individuals’ registration cards. The data collected was based on the practical test done by all male Taekwondo athletes invited to National Team Camp during 2002 and 2005.
Results: The best record in vertical jump (score= 53/9), sit ups (score=69), agility (score=16/69), flexibility (score=42) and reaction time (score=356/9) registered was during the year 2004. The worst ones registered included vertical jump (score=49/2 in 2005), sit ups (score=55/7 in 2003), agility (score=17/36 in 2002), flexibility (score=36/9 in 2005) and reaction time (score=464/4 in 2002).
Conclusion: The best record registered was during year 2004 with 25 score, while the worst ones were registered in 2003 with 16 score. Successful Taekwondo athletes, therefore, had remarkable anthropometric and physiological characteristics. They also had a low amount of body fat, high speed in performing skills, and perfect agility for rapid movements.
Keywords: physical fitness; male, taekwan-do athletes; Iran.

INTRODUCTION

In Bejing 2008, Taekwondo became recognized as an official sport at the Olympics.

Understanding the anthropometric and physiological characteristics is an important, determinant and influential factor in the performance of athletes. The athletes are aware of these important characteristics and they compare themselves with other athletes to overcome their weaknesses and to design their exercise programs. Achieving the optimum athletic performance and best position in sport requires special anthropometric and physiological characteristics besides scientific exercise program and having access to experts of sport sciences to enough facilities.1,2

On the other hand, lack of deep understanding of the education of elite athletes and also not paying attention to personal differences may lead athletes to the sports which are not compatible with their physical characteristics and abilities. Most studies on taekwondo have been
conducted on adults. Few studies are available on young taekwondo participants and most were done in the West. Research studies related to Taekwondo have tended to concentrate on injury rates. Studies have been conducted on the epidemiology of trauma which is proposed to be related to skill level, gender, weight, age, mechanism, body part, situation, and years of experience. 

There are several factors influencing the achievement of the best athletic performance among which is, for sure, physical and physiological abilities. Although every athlete, needs a certain degree of feature to perform optimally such as explosive power, agility, speed and other physical and physiological abilities, the need of each athlete to each of these feature sport is Taekwondo the success in which demands special physical characteristics.

Melhim found no significant differences in either resting heart rate or aerobic power after training; however, significant differences were observed in anaerobic power and anaerobic capacity. Markovic et al. examined the differences between successful and less successful Croatian national Taekwondo champions and found that successful athletes achieved significantly higher maximum running speed, significantly higher ventilator anaerobic threshold at significantly lower heart rate, significantly higher explosive power, anaerobic alactic power and lateral agility, somewhat lower body fat (2.3%), and were slightly taller (by 5.8 cm) than less successful athletes. On the other hand, other researchers agree that the possession of specific anthropometric qualities alone cannot guarantee a gold medal. Success in competition is indeed a combination of physical attributes, talent, skill, technique, determination, strategy and psychological preparedness.

Physical fitness is one of the main factors for athlete. It has been shown that a high level of elements of physical fitness such as endurance, flexibility and speed is useful and effective in achieving success in different sport fields. Nowadays before being sent to the competitions, teams are given a test for the evaluation of physical status of the members. Iranian National Team of Taekwondo follows the same rule and has given this responsibility to the Center of Physical Capability Assessment of National Academy. In this sport, movement speed, reaction speed, jumping power and anaerobic power plus some anthropometric characteristics play an important role in the performance.

In Bump’s idea, throughout the competition, both aerobic and anaerobic systems should be used. Cho found that muscular and explosive power, flexibility, muscular endurance, reaction time play an important role in Taekwondo. Due to the fact that discovering physiological characteristics plus true planning of exercises and discovering the talents, strengths and weaknesses are some important factors in preventing the wasting of resources, conducting some investigations in the field of these factions seems to be necessary.

The researcher decided to investigate the status of physical and anthropometric characteristics fitness of adolescent Iranian male Taekwondo competitors so that coaches, taking account of this fundamental information besides personal and performance differences among athletes, prepare calculated and specific plans for the selection and preparation of athletes. Unlike most sports in which many investigations have been done to determine the relationship of between characteristics, Taekwondo had been the subject of only a few studies.

The objective of this study was to survey the physical fitness (anthropometrics and physiological characteristics) of the adolescent male Taekwondo athletes of Iran national team during 2002-2005 years.

**METHODS**

In this descriptive study, the researchers compared the results of practical tests of athletes, during 2002 and 2005, who were invited to adolescent Taekwondo National Team Camp. All the results were written on individuals’ registration cards. The data collected was based on the practical test. Here, all adolescent male Taekwondo athletes of National Team during 2002 and 2005 were studied and thus decided to be the research population. Each year, adolescent Taekwondo team consists of 10 people. To conduct the research, necessary coordination was made by Assessment Center of National Olympic Academy. Having provided with the description and implications of the study, the researcher received the necessary information to evaluate the physical fitness in following terms.

The counter-movement vertical jump (CMJ) was used to assess **explosive power** of the legs. The subjects were allowed three jumps with 1- minute rest in between. The highest jump was used for statistical analysis. Muscle **endurance** was assessed using the one minute timed test for bent knee sit ups and push ups. For the sit ups, subjects were lying in a supine position with both
knees bent at right angles and both feet were shoulder width apart. Both arms were placed at the side of the trunk. All subjects were asked to perform as many sit ups as possible within one minute.

The Illinois Agility Run Test was conducted with the athlete lying face down on the floor at the start point. On the assistant's command the athlete jumped to his/her feet and negotiated the course around the cones to the finish. The assistant recorded the total time taken from their command to the athlete completing the course. A sit and reach flexibility box (Novell Products, Rockton, Illinois, USA) was used to assess low back and hip joint flexibility. Each subject sat with legs fully extended with the bare soles of the feet placed flat against the flexibility box. With the knees fully extended, arms evenly stretched, palms down, the participants reached forward without jerking. The subject pushed the sliding marker along the scale with the fingertips as far as possible. The position of maximum trunk flexion was held for about two seconds. The test was repeated three times. The best value in cm was documented and used for data analysis.

Height was measured by means of a wall-mounted stadiometer (Lafayette Instrument Co. USA) and body mass on a calibrated digital scale (SECA, Vogel & Halke, GmbH & Co, Hamburg, Germany).

Using descriptive statistics, the researcher measured the indices distribution and central tendency. The mean values were compared to determine any significant difference between them.

RESULTS

Anthropometrics and physical fitness characteristics of the adolescent male taekwondo athletes in age, weight, height, vertical jump, sit ups, agility, flexibility and reaction time are presented in Table 1.

The mean age of athletes invited to the National Team Camp, in 2002 and 2003 were similar in their mean age, but in 2005, they were at the lowest age and, in 2004, they were at highest age. It was also noticed that the members of National Team Camp in 2003 were taller than other years and shortest in 2005.

Table 1 also shows the differences in motor abilities between male Taekwondo athletes in different years. The athletes in 2004 had higher explosive power test (vertical jump), sit ups, agility test and reaction time, whereas in 2005 had lowest record in vertical jump. They mean sit ups had lowest score in 2003 and the worst scores of agility test and reaction time in 2002. The mean flexibility (sit-and-reach) was best record and reaction time was worst scored in 2004.

**Table 1**: The Mean Anthropometrics and physical fitness Characteristics in different years

<table>
<thead>
<tr>
<th>Variable</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (year)</td>
<td>16/7</td>
<td>16/7</td>
<td>17**</td>
<td>15/9*</td>
</tr>
<tr>
<td>Mean Weigh(kg)</td>
<td>61/2</td>
<td>72/2**</td>
<td>62</td>
<td>51/6*</td>
</tr>
<tr>
<td>Mean Height(cm)</td>
<td>170/7</td>
<td>181/7*</td>
<td>175/1</td>
<td>169**</td>
</tr>
<tr>
<td>Mean vertical Jump(cm)</td>
<td>53</td>
<td>49/4</td>
<td>53/9*</td>
<td>49/2**</td>
</tr>
<tr>
<td>Mean sit ups test(repeat)</td>
<td>62/8</td>
<td>55/7**</td>
<td>69</td>
<td>63/8</td>
</tr>
<tr>
<td>Mean Illinois Agility run(second)</td>
<td>17/36**</td>
<td>17/28</td>
<td>16/9*</td>
<td>17/11</td>
</tr>
<tr>
<td>Mean of Sit-and-reach test (cm)</td>
<td>41/2</td>
<td>38/4</td>
<td>42*</td>
<td>36/9**</td>
</tr>
<tr>
<td>Mean of Reaction time</td>
<td>464/4*</td>
<td>436/9</td>
<td>359/9*</td>
<td>404/5</td>
</tr>
</tbody>
</table>

*The best record in different years

**The worse record in different years

According to figure 1, the members of National Team Camp had best qualification in 2004 with 25 score and had the worst condition in 2003 with 16 score.
DISCUSSION

Both male and female taekwondo athlete tended to be somewhat younger than the average age in their respective weight category average. Application of scientific training principles early in their development could be another reason for having younger winners. Taekwondo is one of the most popular sports which have a lot of supporters in many countries. Recently it has been included in the Olympic Games.2

Generally, in order to select the athletes for a special sport, a profile of their basic fitness and their process of exercises should be made. In this selection, emphasis should be placed on such characteristics and abilities that have a noticeable effect on the performance and that are influenced by genetic factor. Some researchers have found that aerobic power is not important in Taekwondo performance.17,18 Others have also argued that improving aerobic power may be of importance in achieving success in Taekwondo competition.2

When the cardio respiratory function, energy expenditure and blood lactate system are well controlled only then an athlete can show potential and maintain high performance. This is very important to both coaches and athletes.19

Male and female athletes are young on an average than other competitors of the same weight. That is why in Olympic Games younger competitors are preferred. Moreover, paying attention to basic principles of special exercises for growth and improvement can be another reason for success. The winning athletes are also found to be taller than other competitor of the same weight. Gao et al. concluded that to gain the highest possible VO2max (aerobic ability) in Taekwondo, decreasing body fat percentage and increasing lean body mass are needed.10 The nature of Taekwondo performance mainly requires bursts of sudden, fast and powerful kicks that lend itself to having a speed and power athlete profile and not an endurance athlete physiological profile suggested by Gao et al.10 Flexibility plays an important role in taekwondo competition to enable athletes to execute high kicks. Toskovic et al. reported values of 31.7 cm (novice males), 39.1 cm (experienced males), 37.0 cm (novice females), and 35.9 cm (experienced females) for American recreational taekwondo-in using the conventional sit-and-reach test.17 Markovic et al. found 55.8 cm for the total group of elite Croatian female taekwondo-in.18

American recreational taekwondoin recorded heights of 43.7 cm (novice males), 51.5 cm (experienced males), 32.1 cm (novice females), and 31.3 cm (experienced females).19

Yiau et al. reported that winning Malaysian female taekwondo-in competing at the 2004 Malaysian Games jumped higher (39.1 cm) than their less successful colleagues (35.1 cm).20

Muscle endurance is the ability of a muscle group to execute contractions over a period of time sufficient to cause muscular fatigue. Douris studied the balance, flexibility, power and muscular endurance of male female Taekwondo athletes and found that at all age levels and in either gender group the average of measurement indicators were more than that in the non-athletes.21 It was the case for both young and old athletes in other fields of martial art.22-24 The reaction time, speed and agility all have a significant relationship with the success of Taekwondo athletes. Many experts believe that reaction time is more related to hereditary factors than to the exercises. In their opinion, exercise can improve the movement time but it cannot improve the reaction time.25

However Cho believed that exercise can contribute to the improvement of reaction time.16 Heler found aigner between reaction time and competitive performance of tech at competitor.11 In the same vein, Bompa reported that having high speeds contain the score for the Taekwondo competitors.15 Melhim also observed that after period of Taekwondo exercises anaerobic power increased as much as 24 percent.7 According to the findings of this study and also those of the studies mentioned above, it can be said that factors such as speed, flexibility, reaction, weight and to a lesser degree, age, are very important in success and gaining better scores in most of the sports special martial arts. Therefore having a suitable physical fitness is important in every sport.

CONCLUSIONS

Based on the results of this study, it is clear that successful Taekwondo athletes have got to have remarkable anthropometric and physiological characteristics. They should also have a low amount of body fat, high speed in performing skills, perfect agility for rapid movements and, suitable reaction time against opponent's attacks thus, stopping the opponent's scoring
REFERENCES


ORIGINAL ARTICLE

PEROPERATIVE TRANSESOPHAGEAL ECHOCARDIOGRAPHY: CLINICAL BENEFIT DURING CARDIAC SURGERY

Sadqa Aftab\textsuperscript{1}, Shams Rashdi\textsuperscript{1}, Abdul Bari\textsuperscript{2}, Mudassir Iqbal Darr\textsuperscript{2} and Aftab Mehmood\textsuperscript{1}.

ABSTRACT

Objective: To evaluate the benefit of peroperative Transesophageal echocardiography (TEE) during cardiac surgery.

Design: An observational analytic study.

Place and duration of study: This study was carried out in the department of Cardiac Surgery Civil Hospital, Dow Medical College Karachi and Dow University of Health Sciences, from April 2001 to May 2007.

Subject and Methods: In 385 patients undergoing cardiac surgery, preoperative transesophageal echocardiography was performed according to ASA guidelines. Category I in which TEE considered useful, and category II are those where TEE is potentially useful but indications are less clear. All TEE examination was reviewed by cardiologist and anesthesiologist. For each patient, the diagnostic decision making and patient care was assessed using three criteria 1) Change in medical therapy; 2) Change in surgical procedure; 3) Confirmation of suspected diagnosis.

Results: TEE had greater utility in category I than in category II indications 17/70 (25\%) versus 57/315 (18\%) respectively. The nature of the clinical benefit was as follows: modification of medical therapy in 23/74 (31.08\%), modification of planned surgical intervention in 49/74 (66.2\%), confirmation of a diagnosis in 2/74 (2.70\%). The benefit on therapy was (23.3\%) in valvular replacement, (12.6\%) in coronary artery bypass surgery and (5\%) in congenital heart disease and intracardiac tumors.

Conclusion: present study validate the usefulness of the ASA practice guidelines, demonstrating a greater benefit of TEE on clinical management for category I indications than for category II. The TEE was more useful in diagnostic decision making in valvular replacement rather than other procedures.

Keyword: Transesophageal Echocardiography, Cardiac Surgery, Perioperative benefit.

INTRODUCTION

Echocardiography was introduced in the operating room in 1970, with its initial application involving epicardial echocardiography. The use of transesophageal echocardiography during surgery was first reported in 1980 and did not become common place until high frequency transducer and color Doppler imaging became available in mid 1980's.\textsuperscript{1}

The improved quality of image enabled anesthesiologist and surgeons to use TEE intraoperatively to diagnose myocardial ischemia, confirm adequacy of valve reconstruction and other surgical repair, determine the cause of hemodynamic disorders and other intraoperative complications, and provide diagnostic information that could not be obtained preoperatively.\textsuperscript{2,3}

Real time access to this information has enabled surgeons to correct inadequate repair before patient leave the operating room, has reduced the need of reoperation and has facilitated the prevention and early treatment of perioperative complications.\textsuperscript{4,5}

Several indications for perioperative TEE have become...
well established and include evaluation of valvular function intra and postoperatively, evaluation of mitral valve repair and prosthetic valve surgery, assessment of global left ventricular function and regional wall motion abnormalities, to assess congenital heart repairs requiring bypass, to see optimal deairing after open heart surgery and evaluation of life threatening conditions requiring immediate intervention. However, its routine use in the management of patients undergoing coronary artery bypass surgery remains controversial. 

In 1996, guidelines for perioperative transesophageal echocardiography were published jointly by the Task Force Commission of American Society of Anesthesiologist (ASA) and society of cardiovascular Anesthesiologists. These guidelines were developed to define categories of indications for TEE in the perioperative setting. (Table: 1)

The usefulness of intraoperative TEE in clinical management of patients undergoing cardiac surgery has been evaluated only in few studies in our country. The purpose of this study was to review the benefit of perioperative TEE in our clinical practice and to determine the usefulness of category based TEE indications.

**PATIENT AND METHODS:**

Following departmental approval and informed consent from patients, TEE examination was performed in 392 patients from April 2003 to May 2007 and recorded and analyzed on a data sheet. Category I, II and III indications were defined according to the ASA guidelines on perioperative TEE. For example intraoperative repair of mitral valve or congenital heart repairs are considered category I indications and example of category II indications include assessment of valve replacement, evaluation of removal of cardiac tumor and in patient with increased risk of myocardial ischemia or infarction.

The TEE examination were done using a multiplane 5 MHZ transducer (Toshiba power vision 5000) each examination comprised four chamber view and short axis transgastric view, color Doppler interrogation of mitral, aortic and tricuspid valve was also performed. A second opinion by a cardiologist was requested for confirmation and for more specific examinations.

All TEE examination and data sheets were reviewed by anesthesiologist and cardiologist. In the review, the clinical benefit of TEE on current therapy or patient management was noted. This was further classified using three criteria 1) TEE findings altered medical therapy, for instance, adding an inotrope or volume expansion 2) TEE findings altered surgical management, such as unplanned intervention or return to cardiopulmonary bypass 3) TEE findings confirmed a suspected diagnosis.

Statistical analysis was done using SPSS version 10, statistic on patients, modification in therapy are given in percentages.

**Table 2: Indications for Perioperative Transesophageal Echocardiography**

<table>
<thead>
<tr>
<th>Category I</th>
<th>Supported by strongest evidence or expert opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative evaluation of acute, persistent and life threatening hemodynamic disturbances</td>
<td></td>
</tr>
<tr>
<td>Intraoperative use in valve repair, congenital heart surgery requiring cardiopulmonary bypass, repair of hypotrophic obstructive cardiomyopathy, endocarditis, unstable patient with suspected aortic aneurysm, to assess valve function in repair of aortic dissection, evaluation of pericardial window procedures and in intensive care for unstable patients</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category II</th>
<th>Supported by weaker evidence and expert consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in patients with risk of myocardial ischemia or infarction, increased risk of hemodynamic disturbances, assessment of valve replacement, assessment of repair of cardiac aneurysm, evaluation of removal of cardiac tumor, detection of foreign bodies, detection of air emboli during cardiothoromomy, heart transplant operation and upright neurosurgical procedures, intracardiac thrombectomy, for suspected cardiac trauma, suspected acute thoracic aortic dissection aneurysm or disruption, detection of aortic aneurysm or dise or other source of aortic emboli, pericardectomy, pericardial effusion or pericardial surgery, evaluation of anastomotic sites during heart or lung transplantation, monitoring placement and function of assist devices</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category III</th>
<th>Little current scientific or expert support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative evaluation of myocardial perforation, coronary artery anotomy or graft patency, use during repair of cardiomyopathies other than obstructive cardiomyopathy, for uncomplicated endocarditis during non cardiac surgery, monitoring emboli on orthopedic surgery, assessment of repair of thoracic aortic injuries, for uncomplicated pericarditis, evaluation of pulmonary embolism, monitoring placement of intraaortic balloon pump, monitoring placement of intravenous catheters, intraoperative monitoring of cardiopulmonary bypass</td>
<td></td>
</tr>
</tbody>
</table>

**RESULT**

During the six year period, 1300 cardiac surgical procedures were performed and TEE was used in 385(29.6%) patients.

Using the ASA guideline, 70(18.2%) of patient had category I indications and 315(81.8%) patient had category II indications. No category III indications were observed in our cardiac surgical procedures.

Among 385 patients, TEE finding caused therapeutic modifications in 74(18.9%) patients (Table 2). The clinical benefit was greater in category I indications where it altered therapy in 24.3% of the time compared with category II indications where therapy was modified only in 18.1% of the time. The diagnostic decision making was greater in patients with valve replacement in 23.3% than in patient with coronary artery bypass surgery in 12.6% and in patients with congenital heart disease or intracardiac
comprising tumors 5%.
The most frequent reason for changing clinical management was altered surgical management in 49 (66.2%) patients, followed by modification of medical therapy in 23 (31.08%) patients and confirmation of suspected diagnosis in 2 (2.70%) patients.

**Table 3.** The decision making in altering the surgical procedure was greater in category I than in category II, and benefit in changing medical therapy was greater in category II than in category I

<table>
<thead>
<tr>
<th>Table 2: Transesophageal echocardiography examination data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of patients</strong></td>
</tr>
<tr>
<td>Category I</td>
</tr>
<tr>
<td>Category II</td>
</tr>
<tr>
<td>Number of surgical procedures</td>
</tr>
<tr>
<td>Revascularization procedure</td>
</tr>
<tr>
<td>Valvular surgery</td>
</tr>
<tr>
<td>Valve repair</td>
</tr>
<tr>
<td>Valve replacement</td>
</tr>
<tr>
<td>AVR</td>
</tr>
<tr>
<td>MVR</td>
</tr>
<tr>
<td>DVR</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Other surgical procedures</td>
</tr>
<tr>
<td>ASD closure</td>
</tr>
<tr>
<td>Tumor resection</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The utility of intraoperative transesophageal has become increasingly more evident as anesthesiologists, cardiologist and surgeons continue to appreciate its potential application as an invaluable diagnostic tool and monitor cardiac performance for the management of cardiac surgical patients.10

A present study reviewed our experience, to determine benefit of perioperative TEE in category based TEE indications according to the ASA guidelines in patients undergoing cardiac surgery. It was found that TEE was used more frequently for category II (82%) than for category I (18.58%) indications. However, the benefit was greater in category I indications, changing therapy in 25% of the patient, compared with 18% for category II indications.

TEE had profoundly affected valvular heart surgery by providing the surgical team with a definitive evaluation of their intervention in the operating room where any needed revisions can be accomplished immediately.11,12

In a study of 154 patients undergoing valve surgery, intraoperative TEE documented unsatisfactory repairs in 10 patients (6%) requiring immediate further surgery.13

In present study Mitral valve assessed, before and after repair by TEE, the valve morphology, the presence and severity of mitral regurgitation and valve dysfunction.

Intraoperative echocardiography revealed a successful mitral valve repair in 50 patients, except 5 (10%) in whom, for persistence of severe mitral regurgitation after repair valve replacement was performed.

In valvular surgery among study patients, the most frequent pre cardiopulmonary bypass finding that influence surgical decision making was change in preoperatively diagnosed valve pathology, as mitral valve was repaired in 10 patients and planned valve replacement was omitted. In another 10 patients double valve replacement (mitral and aortic valve) was performed instead of planned single mitral valve replacement.

Transesophageal echocardiography provides useful information after valve replacement, allows immediate assessment of operative results,14 it reliably detects periprosthesis leaks (surprisingly common). Although moderate or severe periprosthesis leaks patient15 should almost always undergo immediate repair before chest closure in.
In present study valve malposition was diagnosed in 19 patients after valve replacement, which was the cause of hemodynamic instability.

In addition to its valuable role in altering surgical management in valve surgery, TEE have a benefit during coronary artery surgery, and used as a continuous monitor for regional and global ventricular function and in detecting new regional wall motion abnormalities associated with possible graft kinking or occlusion.\(^16\)

In a study of 50 patients, TEE identified two patients in whom new Segmental wall motion abnormalities provided the only immediate sign of unsuspected graft occlusion and prompted graft thrombectomies.\(^17\)

In present study, a revision of previously placed grafts was required in 5 cases out of 79 patients who underwent coronary artery bypass surgery.

TEE reveals changes in Left ventricular preload, an end diastolic cross section area of less than 12 cm\(^2\) indicates hypovolemia. However, when a volume challenge increases End diastolic cross section area, then stroke volume also increases.\(^18\)

During acute hypotension, qualitative estimates of LV filling and ejection serve as the practical guide for administration of fluids, inotropes, and vasopressors. For example, Severe hypovolemia is easily recognized as a marked decrease in Left ventricular end diastolic cross section area and a marked increase in LV ejection.\(^19\)

In present study, intraoperative TEE examination contributed to medical management in 5 patients undergoing coronary artery bypass surgery, and in 18 patients undergoing valvular surgery by monitoring ventricular function for detecting hypovolemia and hypervolemia, TEE helped in decision making regarding modification in inotropic support and volume therapy.

TEE can reveal unsuspected cardiovascular disease and the need for major changes in management.\(^20\) For example, in a study five of 182 patients scheduled for coronary artery surgery, intraoperative TEE detected unsuspected mitral regurgitation so severe that unscheduled mitral valve repair was performed.\(^21\)

In the present study TEE provided useful information for confirmation of suspected diagnosis, in one out of 12 cases of left atrial myxoma, where the prebypass examination revealed severe mitral valve insufficiency due to invasion of mitral valve by myxoma, that leads to change in surgical procedure i.e. excision of myxoma and mitral valve replacement. In another case TEE detected a small ventricular septal defect rather than subaortic membrane which was diagnosed by transthoracic echocardiography.

Unplanned surgical intervention (45.9% vs. 20.2%) as a result of the TEE examination was more common in category I than II. In altering medical therapy 17.5% in category I and 13.5% in category II.

These results, obtained prospectively in group of patients from a single centre, support the greater benefit of TEE on medical management for category I than category II indications. As secondary findings that present study document, was that TEE influenced most often surgical therapy (66.2%) followed by changes in medical therapy (31.08%) and in confirming a suspected diagnosis (2.07%).

Intraoperative TEE examination was not performed in all patients, specific reason why intraoperative TEE was not performed in the remaining 915 cardiac surgical patients was not available from the data. However in the institution where the study was conducted, intraoperative TEE for valvular surgery was performed on surgeons preference, while in patient undergoing coronary artery artery bypass surgery TEE examination was only done when preoperative ejection fraction was less than 40%.

**CONCLUSION**

Present study conclude a greater benefit of TEE on clinical management for category I indications than for category II. The TEE was more useful in diagnostic decision making in valvular replacement rather than other procedures.

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Peroperative Transesophageal Echocardiography: Clinical Benefit During Cardiac Surgery


CASE REPORT

ENDOMETRIOSIS IN CAESARIAN SECTION SCAR

Farzana Memon and Abu Bakar Hafeez Bhatti

ABSTRACT

Endometriosis is a very common benign gynecological condition. It is the presence of functional endometrial tissue outside the uterine cavity. Though it can involve most parts of the body, scar endometriosis is an infrequent condition. The wide array of clinical presentations makes it difficult to diagnose preoperatively. Here, we report two cases of caesarian section endometriosis. One presented as a painful swelling and the other as an area of induration in the scar. Only one of the patients had been on medical treatment with Danazol. Despite that both patients remained symptom free after excision of their lesions.

Keywords: Endometriosis, Caesarian section, Danazol, excision, scar.

INTRODUCTION

It has been known and described since early 1900’s that endometrial tissue can present outside the uterine cavity. External endometriosis is the presence of uterine mucosa (glands and stroma) outside the uterus. The most common location is within the pelvis and has been reported to occur in as many as 44% of women undergoing laparoscopy for non gynecological symptoms. Extra pelvic endometriosis is not only uncommon but also difficult to diagnose. The various sites for extra pelvic endometriosis are bladder, kidney, bowel, omentum, lymph nodes, lungs, pleura, extremities, umbilicus, hernial sacs and abdominal wall. The presence of endometriomas within cesarean section scars have been documented in the gynecologic literature since 1956. Keflaski et al reviewed pathology reports of hysterectomy specimens for seven years and only found two cases of caesarian section scar endometriosis. Here, we report two cases of caesarian section scar endometriosis. One presented as a hard nodule and the other as an area of indurations. The purpose of this paper is to highlight the different clinical presentations, scar endometriosis can present with and variable response of patients to medical treatment.

CASE REPORT 1

A 26 year old female presented with complain of swelling in caesarian section scar for a period of one year associated with pain. The patient had underwent an uneventful caesarian section delivery one year back. At the time of removal of stitches, she noticed a swelling in the right side of the scar. The swelling gradually increased in size and became painful. Pain was burning in nature and more marked during menstrual cycles and relieved by taking analgesics. She reported a completely normal past gynecological history. On examination a swelling was noticed on the right side of the scar. It was 4x5 cm in size, tender, oval in shape and firm to hard in consistency. A cough impulse was positive. Initial diagnosis of incisional hernia was made.

Ultrasound abdomen and pelvis showed normal pelvic
adnexa and abdominal contents. It also revealed a small incisional hernia with fibrotic nodules in the scar tissue.

Excision of the fibrotic nodule and repair of incisional hernia was performed. Histopathology of the nodule was sent in the form of three separate tissue specimen. All revealed presence of endometrial glands, stroma and hemosiderin pigment with mixed inflammatory infiltrate around it suggestive of extensive endometriosis in the scar tissue.

After smooth post operative recovery, patient was put on danazol due to presence of extensive endometriosis. The patient has been in follow up for three months. She has remained symptom free and has suffered no recurrence.

CASE REPORT 2

A 30 year old female presented with complain of pain in caesarean section scar for a period of four years. Pain started few weeks after her caesarean section delivery and gradually increased. The intensity of pain increased during menstruation. The patient reported a normal gynecological history prior to the development of pain in the caesarean section scar. She had an uneventful pregnancy with full term delivery.

On examination, a localized area of induration measuring 5x4 cm in size was noticed on the left side of the caesarean section scar. It was tender and fixed to the scar tissue. Excision of the affected tissue was done after ultrasound of abdomen and pelvis revealed no abnormalities.

Histopathology confirmed the diagnosis of endometriosis with presence of glands and stroma in one of the four specimens sent for histopathology. Patient was not put on any medications and has remained symptom free for the last three years.

DISCUSSION

Endometriosis tends to occur in 10% of the female population and affects exclusively the reproductive age group. Because they are hormone dependant, endometriotic lesions tend to bleed with each menstrual cycle. The patient experiences cyclic pain and discomfort because these lesions are more congested and larger in size at this time. The authors observed similar clinical findings of cyclic pain with menstrual cycle in both patients as suggested in the literature.

Transportation of endometrial tissue during surgical procedures to the abdominal wall and later it’s stimulation by estrogen is thought to be the likely etiology. Review of the gynecologic literature indicates that the presentation of patients with cesarean section scar endometrioma is made easily on clinical grounds. Classically, the scenario is that of a parous woman complaining of a painful nodule, varying with menses, at the incision site. Conversely, review of the surgical literature indicates that often this diagnosis is not easily made and incorrect. The authors feel that indeed the presentation in patients with cesarean section scar endometriosis is not straightforward. The above mentioned patients were not operated with a diagnosis of endometriosis in mind as was later confirmed by histopathology.

Endometriosis located in a surgical scar is an unusual complication. The incidence of scar endometrioma resulting from cesarean section is 0.1%, and approximately 25% of women with this condition have concomitant pelvic endometriosis. The authors observed only two cases of cesarean section scar endometriosis in a period of five years. Both cases were referred to the surgical outpatient department since the clinical findings of pain, swelling and incisional hernia without any previous history of gynecological abnormalities were suggestive of a surgical etiology and so, were operated in the surgical department. The authors found no associated abnormalities in any of the pelvic organs.

CT scan and MRI have been used for making the diagnosis. CT scan usually shows a well circumscribed mass. MRI is more helpful with smaller lesions due to its high spatial resolution; furthermore it performs better than CT scan in detecting the planes between muscles and abdominal subcutaneous tissue. In the above mentioned patients, ultrasound suggested disease limited to the skin and adjacent tissue; furthermore no abnormality was noticeable in the abdomen and pelvic adnexa. So, CT scan and MRI were not considered in these patients.

Medical therapy with Danazol and anti gonadotropins has been used for endometriosis but not without side effects. Though they can temporarily relief symptoms of caesarean scar endometriosis, they cannot ablate the lesion. Due to side effects compliance is very difficult to achieve. Surgical therapy involves total wide excision of the lesion to prevent recurrence. It is often necessary to remove a portion of the abdominal fascia to achieve complete excision. In patients in whom a large defect remains, mesh has been used for repair. Recurrences have been reported.
and have been managed successfully with re-excision.\(^1\) In this case series, one of the patients was started on post operative Danazol due to extensive involvement of excised tissue with endometriosis. In the other patient, mild to moderate endometriosis was found only in one segment of resected tissue and so post operative Danazol was not considered necessary. Both patients showed an immediate response to surgery in terms of relief from pain and return no normal activities within a few days post operatively.

To conclude scar endometriosis should be suspected in all females of reproductive age with a history of a painful lump or induration in scar of caesarean section and a change in intensity of pain with menstruation. Imaging studies like Ultrasound, CT scan and MRI might help but the final diagnosis and standard treatment rests on excision of the affected area. Response to medical treatment is variable in different patients. Patient should be kept in follow up as recurrence can not be ruled out.

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CASE REPORT

CONGENITAL SEGMENTAL DILATATION OF SIGMOID COLON, PENILE AGENESIS AND UMBLICAL CORD HERNIA - A NEW ASSOCIATION

Muhammad Talat Mehmoody1, Farhan Shahzadz, Muhammad Sajjad Ashrafy, Muhammad Shahab Athary and Javed Ahmad4

ABSTRACT

Congenital segmental dilatation of the colon, penile agenesis and umbilical cord hernia are individually rare congenital malformations. An association between all three malformations has not been previously reported. We report a neonate with congenital segmental dilatation of the colon, penile agenesis and umbilical cord hernia all coexistent in a new born.

Keywords: Segmental dilatation of Sigmoid Colon, Penile Agenesis, umbilical cord hernia.

INTRODUCTION

Congenital segmental dilatation of the colon is a rare disease. Since its first description by Swenson and Rathouser in 1959, the entity has been reported mostly in children beyond neonatal period.1,2 There are only 11 cases of congenital segmental dilatation of the colon in neonates majority of them were associated with anorectal malformations.3-13

Congenital absence of the penis, or aphallia, is also a rare anomaly with an approximate incidence of 1 in 10 million populations14 while umbilical cord hernia is very rare and accounts for only 20 % of all the congenital abdominal wall defects.15

As far as our knowledge is concerned and as per literature search, the occurrence of all three malformations (congenital segmental dilatation of sigmoid colon, penile agenesis, and umbilical cord hernia) in a neonate has not been reported so far. We are reporting it for the first time.

CASE REPORT

A 12 hour old baby presented with absence of penis, abdominal distention, umbilical swelling and bilious vomiting. On physical examination, the abdomen was distended with visible intestinal loops. A small umbilical swelling about 2 cm. in size covered with sac, along with centrally attached cord (umbilical cord hernia). There was absence of penis and no urinary opening could be identified in the perineum. The scrotum was fully developed with well descended testis. Anus was normal. On plain X-ray of abdomen in erect and supine, there were signs of intestinal obstruction. Ultrasound examination revealed bilateral hydronephrotic kidneys with distended urinary bladder and dilated bowel loops.

At laparatomy, segmental dilatation of sigmoid colon was found, 6 cm in length with normal caliber of sigmoid colon proximally and distally. Urinary bladder was also distended. Colostomy, proximal to dilated sigmoid colon, vesicostomy and repair of umbilical cord hernia was performed (Figure I).

Figure 1: Photograph showing absent penis, suprapubic vesicostomy & sigmoid colostomy

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Multiple biopsies were taken from dilated as well as from normal sigmoid colon that came out to be normal. Post operative recovery was uneventful. Post operative ante-grade cystogram through vesicostomy showed narrow urethral opening into anterior rectal wall and left Vesico-uretic reflux (Figure II). Further management including gender reassignment was discussed with the parents. They did not turn up for follow up.

![Figure 2: Antegrade cystogram through vesicostomy showing urethra pening into rectum & VUR in left sided duplex system.](image)

**DISCUSSION**

Congenital segmental dilatation of the colon (SDC) is an extremely rare anomaly.\(^1\) It is the presence of single, well defined segment of dilated intestine without any mechanical obstruction or anomaly of innervations with more or less abrupt transition to normal bowel proximally and distally.\(^1,2\) It can affect any part of the large bowel from caecum to rectum with the recto sigmoid being the commonest affected site.\(^2\) In this patient mid sigmoid colon was involved. The fact that symptoms in all cases dates back to very early life, indicates congenital origin of the malformation.\(^3\) However the exact cause of SDC is unknown. Several theories have been proposed to explain its pathogenesis. Intra uterine vascular accident, congenital damage to the myenteric plexus, primary dysplasia, abnormal organogenesis, disturbance during splitting of the notochord from the endoderm have all been suggested as causative factors.\(^3,5,6\)

Most of the affected patients present beyond the neonatal age with history of chronic constipation and abdominal distention that is commonly treated as functional constipation or confused with Hirschsprung’s disease.\(^1,2,4\)

Only 11 cases have been reported in neonatal age and all presented as intestinal obstruction.\(^3,13\) Majority have associated anorectal malformations.\(^6,7,10,13\) The other congenital abnormalities associated with SDC include extrophy of bladder,\(^7\) malrotation,\(^4,13\) short small intestine, dysmorphism,\(^3\) undescended testis,\(^3\) heteropic oesophageal mucosa,\(^2\) trisomy 21,\(^4\) Meckel’s diverticulum and hydrops gallbladder,\(^5\) colonic atresia,\(^8,11\) myeloschisis and duplication of appendix.\(^10\) Definitive treatment of segmental dilatation of colon consists of segmental resection and primary anastomosis; however staged operations may be necessary if the patient’s general condition is poor.

On the other hand congenital absence of the penis, or aphallia, is also a rare anomaly caused by developmental failure of the genital tubercle.\(^14\) The approximate incidence is 1 to 10 million populations.\(^14\) The phallus is completely absent, including the corpora cavernosa and corpus spongiosum. Usually, the scrotum is normal and the testes are descended. The urethra opens at any point in the perineum in midline from over the pubis to, most frequently, the anus or anterior wall of the rectum.\(^16\) Associated malformations are common and include cryptorchidism, renal agenesis, dysplasia or duplex system, vesicoureteral reflux, horseshoe kidney, anorectal malformations, musculoskeletal and cardiopulmonary abnormalities.\(^16\) This patient had left sided vesicoureteral reflux with duplex system.

Current recommendations are to reassign female gender to these patients by appropriate surgical and endocrine techniques.\(^17\) Infants with penile agenesis historically have undergone gender reassignment surgery, including bilateral orcheidectomy with preservation of the scrotal skin for later vaginal reconstruction and urethral transposition,\(^16\) however, questions remain regarding in-utero gender imprinting and the long-term psychological effects of gender conversion. Considerable controversy surrounds the timing, role and the necessity of gender
reassignment. The long-accepted notion regarding the presence of a phallus or phenotypic phallic growth potential should not be the major criterion in recommending gender reassignment.

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OVERVIEW

APOPTOSIS IN ORAL DIAGNOSTICS: AN OVERVIEW

Amynah Shaikh¹, Sadiqa Syed² and Masood A Qureshi³

ABSTRACT

Apoptosis describes the molecular and morphological processes leading to controlled cellular self destruction. In recent years, it has been investigated for its biological significance in numerous physiological processes including embryogenesis, differentiation, proliferation/homeostasis and in the regulation of immune system. Its dysfunction and deregulation seems responsible for variety of pathological conditions e.g. immune deficiency, autoimmune diseases, neuro-degenerative diseases and cancer.

This communication updates molecular understanding of this natural phenomenon and its application in oral diagnostics. The present concept of signaling pathways for initiation of apoptotic characteristic changes is illustrated and the role of certain apoptotic genes identified so far is discussed. Abnormality of apoptosis and apoptotic regulatory genes during oral carcinogenesis, though conflicting, is presented. Further, clinical potential for monitoring reactions to chemo-radiotherapy is evaluated from human and animal studies and their usage as physiological markers for oral preneoplasia and squamous cell carcinoma is analyzed.

On the basis of oral cytology the application of new physical and molecular methodological techniques is outlined e.g. cytophotometry, DNA cytometry in relation to molecular studies and their diagnostic and prognostic implications.

Understanding of molecular mechanisms provides development of newer therapeutic approaches in disease management and in future biomedical research. This overview updates molecular understanding of this natural phenomenon as its applications seem to have potential for managing common diseases in future.

Keywords: Apoptosis, cell death, oral mucosa

INTRODUCTION

Cell renewal or programmed cell death is an evolutionary, physiologically conserved pathway needed for embryogenesis, tissue homeostasis and regulation of immune system. Being a gene-directed, cellular self destruction method, apoptosis is a highly regulated process of cell death characterized by membrane blebbing, cell shrinkage, chromatin condensation, DNA fragmentation followed by immediate engulfment by surrounding cells in the absence of an associated inflammatory response.¹

It plays a fundamental role in the maintenance of tissue homeostasis as it is a normal component of the development and health of the multicellular organisms.²

The number of cells in the adult organisms is maintained relatively constant by cell division and cell death. Diseased or malfunctioning cells are replaced and proliferation compensates cell death, thus balancing homeostasis.³

Apoptosis in the average human adult (50-70 billion cells/day) amounts to an individual’s body weight.

Cells die in response to a variety of stimuli (including irreparable DNA damage). Apoptosis is a form of cell death in which the cell itself initiates, regulates and
executes using extensive components of cellular and molecular pathways, making apoptosis distinct from the other type of cell death i.e. necrosis. The later involves uncontrolled cell death leading to inflammatory response, lysis of cells and potentially to serious health problems. Inhibition of apoptosis contributes to many disease states namely immunodeficiency, autoimmune disease, neurodegenerative diseases, viral infections and cancers, whereas initiation of apoptosis is beneficial in prevention of cancers and transplant rejection. The molecular mechanisms responsible for death signals, genetic regulation and activation of effectors are involved in its present day usage as anti inflammatory and anti cancerous. In view of its increasing importance in future biomedical research, related to newer strategies for diagnostics, the phenomenon of apoptosis is reviewed.

**Historical perspectives and Definition**

Apoptosis is a Greek word meaning “falling off” as it occurs in leaves falling from trees, used by Hippocrates (460-370 BC) 2000 years ago as “falling of bones” and later on Gallen extended its meaning to “dropping of scabs”. Medical concept is that of a natural cell death involving an active and defined process essentially responsible for the regulation of cell population in tissues both under physiological and pathological conditions. It is defined as a type of cell death in which cell uses a specialized cellular apparatus to kill itself, a cell suicide mechanism that results in controlling cell number and eliminating the cells that threaten organism’s survival. Though Embryologists were familiar with this term long before, but the mechanisms of apoptosis were recognized by pathologists after 1972. It has emerged as one of the most exciting areas of research in Pathology, Medicine as well as in Physiology where its role is as significant as that of its counterpart mitosis. It plays a complementary but opposite role to mitosis in the regulation of cell population. During the last decade there has been an explosion of interest with apoptosis becoming most widely used word in biomedicine. Since 1990 enormous research is being undertaken because of its implications in many normal and disease processes.

**Physiology of apoptosis**

Programmed cell death is an integral part of both plants and tissue development. Its functions can be considered under different categories.

I. **Apoptosis is an important mean by which an organism not only shapes its tissues and organs during development but even in adult life: Examples include**

- Removal of webbed tissues between fetal fingers and toes during intra uterine development.
- Formation of synapses between neurons, shaping the brain by eliminating the surplus cells in young children.
- Formation of fetus’s eyelids opening.
- Sloughing off the uterine endometrium at the start of menstruation.
- Continuous production and replacement of neutrophils.
- Migration of deeper skin cells to surface, forming protective layer of dead keratinocyte.
- Regression of lactating breast after weaning, atrophy of prostate after castration and ovaries after menopause.
- Resorption of the tadpole tail at the time of its metamorphosis into adult frog.

II. **Apoptosis is needed to destroy the cells that represent a threat to the integrity of the organisms**

That is cells commit suicide in times of distress for the benefit of organism as evidenced by following egs.

- Damage of cell beyond repair.
- Stress conditions such as starvation.
- Viral infected cells killed by cytotoxic T lymphocytes.
- Removal of immature colonies of T and B lymphocytes to prevent them from attacking body constituents, leaving only a small population of memory cells for secondary response.
- Increase production of tumor suppressor gene p53 (a potent inducer of apoptosis) in cells with DNA damage.
Radiotherapy and chemotherapy treated cells.

Factors inducing apoptosis

The decision for apoptosis can come from the cell itself, from the surrounding tissue, or from immune system cells. Normally there is a balance between diverse ranges of cell signals. Apoptosis occurs due to the withdrawal of the positive signals i.e. signals needed for cell survival and receipt of negative signals.

Positive signals: The continued survival of cells, depend upon their continued adhesion to the surface on which they are growing and continuous stimulation from other cells, for examples hormones, growth factors, nitric oxide, and Cytokines (e.g. Interleukin-2 an essential factor for mitosis of lymphocytes).12

Negative signals: for survival include increased levels of oxidants within the cell; damage to DNA by any agent like ultra violet light, x- rays, chemotherapeutic agents and oxidants;10 accumulation of abnormal proteins and presence of molecules that bind to specific receptors on the cell surface and signal the cell to begin the apoptosis program.

Regulation of apoptosis

Two types of signal molecules can cause the cell to undergo apoptosis.13, 14 External signal molecules called death activator proteins e.g. tumor necrosis factor (TNF-á), lymphotoxins, Fas ligand (Fas-L) and reactive oxygen species (ROS) etc. Intracellular molecules that monitor the damaging events such as DNA damage by heat and radiations, nutrient deprivation, viral infection, hypoxia, binding of nuclear receptors by glucocorticoids.

Biochemical pathways leading to apoptosis

There are three mechanisms by which a cell undergoes apoptosis.

Intrinsic or mitochondrial pathway

- It is the major apoptotic mechanism (Figure-1)
- Outer mitochondrial membrane of a healthy cell contains protein Bcl-2.
- This protein is activated by initial damage to cell

and in turn activates a related protein Bax, which causes holes formation in mitochondrial membrane, causing cytochrome-c to leak out.15

- Cytochrome-c in turn binds to protein apoptotic protease factor 1 (Apaf-1) forming complexes apotosomes.
- Apotosomes bind to and activate protease Caspase-9 (Cystein Aspartate Specific Protease) which activates other caspases in a cascade of reaction.16
- Activation of these caspases results in widespread proteolytic activity resulting in degradation of chromosomal DNA, digestion of structural proteins in cytoplasm and ultimately phagocytosis of cell.8

![Intrinsic Pathway](image)

**Figure 1: Intrinsic Pathway**

2- Extrinsic / death receptor pathway:

- Cell surface has receptors for death activators TNF and Fas-L.17
- Binding of TNF and Fas to their receptors transmit a signal to cytoplasm to activate Caspase-8. (Figure-2).18
- This results in a series of reactions activating other caspases, leading to cell destruction and phagocytosis e.g. cytotoxic T lymphocytes after binding to their target produces Fas at their surface.

Caspase are highly specific proteases that can cleave proteins after aspartate residues and regulate proteolysis during apoptotic cell death.
Apoptosis in Oral Diagnostics: An Overview

3- Apoptosis inducing factors (AIF)

Neurons and some other cells do not use caspases for self destruction. AIF is a protein normally located in the mitochondrial inter-membrane space, is released upon receiving a signal (Figure 3). It enters into nucleus, binds to DNA and initiates destruction of DNA and cell death. Whatever is the pathway the morphologic changes seen under microscope include:

- cell shrinkage
- appearance of bubble like blebs on cell surface called Zeiosis.
- nuclear chromatin is degraded creating a vacuolar nucleus.
- mitochondrial breakdown with release of cytochrome-c.
- fragmentation of cell into apoptotic bodies.
- membrane lipids are exposed on the surface, which attract phagocytes. Phagocytes recognize them and secrete cytokines to inhibit inflammation and engulf the cell fragments.

The cascade of events in apoptosis leads to the ordered breakdown of components usually required for cell survival and undesirable effects such as inflammation are prevented.

Methods used in the detection of apoptosis

1. Standard method for identification and quantification

is morphological assessment by Electron microscopy.
2. Use of fluorescent dyes to stain for condensed nuclei or exposed cell surface phosphatidylserine is also employed. DNA Laddering detects fragments of DNA from nuclear breakdown by terminal transferase mediated dUTP-biotin nick end labeling (TUNEL); method to detect the enzymes involved in nuclear breakdown but has a few limitations.

Apoptosis related to disease

Failure of apoptotic mechanisms are considered important determinants of fetal abnormalities. During development of nervous and immune system, unwanted cells fail to undergo apoptosis resulting in multiple congenital abnormalities. Likewise, if a cell is unable to undergo apoptosis, due to mutation or biochemical inhibition, it can continue dividing and develop into a tumor. Thus apoptosis has important role in preventing cancers.

Failure of apoptosis may result from different types of defects in apoptotic pathways. Some cancer associated viruses use tricks to prevent apoptosis of cancerous cells resulting in increased number of tumor cells. e.g. human papilloma virus produces a protein (E6) that binds and inactivates protein p53 causing cervical cancer. Epstein Barr virus produces a protein similar to BCI-2 making the cell more resistant to apoptosis, resulting in mononucleosis. Other non-viral cancers like B-cell leukemia, melanoma etc also use methods to avoid apoptosis. Lungs and colon cancers secrete elevated levels of a molecule that binds to Fas-L preventing it to bind to its receptor.
bind with Fas, making cytotoxic T cells unable to kill the cancer cells.\textsuperscript{26, 27} Genetic variation in caspase genes may play an important role in the etiology of non-hodgkins lymphoma.\textsuperscript{28} Defects in apoptotic machinery may result in autoimmune disease such as rheumatoid arthritis and lupus erythematosis. Some viruses initiate apoptotic pathways e.g. in AIDS human immunodeficiency virus depletes CD4 T helper lymphocytes by various apoptotic mechanisms which lead to a compromised immune system.\textsuperscript{29}

**Apoptosis and oral epithelium**

Progenitor basal cells continuously multiply, differentiate and mature into flattened squames which are finally shed off from the epithelial surfaces. Epithelial cells maintain their contacts with their neighbouring cells and their survival or shedding depends upon their interaction with mesenchyme. Loss of cell-cell contact deprives epithelial cells of necessary intergin –cadherin mediated survival signals (due to lack of organization of cytoskeleton).

**Apoptotic findings in oral lesions**

Apoptotic changes are seen in several oral conditions. The most commonly occurring periodontal condition involves destruction of periodontium leading to tooth loss due to involvement of cytokines and lysosomal enzymes. Oral ulcerations show resistance of lymphocytes to FAS-induced apoptosis and reduced p53, BAX, BCL-X. In oral lichen planus, basal layer apoptosis and lymphocytic infiltration is seen. Molecular findings include increased P53, TNF-x, FAS, FasL, MMP-9, granzyme-B and caspase-3; decrease BCL-2. Viral infections have viral BCL-2 suppression of p53, encoding viral interleukin-6. Auto immune diseases like lymphomas, hemolytic anaemia, thrombocytopenia show massive depletion of CD4 T-cells. Squamous cell carcinoma where epithelial dysplasia and neoplasia are common show inactive p53, inactivation of BAX and BAD and aberrant BCL-2 include increase P53, TNF-x, FAS, FasL, MMP-9, granzyme-B and caspase-3; decrease BCL-2. Viral infections have viral BCL-2 suppression of p53, encoding viral interleukin-6.\textsuperscript{26, 27}

**Future prospects**

Research on apoptosis has increased substantially since 1990 because of its increasingly identified roles in extensive variety of diseases including oncology and organ transplantation. It is now well recognized that many human diseases may be caused by death of cells that should not die or survival of others that should die.\textsuperscript{1} Hence modulation of apoptotic process may offer useful strategies for treatment.

Cytotoxic drugs and radiotherapeutic approaches induce apoptosis in tumor cells and resistance to apoptosis is linked with treatment failure. However these therapies also induce apoptosis in normal cells, a side effect that limits the dose that can be used.\textsuperscript{24}

Latest therapeutic strategies have shown to induce apoptosis in several tumor types e.g. simultaneous use of proteosome inhibition and death receptor ligand could represent a promising therapeutic strategy in the treatment of anaplastic thyroid carcinoma.\textsuperscript{30} Likewise, induction of pancreatic acinar cell apoptosis protects mice against acute pancreatitis.\textsuperscript{31} Caspase inhibitors are being investigated as a possible means to slow the progress of Huntington’s disease, a degenerative brain disease.

Its importance in organ transplantation has recently been identified. The finding that some cells of the body express high levels of Fas-L at all times, thus antigen reactive T cells which express Fas are killed, raise the possibility of a new way of preventing graft rejection. If at least some of the cells on a transplanted kidney, liver, heart etc could be made to express high levels of Fas-L, T lymphocyte attack on graft can be prevented, and long life treatment with immunosuppressive agents can be avoided.\textsuperscript{32}

In view of its importance in most of the challenging diseases of the present era the apoptosis has become the hottest field of biomedical research not only at present but also in future. Mankind is expected to be benefited from the latest research in this field, by better understanding of diseases where apoptosis plays an important role and by adopting methods to minimize the development of horror diseases like cancer and AIDS.

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COMMENT

SOFTWARE MARKERS OF CHROMOSOMAL ANEUPLOIDIES

Aqeela Mustafa

ABSTRACT

Soft markers are transient, non specific signs seen during routine second trimester ultrasounds in many foetal organ systems, which may be present in normal foetuses but have been found in association with abnormal karyotypes as well. This article discusses the sonographic features to correctly elicit the soft markers and eliminating artefacts which may create false positive identification of these markers. Further more the prevalence rates of these soft markers in the affected as well as the general population are discussed along with the change in the background risk for chromosomal aneuploidies once these markers are found. The impacts of these soft markers on the future development of the organ systems along with other associations of the markers are also detailed.

Keywords: Chromosomal abnormalities, cardiac focus, ventriculomegaly, echogenic choroid plexus cysts, echogenic bowel, foetal pyelectasis, cleft lip and plate, single umbilical artery and aberrant subclavian artery.

INTRODUCTION

Chromosomal abnormalities occur in 0.1% to 0.2% of live births. Trisomy 21 (Down syndrome) is the most common clinically significant aneuploidy among live-born infants. Other sonographically detectable aneuploidies include trisomy 13 (Patau’s syndrome), trisomy 18 (Edward’s syndrome), monosomy X (Turner’s syndrome) and triploidy. Second-trimester ultrasound scan is used to detect major foetal structural abnormalities which may be associated with aneuploidy. But during the scan non-specific, often transient markers known as ‘soft markers’, may be readily detected. The Royal College of Obstetricians and Gynaecologists (RCOG) working group believes that a scan specifically undertaken to screen for these markers would not be regarded as routine and therefore falls outside remit. But in everyday life was do come across cases where these markers are seen inadvertently. The purpose of this article is to create awareness regarding the diagnosis, implications and management of soft markers of chromosomal aneuploidies.

According to the RCOG working party report following are the markers of chromosomal anomalies.

1. Ventriclemegaly ( > 10mm at the atrium)
2. Choroid plexus cyst
3. Head shape
4. Nuchal pad (>5 mm at 20 weeks)
5. Cisterna magna
6. Cleft lip
7. Echogenic cardiac focus
8. Echogenic bowel
9. Dilated renal pelvis (>5 mm AP)
10. Short humerus / femur
11. Talipes
12. Sandal gap
13. Clinodactyly
14. Clenched hand
15. 2 vessel cord
Once a soft marker is seen, a detailed anatomical survey of the foetus is required preferably in a tertiary foetal medicine centre to rule out structural defects as well as search for other soft markers.

VENTRICULOMEGALY

Borderline ventriculomegaly (Figure 1) is considered as posterior horns of the lateral ventricles measuring between 10-12 mm by some authorities and 10-15 mm by others. This is seen in 1% of all pregnancies from 18-23 weeks gestation but incidence of hydrocephalus at birth is 2 per 1000. It is a common finding in male foetuses and large for gestational age foetuses. The reason being calvaria are larger in the male foetuses compared to female foetuses, as the brain size is similar the extra intracranial room is taken up by the subarachnoid and ventricular volume. Other associations include infections like cytomegalus virus, toxoplasmosis, tumours, haemorrhage and Down’s syndrome.

In view of the many possibilities, ventriculomegaly should undergo further investigations namely, serologic evaluation for congenital infections (tongh profile); a targeted ultrasound examination inclusive of other markers of chromosomal aneuploidy, visualization of the corpus callosum and a foetal echocardiogram. For this purpose the patient must be referred to a tertiary foetal medical centre where along with this foetal karyotyping may be performed.

About 40% of cases of mild isolated ventriculomegaly resolve spontaneously. The parents need to be counselled and reassured that usually this is not significant but the child may have mild to moderate neurodevelopmental delay in 10% of cases or progress to further ventricular enlargement hence serial scans are needed. In addition few cases with apparently isolated mild ventriculomegaly, may have underlying cerebral maldevelopment (such as lissencephaly) or obstructive lesion (such as periventricular leukomalacia). In the presence of ventriculomegaly the background risk for Down’s syndrome remains the same. Unfavoured outcome criteria include ventricular atrial width greater than 12 mm, progression of enlargement and asymmetrical and bilateral ventriculomegaly.

In utero Magnetic Resonance Imaging (MRI) is a useful adjunct to ultrasound (US) as in cases of foetal cerebral ventriculomegaly with MRI additional abnormalities are identified in 50% of cases. When referred after initial diagnosis using ultrasound.

CHOROID PLEXUS CYSTS (CPC)

Choroid plexus cysts are diagnosed by the presence of single or multiple cystic areas (greater than 2 mm in diameter) in one or both choroid plexus. Choroid plexus cysts are seen in 2% of pregnancies at 20 weeks. Nearly 50% of trisomy 18 and 1% of karyotypically normal foetuses exhibit CPC. Usually benign they do not warrant further follow up scans if isolated as they usually disappear before 28 weeks gestation, neither do they require any change in obstetric management. They are unlikely to be associated with significant neurocognitive delays in early childhood.

Isolated choroid plexus cysts increase the background risk of trisomy 18 and trisomy 21 by a factor of 1.5 times. Detection of CPC prenatally can evoke profound, negative maternal emotional responses despite accurate counselling. Practitioners should consider these responses when counselling parents about these and other structural variants of unclear functional significance.

HEAD SHAPE

Strawberry shaped head (brachycephaly) is associated with trisomy 18 and so is the lemon shaped head. 52% of cases of trisomy 18 have strawberry shaped head and 43% have lemon shaped head and it may be a normal variant in 1% of cases. An abnormal head shape in other cases may be positional or due to the pressure of the ultrasound probe. Release of the pressure may cause the
head shape to return to normal. Abnormal head shape may also be due to craniosynostosis or a more flexible skull due to loss of bone density seen in osteogenesis imperfecta and other demineralising conditions.

**CISTerna MAGNA**

The normal dimension of cisterna magna is 4 – 10 mm. A small or absent cisterna magna is associated with open neural tube defects. A large cisterna magna may be part of Dandy Walker syndrome. Neural tube defects, Dandy Walker malformations and large cisterna magna *per se* are all associated with trisomy 18.

The cisterna magna may appear larger due to scanning artefact hence the scanning angle should be changed and measurement rechecked. But it should be remembered that isolated enlargement of the cisterna magna to more than 10 mm is associated with normal pregnancy and neonatal outcome.8 Hence genetic amniocentesis and follow up is not indicated.

**CLEFT LIP AND PALATE.**

![Figure 2: Transverse view of the foetal head at the level of the maxilla showing bilateral cleft palate.](image)

Incidence of cleft lip and palate is 1 in 800 live births. Cleft lip and palate are associated with almost 300 multiple malformation syndromes. Approximately 60% cases are isolated and 10 % cases are seen in association with chromosomal abnormalities.8 Trisomy 13 usually presents with a median cleft and other central defects.

Cleft lip and palate are diagnosed in the transverse view of the foetal head through the mandible which will show a breach in the palate (Figures 2 and 3), a profile view of the face which will show a premaxillary protuberance (Figures 4 and 5), and the coronal view through the anterior midface will show a cleft lip.

Once seen the patients should be referred immediately to specialist centres for foetal echocardiography along with a detailed scan. Here the parents should be offered amniocentesis and karyotyping. The cases which have associated abnormalities but a normal karyotype should be referred to a clinical geneticist. Those with isolated cleft lip and palate need to be referred to a multidisciplinary
cleft team. Cleft lip or a cleft palate, or both, can be traumatic to the family and details of the special needs of the baby after birth, the need for multiple surgeries and the final cosmetic effect need to be discussed with the parents.

**ECHOCARDIC FOCUS (EIF)**

Echogenic cardiac foci are seen in 4% of normal pregnancies and 12% of pregnancies with Down syndrome. In 95% of cases they are seen in the left ventricle and in 5% cases in the right ventricle. In 98% they are unilateral and in 2% they are bilateral.\(^3\)

As an isolated finding, the background risk of having a baby with trisomy 21 increases by a factor of 4.\(^3\) Amniocentesis need not be offered to patients who are otherwise at low risk and have an isolated echogenic intracardiac focus. It should not be the sole indication for foetal echocardiography.\(^13\) They resolve in 90% of cases by the third trimester of pregnancy. Isolated foetal echogenic intracardiac foci do not need any further follow up scans. Prenatally diagnosed intracardiac echogenic foci are not associated with childhood myocardial dysfunction.\(^14\)

**ECHOCARDIC BOWEL**

Echogenic bowel is seen in 0.5% of pregnancies. Ultrasound assessment of echogenic bowel is usually done by comparing the echogenicity with adjacent bone. A sonographic finding of echogenic foetal bowel should be interpreted cautiously because the use of special image processing techniques like tissue harmonics and high power can artificially enhance the apparent level of echogenicity of the bowel. Ideally the power should be low with harmonics switched off and the gain reduced; the bowel should then appear as bright as the adjacent bone in both longitudinal and transverse planes.

Foetuses born to Asian mothers were significantly more likely to have an EIF. This racial difference should be taken into account when counselling patients about the potential for Down syndrome.\(^10\)

On ultrasound they are visualized as bright spots in the papillary muscles. A specular reflection from the moderator band may be judged as the false echogenic intracardiac focus. The rate of specular reflection from the moderator band is seen in around 5.5% cases. Because it is possible to generate a specular reflection from an interface in the foetal heart in virtually any patient, it is important to exercise caution before diagnosing an echogenic intracardiac focus.\(^11\) The echogenic cardiac focus is more likely to be diagnosed in patients with a lower body mass index and scanning with the foetal heart in the apical view. The orientation of the foetal 4-chamber heart view exerts significant influence on detection rates for the echogenic cardiac focus, implying that the more technically facile the sonographic study, the more likely an echogenic cardiac focus will be found.\(^12\)

Echogenic bowel is associated with several pathological conditions that include intrauterine infection with cytomegalus virus and toxoplasmosis, bleeding during pregnancy, intrauterine growth restriction, cystic fibrosis and chromosomal abnormalities. Hence the work up of echogenic bowel includes taking maternal blood for torch profile. Blood from both parents should be obtained for cystic fibrosis screening. A detailed history is needed enquiring about any bleeding / invasive intrauterine procedure during pregnancy. A detailed anomaly scan is required and the parents should be offered amniocentesis for karyotyping and detection of cystic fibrosis gene mutation. The risk of Down syndrome is increased by a factor of 7 from the a priori risk.\(^3\)

Foetal echogenic bowel is an important marker of placental damage. This finding in the second trimester is strongly associated with adverse pregnancy outcome due to utero placental insufficiency, particularly in women with elevated maternal serum alpha foetoprotein concentration due to severe foeto - maternal bleeding. In view of this association
scans should be performed at regular intervals for foetal well being and to pick up growth restriction early.

In many pregnancies there are multiple factors associated with foetal hyperechogenic bowel. Thus identification of one potential underlying cause should not preclude further testing. Once chromosome defects, cystic fibrosis, structural abnormalities, infection and growth restriction has been excluded, parents can be counselled that the prognosis is good, irrespective of the presence or absence of blood stained amniotic fluid.\(^\text{15}\)

There is no evidence of any serious long term bowel pathology associated with isolated foetal echogenic bowel.\(^\text{16}\)

**PELVICALYCEAL DILATATION**

Mild pelvicalyceal dilatation is seen in 1-2 % of pregnancies at 18 – 23 weeks of gestation.\(^\text{3}\) This means the renal pelvis should measure from anterior to posterior between 5 – 10 mm in a transverse view of the abdomen with the spine at 12’ o clock or 6’ o clock position. The cut off for mild pelvicalyceal dilatation in the third trimester is 7 – 10 mm.

Maternal hydration influences foetal renal pelvic diameter. The larger foetal renal diameters seen in the hydrated group support physiologic theories that the effects of maternal hydration on amniotic fluid volume are partially mediated via foetal urine production.\(^\text{17}\) A higher prevalence of pyelectasis is seen in male foetuses. But the prevalence of major trisomies among foetuses with pyelectasis is unlikely to be dependent on foetal gender. Thus, counselling patients with regard to the genetic implications of foetal pyelectasis should be gender independent.\(^\text{18}\)

Pelvicalyceal dilatation is associated with a number of obstructive renal pathology like pelvi ureteric junction obstruction, vesico ureteric junction obstruction and reflux, posterior urethral valves, ureterocoele, urethral obstruction or multicystic dysplastic kidney. Apart from renal pathology it is also commonly seen in cases of trisomy 21.

Seventy four percent (74%) of pregnancies in the mild pyelectasis subsequently show spontaneous resolution. Invasive testing for Down syndrome is not justified as most of these are a transient finding and in 12% of cases its related to vesicoureteric reflux and in 4 % of cases to major renal pathology.\(^\text{19}\) A follow up scan should be arranged in the third trimester and persistent cases need antibiotic cover after birth till reflux is ruled out by postnatal scanning and other renal function tests. Children with a mild foetal pyelectasis which does not persist beyond the second trimester do not have more urinary tract morbidity during childhood than children without this finding. Therefore, there seems to be no need for additional investigation after birth.\(^\text{20}\)

For isolated mild hydronephrosis the risk for trisomy 21 is 1.5 times the background risk.\(^\text{3}\)

**SHORTENED LONG BONES**

Second-trimester foetal long-bone biometry is useful in detecting trisomy 21 and may be used to adjust the a prior risk of both high- and low-risk women for trisomy 21 and, therefore, the need for genetic amniocentesis.\(^\text{21}\)

Shortened long bones below the 5\(^{\text{th}}\) centile may also signify wrong dates, constitutional shortness, intrauterine growth restriction or skeletal dysplasia.

Hence in order to differentiate the cause, the first step in the management is to check menstrual dates and cycle length excluding wrong dates. A family history and parental heights will exclude familial disposition. Foetal echocardiography along with a detailed anomaly scan should be performed upon diagnosing short long bones. All the long bones should be measured and plotted on a graph. A complete skeletal survey routes out skeletal dysplasias. Invasive testing may be offered to exclude Down syndrome in high risk cases. Regular follow up scans should be arranged for early detection of intrauterine growth restriction (IUGR).

It has also been seen that shortened humerus length has a greater sensitivity than femur length in cases of trisomy 21. Hence in foetuses at risk for trisomy 21 humerus length should be determined, because it may, aid in the prenatal diagnosis, if shortened.\(^\text{22}\)

**INCREASED NUCHAL FOLD**

Nuchal thickening remains one of the most sensitive and important markers during the second trimester. An increased nuchal fold of more than 5 mm at 18 – 23 weeks is a strong marker for Down syndrome with an increase
in the background risk by a factor of 10 from the a priori risk. It is seen in 0.5 % of fetuses.3

The nuchal fold in the second trimester is seen in the trans cerebellar view and measured from the outer border of the bone to the outer border of the skin. An increased nuchal thickness warrants a referral to a tertiary foetal medicine centre for foetal echocardiography and genetic amniocentesis may be carried out.

TALIPES AND HAND ABNORMALITIES

The guideline by the RCOG does not recommend scanning hands and feet or counting fingers at the routine 18 -23 weeks anomaly scan. But both hand and feet anomalies like talipes, clenched hand, clinodactyly (shortened middle phalanx of the 5th finger) and overlapping fingers are associated with chromosomal disorders.

Talipes may be familial so a detailed family history is required or it may be a part of other disorders like arthrogryposis, in such a case a detailed scan will reveal flexed joints etc. Leakage of liquor may lead to talipes so subjective or objective measurement of liquor volume should be done. If no other markers of chromosomal disorders are found it may be an isolated finding.

Hand anomalies are associated with various chromosomal disorders like clinodactyly is associated with trisomy 21, overlapping fingers with trisomy 13 and clenched hands with trisomy.

SINGLE UMBILICAL ARTERY

Single umbilical artery is one of the most common congenital malformations. Single umbilical artery is seen in 0.8% of multiple gestations and 0.46% of single live births and 6.1 – 11.3% of infants with aneuploidy. More than 50% of cases with trisomy 18 and 10 -50% cases of trisomy 13 have a single umbilical artery2. This vascular abnormality of the umbilical cord is frequently associated with other congenital malformations like cardiovascular, genitourinary and limb skeletal system anomalies as well as some adverse perinatal events such as intrauterine growth restriction (IUGR), premature delivery, and increased perinatal mortality.

The absence of the left artery is more frequent than the absence of the right artery. The association with chromosomal abnormalities seems to be equal on each side.23

If seen as a solitary finding it is not an indication for chromosomal analysis among low risk patients and the obstetric management remains unchanged. However, the babies need to be evaluated thoroughly postnatally as they may be at risk of subtle anomalies.

OTHER MARKERS

Two other markers deserve mention here although they are not included in the list of the RCOG working party report. These are small or absent nasal bone seen in the second trimester and aberrant right subclavian artery.

Nasal bone is measured in the facial profile view and it has been seen that nasal bone length seems to be a useful marker for Down syndrome with a high sensitivity and a low false-positive rate.24

The right subclavian artery arises normally as the first vessel from the brachiocephalic artery of the aortic arch. An aberrant right subclavian artery arises as a separate vessel from the aortic isthmus and crosses to the right, behind the trachea. This variant is present in <1% of the normal population; however, in subjects with Down syndrome, an incidence between 19% to 36% was reported.

Hence, in utero identification of an aberrant right subclavian artery may be a new ultrasound marker to be found in foetuses with Down syndrome.25

CONCLUSION

In conclusion the sonographer or the obstetrician evaluating the result of the obstetric scan should be aware of the implications of these soft ultrasound markers. The detection of any abnormal finding on ultrasound should prompt an immediate detailed ultrasound evaluation of the foetus by someone experienced in the diagnosis of foetal anomalies where this is not possible the patient should be referred to a tertiary foetal medical centre. The most important thing is to convey the result to the patient in a way wherein anxiety is not created as most markers seen as a solitary finding are benign and do not require a genetic amniocentesis or further follow up.
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GUIDELINES ON GOOD PUBLICATION PRACTICE BY COMMITTEE ON PUBLICATION ETHICS (COPE)

Why the guidelines were developed

These guidelines should be useful for authors, editors, editorial board members, readers, owners of journals, and publishers.

What they aim to do

These guidelines are intended to be advisory rather than prescriptive, and to evolve over time. We hope that they will be disseminated widely, endorsed by editors, and refined by those who use them.

1 Study design and ethical approval

Definition

Good research should be well justified, well planned, appropriately designed, and ethically approved. To conduct research to a lower standard may constitute misconduct.

Action

(1) Laboratory and clinical research should be driven by protocol; pilot studies should have a written rationale.

(2) Research protocols should seek to answer specific questions, rather than just collect data.

(3) Protocols must be carefully agreed by all contributors and collaborators, including, if appropriate, the participants.

(4) The final protocol should form part of the research record.

(5) Early agreement on the precise roles of the contributors and collaborators, and on matters of authorship and publication, is advised.

(6) Statistical issues should be considered early in study design, including power calculations, to ensure there are neither too few nor too many participants.

(7) Formal and documented ethical approval from an appropriately constituted research ethics committee is required for all studies involving people, medical records, and anonymised human tissues.

(8) Use of human tissues in research should conform to the highest ethical standards, such as those recommended by the Nuffield Council on Bioethics.

(9) Fully informed consent should always be sought. It may not always be possible, however, and in such circumstances, an appropriately constituted research ethics committee should decide if this is ethically acceptable.

(10) When participants are unable to give fully informed consent, research should follow international guidelines, such as those of the Council for International Organizations of Medical Sciences (CIOMS).

(11) Animal experiments require full compliance with local, national, ethical, and regulatory principles, and local licensing arrangements. International standards vary.

(12) Formal supervision, usually the responsibility of the principal investigator, should be provided for all research projects: this must include quality control, and the frequent review and long term retention (may be up to 15 years) of all records and primary outputs.

2 Data analysis

Definition

Data should be appropriately analysed, but inappropriate analysis does not necessarily amount to misconduct. Fabrication and falsification of data do constitute misconduct.

Action

(1) All sources and methods used to obtain and analyse data, including any electronic pre-processing, should be fully disclosed; detailed explanations should be provided for any exclusions.
(2) Methods of analysis must be explained in detail, and referenced, if they are not in common use.

(3) The post hoc analysis of subgroups is acceptable, as long as this is disclosed. Failure to disclose that the analysis was post hoc is unacceptable.

(4) The discussion section of a paper should mention any issues of bias which have been considered, and explain how they have been dealt with in the design and interpretation of the study.

3 Authorship

Definition

There is no universally agreed definition of authorship, although attempts have been made. As a minimum, authors should take responsibility for a particular section of the study.

Action

(1) The award of authorship should balance intellectual contributions to the conception, design, analysis and writing of the study against the collection of data and other routine work. If there is no task that can reasonably be attributed to a particular individual, then that individual should not be credited with authorship.

(2) To avoid disputes over attribution of academic credit, it is helpful to decide early on in the planning of a research project who will be credited as authors, as contributors, and who will be acknowledged.

(3) If professional writers employed by pharmaceutical companies, medical agencies, or other parties have written the paper, then their names should be included, and any conflicts of interest declared.

(4) All authors must take public responsibility for the content of their paper. The multidisciplinary nature of much research can make this difficult, but this can be resolved by the disclosure of individual contributions.

(5) Careful reading of the target journal’s “Advice to Authors” is advised, in the light of current uncertainties.

(6) Authors should be vigilant about allowing their name to be used on a piece of work to add credibility to the content.

4 Conflicts of interest

Definition

Conflicts of interest arise when authors, reviewers, or editors have interests that are not fully apparent and that may influence their judgements on what is published. They have been described as those which, when revealed later, would make a reasonable reader feel misled or deceived.

They may be personal, commercial, political, academic or financial. “Financial” interests may include employment, research funding, stock or share ownership, payment for lectures or travel, consultancies and company support for staff.

Action

(1) Such interests, where relevant, must be declared to editors by researchers, authors, and reviewers.

(2) Editors should also disclose relevant conflicts of interest to their readers. If in doubt, disclose.

(3) Editors should also consider disclosing to readers their own conflicts of interest and those of their teams, editorial boards, managers, and owners.

(4) Sometimes conflicts of interest may be so extreme that publication will not be possible or people (for example, reviewers or editors) may have to be excluded from decisions on publication.

5 Peer review

Definition

Peer reviewers are external experts chosen by editors to provide written opinions, with the aim of improving the study. Working methods vary from journal to journal, but some use open procedures in which the name of the reviewer is disclosed, together with the full or “edited” report.

Action

(1) Suggestions from authors as to who might act as
reviewers are often useful, but there should be no obligation on editors to use those suggested.

(2) The duty of confidentiality in the assessment of a manuscript must be maintained by expert reviewers, and this extends to reviewers’ colleagues who may be asked (with the editor’s permission) to give opinions on specific sections.

(3) The submitted manuscript should not be retained or copied.

(4) Reviewers and editors should not make any use of the data, arguments, or interpretations, unless they have the authors’ permission.

(5) Reviewers should provide speedy, accurate, courteous, unbiased and justifiable reports.

(6) If reviewers suspect misconduct, they should write in confidence to the editor.

(7) Journals should publish accurate descriptions of their peer review, selection, and appeals processes.

(8) Journals should also provide regular audits of their acceptance rates and publication times.

6 Redundant publication

Definition

Redundant publication occurs when two or more papers, without full cross reference, share the same hypothesis, data, discussion points, or conclusions.

Action

(1) Published studies do not need to be repeated unless further confirmation is required.

(2) Previous publication of an abstract during the proceedings of meetings does not preclude subsequent submission for publication, but full disclosure should be made at the time of submission.

(3) Re-publication of a paper in another language is acceptable, provided that there is full and prominent disclosure of its original source at the time of submission.

(4) At the time of submission, authors should disclose details of related papers, even if in a different language, and similar papers in press.

Dealing with misconduct

1 Principles

(1) The general principle confirming misconduct is intention to cause others to regard as true that which is not true.

(2) The examination of misconduct must therefore focus, not only on the particular act or omission, but also on the intention of the researcher, author, editor, reviewer or publisher involved.

(3) Deception may be by intention, by reckless disregard of possible consequences, or by negligence. It is implicit, therefore, that “best practice” requires complete honesty, with full disclosure.

(4) Codes of practice may raise awareness, but can never be exhaustive.

2 Investigating misconduct

(1) Editors should not simply reject papers that raise questions of misconduct. They are ethically obliged to pursue the case. However, knowing how to investigate and respond to possible cases of misconduct is difficult.

(2) COPE is always willing to advise, but for legal reasons, can only advise on anonymised cases.

(3) It is for the editor to decide what action to take.

3 Serious misconduct

(1) Editors must take all allegations and suspicions of misconduct seriously, but they must recognise that they do not usually have either the legal legitimacy or the means to conduct investigations into serious cases.

(2) The editor must decide when to alert the employers of the accused author(s).

(3) Some evidence is required, but if employers have a process for investigating accusations—as they are increasingly required to do—then editors do not need to assemble a complete case. Indeed, it may
be ethically unsound for editors to do so, because such action usually means consulting experts, so spreading abroad serious questions about the author(s).

(4) If editors are presented with convincing evidence—perhaps by reviewers—of serious misconduct, they should immediately pass this on to the employers, notifying the author(s) that they are doing so.

(5) If accusations of serious misconduct are not accompanied by convincing evidence, then editors should confidentially seek expert advice.

(6) If the experts raise serious questions about the research, then editors should notify the employers.

(7) If the experts find no evidence of misconduct, the editorial processes should proceed in the normal way.

(8) If presented with convincing evidence of serious misconduct, where there is no employer to whom this can be referred, and the author(s) are registered doctors, cases can be referred to the General Medical Council, like PMDC.

(9) If, however, there is no organisation with the legitimacy and the means to conduct an investigation, then the editor may decide that the case is sufficiently important to warrant publishing something in the journal. Legal advice will then be essential.

(10) If editors are convinced that an employer has not conducted an adequate investigation of a serious accusation, they may feel that publication of a notice in the journal is warranted. Legal advice will be essential.

(11) Authors should be given the opportunity to respond to accusations of serious misconduct.

4 Less serious misconduct

(1) Editors may judge that it is not necessary to involve employers in less serious cases of misconduct, such as redundant publication, deception over authorship, or failure to declare conflict of interest. Sometimes the evidence may speak for itself, although it may be wise to appoint an independent expert.

(2) Editors should remember that accusations of even minor misconduct may have serious implications for the author(s), and it may then be necessary to ask the employers to investigate.

(3) Authors should be given the opportunity to respond to any charge of minor misconduct.

(4) If convinced of wrongdoing, editors may wish to adopt some of the sanctions outlined below.

5 Sanctions

Sanctions may be applied separately or combined. The following are ranked in approximate order of severity:

(1) A letter of explanation (and education) to the authors, where there appears to be a genuine misunderstanding of principles.

(2) A letter of reprimand and warning as to future conduct.

(3) A formal letter to the relevant head of institution or funding body.

(4) Publication of a notice of redundant publication or plagiarism.

(5) An editorial giving full details of the misconduct.

(6) Refusal to accept future submissions from the individual, unit, or institution responsible for the misconduct, for a stated period.

(7) Formal withdrawal or retraction of the paper from the scientific literature, informing other editors and the indexing authorities.

(8) Reporting the case to the General Medical Council, or other such authority or organisation which can investigate and act with due process.

INSTRUCTIONS TO AUTHORS

All materials submitted for publication should be sent exclusively to the Journal of the Dow University of Health Sciences. Work that has already been reported in a published paper or described in a paper sent or accepted elsewhere for publication should not be submitted. However, a complete report following publication of a preliminary report, usually in the form of an abstract, or a paper that has been presented at a scientific meeting, if not published in full in a proceeding or similar publication, may be submitted. Press reports of meetings will not be considered as breach of this rule, but such reports should not be amplified by additional data or copies of tables and illustrations. In case of doubt, a copy of the published material should be included with a manuscript to help the editors decide how to deal with the matter. Dissertation or thesis-based articles should be reformatted according to the instructions to authors.

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If tables, illustrations or photographs, which have already been published, are included, a letter of permission for re-publication should be obtained from author(s) as well as the editor of the journal where it was previously published.

Written permission to reproduce photographs of patients, whose identity is not disguised, should be sent with the manuscript; otherwise the eyes will be blackened out.

MATERIAL FOR PUBLICATION

The material submitted for publication may be in the form of an Original research, a Review Article, evidence-based reports, Special article, Commentary, Short communication, a Case Report, Recent Advances, New techniques, view points on Clinical/Medical Education, Adverse Drug Reports or a Letter to the Editor. Original articles should normally report original research of relevance to clinical medicine, and may appear either as papers or as short communications. The paper should be of about 2000 words, with no more than six tables or illustrations; short communications should be of about 600 words, with one table or illustration and no more than five references. Clinical case reports and brief or negative research findings may appear in this section.

Review article should consist of structured overview of some relatively narrow topics providing background and recent development with reference to the original literature. An author can write a review article only if he/she has written a minimum of three original research articles and some case reports on the same topic.

Letters should normally not exceed 400 words, have no more than 05 references, and be signed by all the authors; preference is given to those that take up points made in contributions published in the journal. Editorials are by invitation.

Authors should keep one copy of their manuscript for reference, and send three copies (laser copies or inkjet, photocopies are not accepted) to the Managing Editor, Journal of the Dow University of Health Sciences. The author should also submit an electronic copy of the manuscript typed in MS Word. Any illustrations or photographs should also be sent in duplicate. People from outside Pakistan can also e-mail their manuscript.

Each manuscript should include a title page (containing e-mail address, fax and phone numbers of the corresponding author), abstract, text, acknowledgements (if any), references, tables, and legends. Each component should begin on a new page, in the following sequence: title page; abstract and at least three key words; text; acknowledgements; references; tables (each table, complete with title and footnotes, should be merged in the manuscript); and legends for illustrations.

The manuscript should be typed in double spacing as a single column on 8 1/2"X 11" (21.5cm X 28.0 cm) white bond paper with one inch (2.5cms) margin on both sides. It should not exceed 3000 words, excluding tables and references. There should be no less than 20 or more than 40 references in an Original Article and no less than 40 or more than 60 in a Review Article. If prepared on a word processor/computer, the diskette, properly protected, or CDs should be sent with the manuscript.
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Tables and illustrations should be merged within the text of the paper, and legends to illustrations should be typed on the same sheet. Tables should be simple, and should supplement rather than duplicate information in the text; tables repeating the information will be omitted. Each table should have a title and be typed in double space without horizontal and vertical lines on an 8 1/2" X 11" (21.5 X 28.0 cms) paper. Tables should be numbered consecutively with Roman numerals in the order they are mentioned in the text. Page number should be in the upper right corner. If abbreviations are used, they should be explained in footnotes and when they first appear in text. When graphs, scatter grams, or histograms are submitted, the numerical data on which they are based should be supplied. All graphs should be merged in the manuscript. For scanned photographs highest resolution should be used.

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