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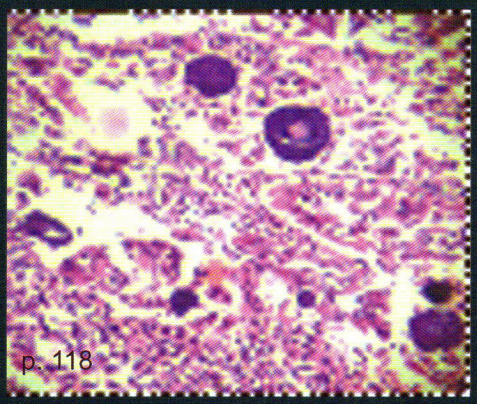
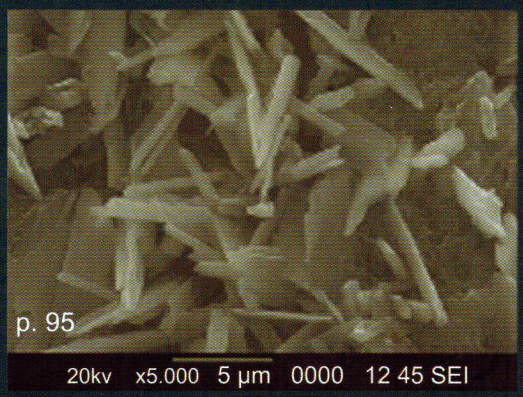
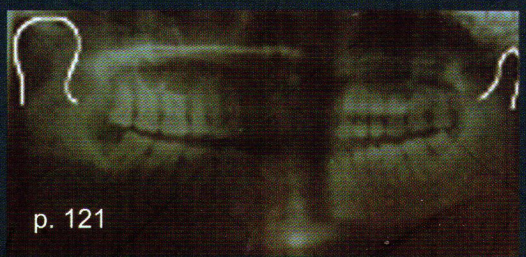


Psammoma bodies (H&E 100X)



Scanning electron micrograph of Gymnemic acid - chitosan nanoparticles. Scale bar =5 µm

Measuring the length of the tendon



Superimposition in OPG showing enlarged condyle on right side

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✍ EDITORIAL

Vitamin D in health and disease

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As medical graduates we were taught, VitD as an anti rachitic vitamin, later it was termed as a hormone – Vithormone with its target mainly in bone and kidney. Vitamin D is mostly synthesized in human body under the skin from 7 dehydrocholesterol using UV–B 290–315 nm energy and a minor quantity is obtained from dietary sources. Vitamin D thus obtained is converted to active forms 25 OH cholecalciferol and 1, 25 dihydroxy cholecalciferol by enzymes 25–hydroxylase and l alpha hydroxylase in liver and kidney respectively. 25 OH cholecalciferol is considered as the best indicator for assaying vitamin D status of the community. Classic functions of vitamin D include absorption of calcium and phosphate from the intestine, mineralization of bone and reuptake of calcium in the renal tubules. The deficiency will manifest as rickets in growing bone and osteomalacia in adults.

Now we are more aware of the extra skeletal functions of vitamin D, its immunomodulatory role and hormone regulation. Vitamin D Receptors (VDR), Calcitriol receptors (NR 111) and l alpha hydroxylase receptors are present in bone, skeletal muscle, Prostate, Breast, Colon, Pancreas, Lungs and immune cells indicating its role in various other functions. There is evidence of the extraskeletal effects of vitamin D, but most derive from observational studies; more clinical trials are required to determine the therapeutic role of vitamin D.

Muscular system: Hypovitaminosis D is associated with myopathy, sarcopenia, muscular strength reduction and increased risk of falls. The vitamin D supplementation increases the muscle functionality indexes.

Cardiovascular system: Low levels of vitamin D are related to increased levels of cardiovascular risk factors, heart failure, stroke, and cardiovascular mortality, while a good vitamin D status is associated with a decreased incidence of cardiovascular diseases.

Diabetes and metabolic syndrome; A good vitamin D status is related to a decreased incidence of type 2 diabetes and metabolic syndrome; a vitamin D supplementation in the early childhood reduces (nearly 30%) the risk of having type 1 diabetes.

Cancer: Vitamin D deficiency is associated with breast, colorectal cancer and melanoma relapses. Low and high levels of 25–hydroxy–vitamin D (25 (OH) D) are related to a higher neoplastic mortality.

Infectious diseases: Hypovitaminosis D is associated with higher incidence of upper respiratory tract infections and worse interferon response in chronic hepatitis C. Vitamin D supplementation decreases the risk of influenza A.

Rheumatic diseases: In rheumatoid arthritis low serum levels of vitamin D metabolites are related to a higher disease activity, while a good vitamin D status is associated with a higher probability of remission or response to therapy and a lower degree of disability.

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Neurologic diseases: Associations between vitamin D deficiency and risk of multiple sclerosis, depression, cognitive deficits, and Parkinson's disease have been reported.

Vitamin D and allergic diseases : Vitamin D insufficiency data is expanding to include evidence on its role in asthma, atopic dermatitis and allergic rhinitis. In addition to its well documented relationship with rickets and bone metabolism, vitamin D is now recognized as an immunomodulator. Even though majority of studies are pointing towards an association of high Vitamin D status with low prevalence of allergic disorders in children, further interventional studies are mandatory to confirm the role of vitamin D as an adjuvant therapy in treatment and prevention of allergic disorders.

Now few questions remain unanswered. Need we supplement Vit D routinely to all children, adults and elderly? American Academy of Paediatrics (AAP) recommends 400units of Vit D daily to all infants. Is there any need to fortify salt or food products with Vit D in India to eradicate vit D deficiency and insufficiency?.

✪ ORIGINAL ARTICLE

Estimation of the Length of Palmaris Longus Tendon from the Length of Forearm - A Study on Indian Population

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Abstract

Introduction: Palmaris longus tendon is commonly used for tendon transfer and reconstruction surgeries. It is the commonly preferred tendon for graft purposes. Prior knowledge of its approximate length helps the surgeon in proper pre-operative planning for the tendon harvest. There is paucity of the data on the morphometry of palmaris longus tendon in Indian population. Aim: This study was conducted to measure the length and width of palmaris longus tendon, and to find out if they can be correlated with the length of the forearm. Materials and methods: The study was carried out in 70 upper limbs, belonging to 26 male and 9 female cadavers. The length of the forearm and tendon were measured using a measuring tape. The width of tendon was measured using vernier calipers. Results: The mean length of the tendon was 162.19±15.48 mm in the males and 165.67±13.34 mm in the females and had statistical significance with the length of the forearms in both males and females (P<0.001) The mean width of the tendon was 3.22±0.77 mm in the males and 3.1±0.48 mm in the females. There was no significant correlation between tendon width and forearm length in both the males and the females (p>0.05). Conclusion: It is possible for the surgeon to estimate the length of the tendon available for grafting purpose. This helps to decide the proximal skin incision while harvesting the tendon.

Keywords: Palmaris longus tendon, length of forearm, vernier caliper, tendon graft

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Introduction

Palmaris longus muscle is a slender muscle seen superficially in flexor compartment of the forearm. The muscle belly is short and is attached to the medial epicondyle of the humerus. The tendon is long, and passes superficial to the flexor retinaculum, partly intermingling with some distal fibres of the retinaculum. It then broadens out and gets incorporated into the palmar aponeurosis[1].

The evolution of the muscle shows a gradual decline in muscle mass as it progresses from arboreal to terrestrial habitat[2]. The muscle is well developed in brachiators like gibbons. In such primates, it consists of four long tendons entering into the hand for insertion onto the sides of proximal phalanges of the medial four digits, and functions as a metacar-pophalangeal joint flexor[3]. But in man since the upper limb is no more used for arboreal locomotion and weight, bearing, it undergoes retrogression as evidenced by a short belly and a long tendon, and the palm component of the muscle is represented by palmar aponeurosis[4].

The muscle has little functional utility to human hand, and when compromised, it does not cause any significant loss of functioning[5,6,7]. This fact has been utilized by the surgeons all over the world for various tendon graft, transfer and reconstruction surgeries. Moreover the tendon has a favorable length and diameter, easily accessible[8], and is considered by many surgeons to be the tendon of choice for harvesting.

The tendon of palmaris longus is commonly used as a graft in ligament and tendon reconstuctions[9,10], frontalis suspension in ptosis correction[11,12], in chronic injuries of flexor tendons of the fingers and the thumb[13,14], reconst-ruction of lip and chin defects[15], in management of facial palsy[16] and

recurrent stress incontinence[17]. It is also commonly utilized for tendon transfer surgeries like opponensplasty[18], lumbrical replacement for ulnar claw hand[19] and abductorplasty for severe thenar atrophy[20].

Considering the wide applications of the tendon, it is imperative to assess the length and width of the tendon in a patient before the tendon harvest. This gives an additional advantage of obtaining the graft by only two skin incisions[21]. Very few studies are available on the length and width of the tendon, and none in India as per the authors' knowledge. So this study was undertaken to measure the length and width of the tendon, and to find if the length of the tendon could be predicted from the length of the forearm in the Indian population.

Material and Methods

The tendon was studied in 70 upper limbs, belonging to 26 male and 9 female cadavers, used for routine undergraduate teaching. The superficial muscles in the flexor compartment of the forearm were exposed using the standard dissection protocol. The tendon of palmaris longus was identified and the following parameters were measured:

(i).The length of the forearm was measured from the tip of the olecranon process of ulna to the tip of ulnar styloid process using a measuring tape (Fig. 1).

Fig.1: Measuring the length of the forearm

(ii) The length of the tendon of palmaris longus was measured from the most distal point of the muscle tendon border to the point where the tendon crosses the line joining pisiform bone and scaphoid tubercle using a measuring tape (Fig.2).

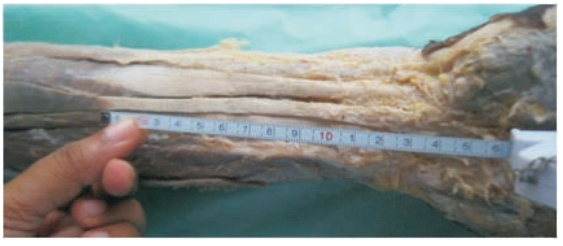

Fig. 2: Measuring the length of the tendon

(iii) The width of the tendon was measured 5 cm proximal to the apex of palmar aponeurosis, with the help of vernier calipers. (Fig. 3)

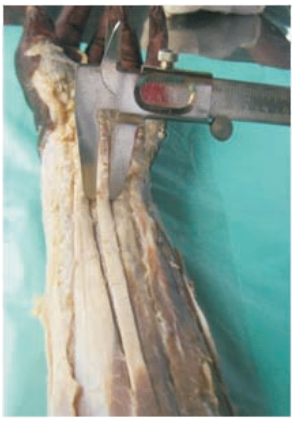

Fig. 3: Measuring the width of the tendon

Results

The muscle was absent on both the sides in one male and one female cadaver. It was absent on the right side in one male cadaver, and on the left side in one male and one female cadavers. The rest of the upper limbs showed the typical morphology of the muscle and the tendon.

The lengths of forearm and tendon, and the width of the tendon were measured and tabulated in table 1. In the males, the length of the forearm was ranging from 241 mm to 300 mm, and the mean was found to be 266.79±12.46 mm. In the females, the range was found to be 230 mm to 290 mm, and the mean was 256.53±15.90 mm.

Table 1: Forearm length, length and width of palmaris longus tendon, percentage ratio of tendon and forearm lengths.

Groups	No. of cases	Length of forearm (mm) Mean±SD	Length of Tendon (mm) Mean±SD	Width of tendon (mm) Mean±SD	Length of tendon/ Length of forearm x 100 Mean±SD
Males	48	266.79±12.46	162.19±15.48	3.22±0.77	60.78±4.94
Females	15	256.53±15.90	165.67±13.34	3.1±0.48	64.57±3.11
Total	63	264.35±13.93	163.02±14.97	3.19±0.71	61.69±4.81

The length of the tendon was ranging from 130 mm to 195 mm in the males, and the mean was 162.19±15.48 mm; whereas in the females the length ranged from 145 mm to 200 mm, with 165.67±13.34 mm as the mean.

The width of the tendon in the males had a range of 1.8 mm to 5.3 mm with a mean of 3.22±0.77 mm; and in the females the range was from 2.5 mm to 4.2 mm, and the mean was 3.1±0.48 mm.

Regression analysis was done, and a significant correlation between the length of the tendon and the length of the forearm was obtained in both the sexes in our study coinciding with the results of previous studies ($r= 0.513$; $p<0.001$ in males; $r= 0.786$; $p<0.001$ in females). (Fig. 4,5)

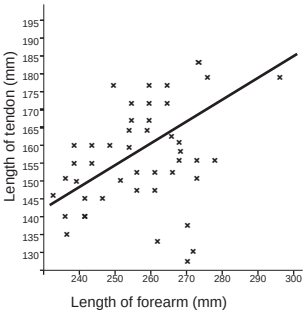

Fig. 4: Scatter diagram showing relationship between tendon length and forearm length in males (r= 0.513; p<0.001)

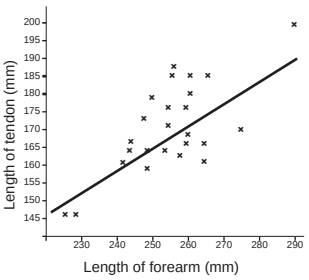

Fig. 5 Scatter diagram showing relationship between tendon length and forearm length in females (r= 0.786; p<0.001)

The mean percentage ratio of the length of the tendon and the length of the forearm was 60.78±4.94 in the males and 64.57±3.11 in the females, respectively, with an average of 61.69±4.81.

In contrast, regression analysis did not show any statistically significant correlation between the tendon width and the length of the forearm in both the males (r=-0.071; p>0.05) and the females (r=0.367; p>0.05). (Fig. 6,7)

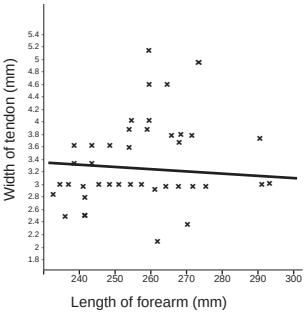

Fig. 6: Scatter diagram showing relationship between tendon width and forearm length in males (r= -0.071; p>0.05)

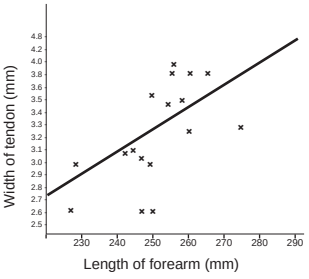

Fig. 7: Scatter diagram showing relationship between tendon width and forearm length in females (r= 0.367; p>0.05)

Discussion

Palmaris longus is seen only in therian mammals[22]. It is functionally more active in non-human primates with arboreal locomotion where the upper limbs were predominantly weight bearing[4], and is absent in higher apes like gorilla and chimpanzee[23]. In man, under the influence evolutionary changes, it presents numerous variations ranging from absence to duplication[24].

Morphogenetically, the development of the muscle and tendon is regulated by HOX genes and other transcription factors[25]. Tendons appear to arise from the limb mesoderm as tendon primordia before the emergence of the muscles[26]. The palmaris longus tendon develops in proportion to the length of the forearm determined before birth, resulting in significant correlation between the lengths of the tendon and the forearm[27,28].

In view of its increasing applications in several tendon graft and reconstruction surgeries, some authors tried to estimate its morphometrical parameters like length and width, in order to facilitate proper preoperative planning. Grechening et al., in 1999, determined the length and the thickness of the tendon using high resolution 10-12 MHz ultrasound probes[29]. Ito et al conducted a simple and cost effective study on the adult Japanese cadavers in 2001[30]. They obtained a statistically significant relation between the lengths of the tendon and the forearm.

The overall agenesis of the muscle and the tendon was 10% in our study. On comparison with results from cadaveric studies on other populations, our agenesis was similar to that reported in Malaysian population (9.67%)[31], but lower than the Iranians (29.6%)[32] and higher than the Japanese (4.1%)[30]. Side and sex differences were analyzed and were not significant.

The various parameters measured were correlated with the data of the previous workers and analyzed. The mean length of the forearm was 266.79±12.46 mm in the males and 256.53±15.90 mm in the females. The average obtained was 264.35±13.93 mm which was similar to 267±27 mm obtained in Malaysian population[31]. But it was higher than 229.8±17.1 mm in Japanese population[30], and lower than 284.7±1.53 mm in Iranians[32], and 275.4 mm in Afro-descendants[21]. The sex differences were analyzed and found to be statistically significant similar to the above mentioned studies.

The mean length of the tendon was found to be 162.19±15.48 mm and 165.67±13.34 mm in the males and females respectively. The average was 163.02±14.97 mm, and was similar to 162.0±19.5 mm in Malaysians[31]. But it was higher than that recorded in many other studies. It was reported to be 116.6±18.5 mm in Japanese[30], 136.2±6.66 mm in Iranians[32] and 119.9 mm in Afro-descendants[21].

The results of this study show that the length of the tendon could be estimated from the length of the forearm as follows:
Tendon length = (0.64xlength of forearm) - 8.03 in the males; and (0.66xlength of forearm) - 3.56 in the females.

If a longer graft is required, we can utilize the additional intramuscular part of the tendon[30] or additional 5 cm length of the palmar aponeurosis, as in the case of high flexor tendon injuries[33].

The mean width of the tendon was 3.22±0.77 mm in the males and 3.1±0.48 mm in the females. The average obtained was 3.19±0.71 mm, much lower than that obtained in previous studies. It was reported to be 4.7±1.2 mm in Malaysians[31], 4.2±0.8 mm in the Japanese[30], 4.0 ±1.98 mm in the Iranians[32] and 4.1±1.5 in the Afro-descendants[21]. Statistically significant correlation was not obtained between the width of the

tendon and the length of the forearm in our study. Most of the previous studies also noted that thewidth of the tendon was almost constant irrespective of the forearm length. This is because the tendon width is determined in its development according to acquired elements such as mechanical stress due to muscle strength.

Estimation of the tendon length has several advantages. Primarily it is useful in determining whether the tendon is long enough for the graft or reconstruction surgery in consideration. The second advantage is that it also helps to decide the level of proximal skin incision on the forearm for harvesting the tendon with only two skin incisions.

Conclusion

Palmaris longus tendon is the tendon of first choice for grafting and reconstruction surgeries. It is possible to estimate the length of the tendon available based on the length of the forearm prior to surgical intervention.

Acknowledgements

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References

1. Standring S. Gray's Anatomy, 39th edition, Elsevier-Churchill Livingstone, London,2005,876-877
2. Roqueline AGMF Aversi-Ferreira, Rafael Vieira Bretas, Rafael Souto Maior, et al., "Morphometric and Statistical Analysis of the Palmaris Longus Muscle in Human and Non-Human Primates," BioMed Research International, vol. 2014, Article ID 178906, 6 pages, 2014. doi:10.1155/2014/178906
3. Mc Minn RMH. In: Last's Anatomy, Regional and Applied, 9th edn, Churchill Livingstone London;1997, 89-90
4. Reimann AF, Daseler EH, Anson BJ, Beaton LE. The Palmaris longus muscle and tendon, a study of 1600 extremities. *Anat Rec* 1944;89:495-505
5. Thompson NW, Mockford BJ, Cran GW. Absence of palmaris longus muscle: a population study. *Ulster Medical Journal* 2001,70(1),22-24
6. Sebastin SJ, Lim AY, Bee WH, Wong TC, Methil BV. Does the absence of the palmaris longus affect grip and pinch strength? *J Hand Surg Br*. 2005 Aug;30(4):406-8
7. Soltani AM, Peric M, Francis CS, Nguyen TJ, Chan LS, Ghiassi A, *et. al*. The Variation in the Absence of the Palmaris Longus in a Multiethnic Population of the United States: An Epidemiological Study. *Plastic Surgery International* Vol 2012 (2012), Article ID 282959, 4 pages8
8. Troha F, Baibak GJ, Kelleher JC. Frequency of Palmaris longus tendon in North American Caucasians. *Ann Plast Surg*. 1990; 25: 477-89
9. Kaufman RA, Pacek CA. Pulley reconstruction using using Palmaris longus autograft after repeated trigger release. J Hand Surg Br. 2006:31(3):285-87
10. Bradley TM, Brown RE. Reconstruction of a Sagittal band and extensor tendon centralization using a Palmaris longus tendon graft. Plast. Reconstr. Surg. 1997;99:1176-1179.
11. Lam DS, Lam TP, Chen IN, Tsang GH, Gandhi SR. Palmaris longus tendon as a new autogenous material for frontalis suspension surgery in adults. Eye (Lond). 1996; 10 (Pt 1): 38–42.42
12. Naugle TC, Faust DC. Autogenous Palmaris longus tendon as frontalis suspension material for ptosis correction in children. *Am J Opthal* 1999; 127: 488-489.
13. Pulvertaft RG. Tendon grafts for flexor tendon injuries in the fingers and thumb; a study of technique and results. J Bone Joint Surg Br. 1956;38(1):175–94.
14. Wehbé MA. Tendon graft donor sites. J Hand Surg Am. 1992; 17(6):1130–2.
15. Carroll CM, Pathak I, Irish J, Neglian PC. Reconstruction of total lower lip and chin defects using the composite radial forearm-palmaris longus tendon free flap. *Arch Facial Plast Surg* 2000; 2(1): 53-6
16. Atiyeh BA, Hashim HA, Hamdan AM, Kayle DI, Musharafieh RS. Lower reconstruction and restoration of oral competence with dynamic Palmaris longus vascularised sling. *Arch Otolaryngol Head Neck Surg* 1998;124:1390-2
17. Poliak A, Daniller AI, Liebling RW. Sling operation for recurrent stress incontinence using the tendon of Palmaris longus. Obstet. Gynecol. 1984;63:850-854
18. Foucher G, Malizos C, Sammut D, Braun FM, Michon J. Primary Palmaris longus transfer as an opponensplasty in carpal tunnel release. J Hand Surg Br. 1991;16:56-60
19. Beine A. Modification of the "Wrap around" tendon anastomosis of fascia lata graft with a slim double tendon of Palmaris longus. Indian Jour. Lepr. 2000;72:246-247
20. Terrono AI, Rose JH, Mulroy J, Millender LH. Camitz Palmaris longus abductor plasty for severe thenar atrophy secondary to carpal tunnel syndrome. Jour. Hand Surg. Am. 1993;18:204-2062
21. Júnior LCA, Angelini FB, de Oliveira BC, Soares SA, Luiz Carlos Angelini LC, Cabral RH Use of the tendon of the palmaris longus muscle in surgical procedures: study on cadavers Acta Ortop Bras. 2012; 20(4): 226–229.
22. Straus WL. The homologies of the forearm flexors. Am. Jour. Anat. 1942;70:281-316
23. Vanderhooft E. The frequency and relationship between the Palmaris longus and the plantaris tendons. *Am J Orthop* 1996;25:38-41
24. Sankar KD, Bhanu PS, John SP Incidence of agenesis of palmaris longus in the Andhra population of India. Indian J Plast Surg. 2011; 44(1): 134-138.
25. Hall BK, Miyake T. All for one and one for all: condensations and the initiation of skeletal development. Bioassays 2000;22(2):138-47
26. Kardon G. Muscle and tendon morphogenesis in the avian hind limb. Development. 1998;128:4019-4032
27. Marecki B, Lewandowski J, Jacubowicz M. Formation of extensor digitorum muscle proportions before and after birth. Gegenbaurs Morphol. Jahrb. 1990;136:735-751
28. Alagoz MS, Uysal AC, Tuccar E, Tekdemir I. Morphologic Assessment of the Tendon Graft Donor Sites: Palmaris Longus, Plantaris, Tensor Fascia Lata. Journal of Craniofacial Surgery
29. Grechenig W, Clement H, Mayr J, Grechenig M. Ultrasound identification and size determination of the Palmaris longus tendon. Biomed. Tech. (Berl.) 1999;44:319-323
30. Ito MM, Akoi M, Kida MY, Ishii S, Kumaki K, Tanaka S. Length and width of the tendinous portion of the Palmaris longus: a cadaver study of adult Japanese. Jour. Hand Surg. Am. 2001;26:706-710
31. Manohar A, Rampal L. Novel Method to Estimate the Length of the Palmaris Longus Tendon. Malaysian Journal of Medicine and Health Sciences. 2013;9(2):19-24
32. Mobarakeh MK, Pasha MG, Moaghari poor M. *Variation, Length* and *Width* of *Tendinous Portion* of *Palmaris Longus* and *Forearm Length* and *Height:* Is *there* a *link?* A *Cadaver Study* of *Adult Iranians. Iran J Med Sci 2008;33(3):164-168*
33. Tolat AK, Stanley JK. The extended palmaris longus tendon graft. Jour. Hand Surg. Br. 1993;18:239-240

PUSHPAGIRI MEDICAL JOURNAL

✪ ORIGINAL ARTICLE

A comparative study of Early Onset versus Late Onset Preeclampsia

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Abstract

Objectives :a) To study the incidence of Early onset and Late onset preeclampsia at a tertiary care centre. b) To compare the risk factors and maternal outcome in mothers presenting with early and late preeclampsia. c) To compare the foetal and neonatal outcome in the two group of mothers. Study design: This was a one year prospective study conducted in the Departments of Obstetrics and Gynaecology and Neonatology at Pushpagiri Institute of Medical Sciences. Fifty nine mothers with preeclampsia were differentiated into Early onset preeclampsia (EOP) (<34 weeks gestation) *[n=33]* and Late onset preeclampsia (LOP) (≥34 weeks of gestation) *[n=26]*. Data about maternal risk factors, maternal complications, foetal and neonatal outcome were analysed and statistical significance determined. Results: Twenty five out of thirty three patients (75.75%) in the EOP developed severe preeclampsia while only sixteen out of twenty six patients (61.53%) in LOP developed severe disease. Maternal complications like oligohydramnios, abruption and postpartum haemorrhage developed more in EOP. More of foetal hypoxia (25% vs. 11.11%) occurred in EOP. Foetal demise (15.15%) occurred only in EOP. Despite expectant management 78.78% preterm deliveries occurred in EOP. Low birth weight and need for ventilation was noted to be more in neonates born to mothers with EOP. Conclusion: Classification of preeclampsia into Early and Late Onset preeclampsia has etiological and prognostic value. The identification and re-routing of patients with EOP from peripheral centres to a tertiary centre for better and effective management is necessary as more adverse maternal, foetal and neonatal outcome has been observed in this group.

Keywords: Early onset preeclampsia, Late onset preeclampsia, Maternal, foetal and neonatal – risk factors and outcome

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Introduction

Hypertensive disorders in pregnancy are an important cause for maternal morbidity and mortality. It is reported to be the second most common cause of maternal mortality worldwide and in Kerala by CRMD (Confidential Review of Maternal Death) 2006 – 2009. Globally, incidence of hypertensive disorders of pregnancy is 5-10%. Data collected by the National Eclampsia Registry (NER) shows the incidence of hypertensive disorders of pregnancy in India as 10.08% [1].

Preeclampsia is characterized by elevated blood pressure and proteinuria with associated organ involvement [2-4]. Recently investigators have begun to classify preeclampsia based on the period of gestation at which first onset of disease occurred. Early onset preeclampsia (EOP) is that which develops before 34 weeks of gestation and Late onset preeclampsia (LOP) is that which develops at or after 34 weeks of gestation [5-8]. The two subtypes have similar clinical presentation but studies indicate that they are associated with different predisposing factors, heritability, biochemical markers and different maternal, foetal and neonatal outcome [1,9].

Early onset preeclampsia (EOP) has been identified to be a placental disease and LOP as a maternal disease. EOP has a familial predisposition suggestive of genetic

factors and high recurrence risk. It is a result of abnormal placentation leading to foetal growth restriction and sequentially poor foetal and neonatal outcome. LOP arises due to metabolic risk factors of the mother such as obesity, chronic hypertension and diabetes. It has a normal placenta, therefore better foetal and neonatal outcome [1,9].

For preeclampsia, the complications often quoted are eclampsia, abruptio placenta, renal failure and DIC [10-13]. Foetal complications are foetal hypoxia leading to intrauterine growth restriction and death. Neonatal morbidity includes prematurity, low birth weight and asphyxia injury necessitating increased need of NICU admission [14,15].

Early Onset preeclampsia in particular confers a higher risk of maternal and foetal complications. Early delivery of the foetus is the only definitive treatment for this condition but this early termination is fraught with the risk of poor neonatal outcome [16, 17]. To counter this, expectant management is a strategy employed by Gynaecologists to improve perinatal outcome, however, this may lead to increased maternal complications [16,17].

Objectives

1. To look at the incidence of Early onset and Late onset presentation of preclampsia in a tertiary care centre
2. Comparison of risk factors and maternal outcome in mothers presenting with Early and Late onset preeclampsia.
3. Comparison of foetal and neonatal outcome in mothers presenting with Early and Late preeclampsia

Study Design

Setting:

Prospective study conducted in the Departments of Obstetrics and Gynaecology and the Neonatal Unit of Pushpagiri Medical College from the period of October 2012 to October 2013. Fifty nine antenatal patients with preeclampsia were included in this study out of a total of 1014 deliveries during this period.

Inclusion criterion:

Antenatal mothers with a blood pressure ≥ 140/90mm Hg at two occasions four hours apart after 20 weeks of gestation along with proteinuria were included. Fifty nine patients were included in the study and differentiated into cases of Early onset preclampsia (Gestation of <34weeks) and Late onset preclampsia (≥ 34 weeks).

Exclusion criterion:

Patients with Gestational Hypertension and Chronic Hypertension complicating pregnancy were excluded from the study.

On admission, maternal details, regularity of seeking antenatal care, POG at which BP diagnosed to be elevated, number of drugs used,associated medical problems, family and personal history were noted. Expectant management was done using antihypertensives, magnesium sulphate and steroids.Strict maternal and fetal surveillance by blood pressure monitoring, laboratory investigation,doppler studies and nonstress test were done. Delivery was expedited when maternal and fetal condition worsened. Data regarding maternal and foetal complications were noted. Neonatal data including birthweight, Apgar score, need for ventilation and surfactant use were noted.

Statistical analysis

Statistical analysis was done using Chi square test and p values were taken. A p value of < 0.05 was

Observation and Results

Table-1. Risk factors

Maternal characteristics / clinical factors		Early preeclampsia [n=33]		Late preeclampsia [n=26]		Chi (X^2) / p values
		Total	% ages	Total	% ages	
Age	≤ 21 years	1	03.03	0	-	2.02 / 0.154
	21-30 years	26	78.78	18	03.03	
	31-40 years	6	18.18	8	03.03	
	> 40 years	0	-	0	-	
Gravida	Primigravida	19	57.57	14	53.84	0.08 / 0.777
	Multigravida	14	42.42	12	46.15	
Profile of referral	In house patient	11	33.33	16	61.53	3.59 / 0.058
	Referred	22	66.67	10	38.46	
Severity of diseas (BP recording in mm Hg)	Mild (>140/90)	8	24.24	10	38.46	0.80 / 0.371
	Severe (>160/110)	25	75.75	16	61.53	
Associated Risk factors/ Co-morbidities	Gestational Diabetes	7	21.21	8	30.76	0.86 / 0.353
	Thyroid	2	06.06	3	11.53	0.23 / 0.634
	Renal	3	09.09	0	-	0.96 / 0.327
	Heart disease	2	06.06	0	-	0.31 / 0.577
	H/O prev. preeclamp.	3	09.09	2	07.69	0.08/ 0.772
	Fam. h/o HT	16	48.48	12	46.15	0.01/ 0.921
	Fam. h/o Diabetes	11	33.33	12	46.15	0.54/ 0.461
	Congenitally malformed fetus	3	9.09	0	-	2.66/ 0.102

Patients in both subtypes of preeclampsia presented more in the 21-30 years age group. Almost double (30.76% vs. 18.18 %) in the later age groups presented with late onset preeclampsia.

Early and late onset preeclampsia was manifested more in primigravida mothers than in multipara mothers (57.57 % vs. 42.42% and 53.84% vs. 46.15% respectively in the two groups) though not significant statistically.The greater proportion of patients with Early onset preeclampsia were referred from outside (33.33% being under regular follow-up vs. 66.67% referred from outside). However majority of patients with late preeclampsia were those attending antenatal clinics in this institution regularly (61.53% vs. 38.46%). This was statistically significant.

Associated risk factors like GDM, thyroid disease, family history of hypertension, preeclampsia in previous pregnancy were found to be similar in both study groups. Three foetuses with congenital anomalies (9.09%) were there in EOP group.

Table-2. Severity of the disease

	Early(n=33)		Late(n=26)		$\div^2$ /p value
	Totals	% age	Totals	% age	
Mild preeclampsia	8	24.24	10	38.46	0.800
Severe preeclampsia	25	75.75	16	61.53	0.371

Severe preeclampsia was found to be more in patients of Early than Late onset preeclampsia (75.75% vs. 61.53%) though no statistical significance was seen.

Table- 3. Indications for termination – LSCS / vaginal

	Early(n=33)		Late(n=26)	
	Totals	% age	Totals	% age
Maternal	13	52.00	16	61.53
Foetal	16	48.00	7	26.92
Maternal + Foetal	4	12.12	3	11.53

Indication of termination for fetal sake was more in early onset than late onset (48% vs 26.92%). The maternal indications for termination were more in late onset group (61.53% vs 52%).

Table-4. Maternal complications

	Early		Late		$\div^2$/ p- values
	Totals	% age	Totals	% age	
Oligohydramnios	5	15.15	3	11.53	0.16 / 0.689
Abruptio placentae	2	06.06	1	03.84	0.05 / 0.823
Post partum haemorrhage	3	09.09	0	-	0.96 / 0.327
Renal failure	1	03.03	0	-	0.01 / 0.920
Impending S/S of eclampsia	1	03.03	4	15.38	1.49 / 0.222
Eclampsia	1	03.03	1	03.84	0.31 / 0.577
Pulmonary oedema	1	03.03	0	-	0.01 / 0.920
Partial HELLP	1	03.03	0	-	0.01 / 0.920

Though not statistically significant, there is a higher percentage of complications like Oligohydramnios (15.15%), abruption placentae (06.06%), Post partum haemorrhage (09.09%) and renal complications (03.03%) in early onset pre-eclampia, the more severe complications like Pulmonary oedma and partial HELLP was also seen to occur in Early onset preeclampsia.

One patient in both groups developed convulsions (Eclampsia).

Table-5. Foetal complications

	Early n=32 *		Late n=27 **		
	Totals	% age	Totals	% age	$\div^2$/ p- values
Hypoxia (Doppler)	8	25	3	11.11	1.86/ 0.170
IUGR on ultrasound	12	37.5	15	55.55	1.92 / 0.965
* There were totally 33 mothers of whom 5 came with IUD. Of the remaining 29, 4 had twin deliveries, hence 32 foetuses were included. ** there were 26 mothers in the Late onset group with one pair of twins					
	n = 33		n=26		$\div^2$ / p- value
Fetal demise	5	15.15	0		4.30 / 0.038
Preterm delivery	26	78.78	12	46.15	4.14 / 0.040

Doppler studies identified hypoxia in 25% foetuses of early onset preeclampsia compared to only 11.11% in the other group however growth restriction was noted more in foetuses in the Late onset group (55.55%).

Despite expectant management in a tertiary centre, 26 (78.78%) preterm deliveries occured in the Early onset group and only 46.15% in late onset. This was statistically significant. All five fetal demises had occurred before referral,and were in EOP group.

Table 6. Neonatal complications

		Early n=32		Late n=27		
		Totals	% age	Totals	% age	
Birth weight	> 3.00	1	03.12	5	18.51	
	>2.500 – 3.000	2	06.25	8	29.62	
	2.000 – 2.499	3	09.75	8	29.62	
	1.500 – 1.999	17	53.12	6	22.22	
	1.000 – 1.499	7	21.87	0	-	
	< 1.000	2	06.25	0	-	
	$\div^2$ for trends / p-value for trends					18.47 / 0.00002
Apgar score <5	1 min	1	03.12	1	03.70	
	5 min	0	-	0	-	
Respiratory support	CPAP	19	59.37	2	07.49	17.25 / 0.00003
	Ventilation	3	09.37	0	-	2.66 / 0.102
	Surfactant		09.37	0	-	2.66 / 0.102
Death		1	03.12	0	-	

[LBW (Low birth weight babies) – babies with weight <2.500 kg (n=29 in EOP and n=14 in the LOP group.)

VLBW (Very low birth weight babies) – babies with weight <1.500 kg (n=9 in EOP and none in the LOP group.)

ELBW (Extremely Low birth weight babies) – babies with weight < 1.000 kg (n=2 in EOP and none in the LOP group)]

A majority of babies born to mothers with preeclampsia (both early and late) were low birth weight (birth weight < 2.500 kg). Twenty nine (90.62%) babies in the Early preeclampsia group and 14 (51.85%) in the Late preeclampsia group were Low birth weight babies. Very low birth weight babies were only seen in babies born to mothers who presented with Early preeclampsia. There were 13 babies (35.13%) who were very low birth weight.

Only EOP group had ELBW babies. The Chi square for trends was 18.47 and was highly significant (p= 0.00002)

In the EOP group 19 (59.37%) babies required only CPAP and only 3 (9.37) were ventilated. In the LOP group, there were 2 babies who needed CPAP and none needed ventilation. This difference was statistically significant.

One baby in each of the groups had perinatal asphyxia and one baby succumbed despite management.

Discussion

In our study conducted in this institution, the overall preeclampsia rate was 5.81%. Rate for EOP was 3.25% and rate for LOP was 2.56%. In a study conducted by Lisonkova S et al [6], the overall rate of preeclampsia was 3.1 %. The rate for EOP was 0.3% compared to 2.72% for LOP. The higher incidence of Early onset preeclampsia in this study was attributable to this institution being the tertiary referral centre in the region.

Though preeclampsia is described in the extremes of age groups, there were no such trends seen in our study.

In this study, the highest proportion of mothers were in the age groups of 20-30 year in both study groups (78.78% vs 69.23%). Primigravidae were more than multigravidae in both groups. (57.57% and 53.84%). There was no statistical significance.

Though not statistically significant, there was a higher percentage of gestational diabetes (30.76% vs 21.21%), thyroid disorders (11.53% vs. 6.03%) in LOP compared to EOP and also family history of hypertension, diabetes in LOP.

Lisonkova et al observed that risk factors like younger age, nulliparity and diabetes associated with LOP and risk factors like black race, hypertension and congenital anomalies were associated with EOP [6].

In this study three mothers with foetal anomalies were also observed in EOP group – anorectal malformation, congenital diaphragmatic hernia and left gangrenous lower limb. Four pair of twins in EOP group and one pair twin in LOP group was noted. Association of twinning as a risk factor specific to Early onset preeclampsia is yet to be proved.

Data analysed by Eun Jeong Jeong et al in China showed no significant difference in risk factors like maternal age, parity, family history of hypertension and diabetes between the two groups.

Referred patients constituted the majority in Early onset preeclampsia (66.6%). This is because obstetricians have identified that this subtype requires management in a tertiary centre for better maternal and perinatal outcome.

Among the two study groups more patients with EOP (75.75% vs 61.53%) progressed to severe preeclampsia and required early termination. In spite of expectant management with antihypertensives, magnesium sulphate and maternal and foetal monitoring, mothers with premature deliveries were more in EOP group (78.78% vs. 46.15%). This was statistically significant. This indicates progression of severity of disease in EOP could not be mitigated and required early termination to prevent maternal and foetal complication.

The incidence of maternal complications like abruption – 6.03%, PPH – 9.09%, renal failure, pulmonary edema and partial HELLP – 3.03% each occurred more in EOP. This was not statistically significant. One patient with placenta percreta underwent hysterectomy and another developed transient weakness of right upper limb. Hall et al [18] similarly observed a higher rate of maternal complications in EOP. According to this study, 20% mothers developed abruption placentae, 1.2% eclampsia, 1% had renal failure [18].

This study showed that foetal hypoxia as diagnosed by Doppler studies were more in EOP than LOP (25% vs 11.11%). There was no statistical significance. Foetal demise (15.5%) occurred in EOP and none in LOP. This was of statistical significance (p=0.038). This corroborates with studies by Lisenkova et al [6]. Murphy et al also reported 16% foetal demise rate [19]. It is to be noted that none of these babies who had intra-uterine demise had associated congenital morbidities. However a higher proportion of growth restricted foetuses were observed in LOP than EOP (55.55% vs37.5%). This did not concur with other similar studies.

Birth weight of the babies born to mothers with Early onset preeclampsia were more affected – could be due to the effect of longer duration of hypertension in the mother especially in the context of expectant management and increased incidence of premature deliveries. This was similar to the study by Long PA et al [20].

Asphyxiated babies were similarly low in both groups. Outcome of all babies in the EOP group was comparable to the LOP group despite being smaller and more premature. This was attributable to good on hand resuscitation and neonatal care available at the tertiary centre.

Despite 78.78% of premature deliveries in the Early onset group, these babies could be significantly managed well with minimal respiratory support in the form of CPAP. This was attributable to effect of antenatal steroid therapy and strict foetal monitoring during expectant management.

Conclusion

The classification of preeclampsia into Early and Late onset based on period of onset has etiological and prognostic importance. This study points out the greater adverse maternal and perinatal impact due to Early onset preeclampsia. This study shows how early diagnosis and referral of a patient with Early onset preeclampsia to a tertiary centre from primary and secondary care centres plays a major role in improving maternal and perinatal outcome. Expectant management at a tertiary centre gains time for better neonatal outcome. However, as the severity of disease progresses, the risk of maternal and foetal complication persists. So we conclude that early referral, expectant management, timely intervention by the obstetrician and resuscitation by neonatologist is the key for successful outcome in early onset preeclampsia.

References

1. Gupte S, Wagh G. Preeclampsia – Eclampsia. Journal of Obst. and Gynaecology of India (Jan-Feb. 2014) 64 (1):4-13.
2. Steegers EAP, Von Dadelszen P, Duvekot JJ, Pijnenborg R, Pre-eclampsia. Lancet 2010; 378:631-44.
3. Hutcheon JA, Lisonkova S, Joseph KS. The epidemiology of pre-eclampsia and the hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecolg 2011; 25:391-403.
4. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005; 365: 785-99.
5. Ness RB, Roberts JM. Heterogenous causes constituting the single syndrome of preeclampsia: A hypothesis and its implication. Am J Obstet Gynecol 1996; 175: 1365-70.
6. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early – versus late – onset disease. Am J Obstet Gynecol 2013; 209:544.e 1-12.
7. Roberts JM, Hubel CA. The two stage model of pre-eclampsia: variations on the theme. Placenta 2009;30 (Supp A):S32-7.
8. Von Dadelszen P, Magee LA, Roberts JM. Subclassification of pre-eclampsia. Hypertens Pregnancy 2003; 22:143-8.
9. Raymond D, Peterson E. A Critical review of Early Onset and Late onset Preeclampia. Obstet Gynecol Surv. 2011 Aug; 66(8):497-506.
10. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF, WHO analysis of causes of maternal death: a systematic review. Lancet 2006; 367:1066-74.
11. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. Obsstet Gynecol 2009; 113:1299-306.
12. Knight M. Eclampsia in the United Kingdom. 2005. BJOG 2007; 114:1072-8.
13. Ananth CV, Savitz DA, Williams MA. Placental abruption and its association with hypertension and prolonged rupture of membranes: a methodologic review and meta-analysis. Obstet Gynecol 1996; 88:309-18.
14. Basso O, Rasmussen S, Weinberg CR, Wilcox AJ, Irgens LM, Skjaerven R. Trends in fetal and infant survival following preclampsia. JAMA 2006; 298:1357-62.
15. Friedman SA, Schiff E, Kao L, Sibai BM. Neonatal outcome after preterm delivery for pre-eclampsia. Am J Obstet Gynecol 1995; 172:1785-8; discussion 8-92.
16. Paruk F, Moodley J. Maternal and neonatal outcome in early- and late-onset pre-eclampsia. Semin Neonatol 2000; 5:197-207.
17. Bombrys AE, Barton JR, Nowacki EA, et al. Expectant management of severe preeclampsia at less than 27 weeks gestation: maternal and perinatal outcomes according to gestational age by weeks at onset of expectant management. Am J Obstet Gynaecol 2008; 199:247.e1-6.
18. Hall DR, Odendaal HJ, Steyn DW et al. Expectant management of early onset, severe preeclampsia: Maternal outcome.Br J Obstet Gynaecol 107:1252 – 1257,2000
19. Murphy DJ,Stirrat GM. Mortality and morbidity associated with early – onset preeclampsia. Hypertens Pregnancy s2000; 19(2):221 – 31.
20. Long PA, Abell DA, Beischer NA. Fetal growth retardation and preeclampsia. Br J Obstet Gynaec. 1980; 87:13-18.

✪ ORIGINAL ARTICLE

Antibacterial activity of gymnemic acid – chitosan nanoparticles against fecal contaminant, *E. Coli*

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Abstract

***Escherichia coli* is a gram-negative, facultative anaerobic, rod-shaped bacterium of the genus *Escherichia* that is commonly found in the lower intestine of warm-blooded organisms. Most *E. coli* strains are harmless, but some serotypes can cause serious food poisoning in their hosts, and are occasionally responsible for product recalls due to food contamination. In the present study, Gymnemic acid - chitosan nanoparticles were prepared and this combination was applied as an antibacterial agent against common food pathogen, *E. coli*. The morphology of the Gymnemic acid – Chitosan nanoparticles were studied by scanning electron microscopy. These unique nanoparticles were used for checking antibacterial activity by well diffusion method and time kill assay. Needle shaped nanoparticles were obtained from the SEM image. The Gymnemic acid showed antibacterial activity against *E. coli* in well diffusion method. The zone of inhibition seen around the well with Gymnemic acid of 2.5mg in 100µl was 2cm and 1.25mg in 100µl was 1.7cm. The antibacterial activity of nanoparticles by time kill assay was increased at different time intervals such as 0 hour, 6 hour and 24 hour when compared to *E. coli* control. The bacterial reduction by Gymnemic acid and Gymnemic acid chitosan nanoparticles was 99.9% and 99.4% at 24 hr incubation.**

Keywords: Gymnemic acid, Chitosan nanoparticles, *E. coli,* Antibacterial activity, Bacterial reduction.

Introduction

Plant derived active molecules against the survival of pathogenic bacteria is an interesting and progressively evaluating aspect. Gymnemic acid, an anti-sweetener, combined with a biocompatible polymer is exploited in this study for revealing its antibacterial property against *E. coli*. The conjugation of molecules with biocompatible polymers will improve the stability of the molecules and also the separation after treatment in the bacterial suspensions. The presence of various secondary metabolites like steroids, alkaloids, phenols, flavonoids, coumarins, saponins, tannins and triterpenoids are the active principles work against various bacteria like Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus vulgaris, Bacillus subtilis, Enterococcus faecalis, Micrococcus luteus, Staphylococcus aureus, Streptococcus pneumoniae (Naidu et.al 2013). **Gymnemic acids** are glycosides isolated from the leaves of *Gymnema sylvestre* (Asclepiadaceae) (Kinghorn and Compadre 1991). ***Gymnema sylvestre*** is a herb native to the tropical forests of southern and central India and Sri Lanka. The anti-sweetener property is attributed to the eponymous Gymnemic acids. *G. sylvestre* has been used in herbal medicine as a treatment for diabetes for nearly two millennia and though there is insufficient scientific evidence to draw definitive conclusions about its efficacy (Yeh, et.al 2003). *G. sylvestre* leaves contain triterpene saponins belonging to oleanane and dammarene classes. Oleanane saponins are Gymnemic acids (Kinghorn et.al 2001).

Escherichia coli, or *E. coli*, is a large group of bacteria that exists in many forms. *E. coli* can exist as pathogenic or non-pathogenic – that is, harmful or non-harmful. Most pathogenic *E. coli* produce a Shiga

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toxin, and are therefore designated as Shiga toxin-producing *E. coli*, or STEC. Ingestion of this pathogen can cause diarrhoea, vomiting, and abdominal cramps, which usually occur 2-8 days after consumption. A mild fever sometimes develops, along with the possibility of infection. Hemolytic uremic syndrome (HUS), a life-threatening complication that causes kidney failure, is diagnosed in 5-10% of STEC cases (Takikawa, et.al 2002).

Chitosan is a linear polysaccharide composed of randomly distributed â-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). It is a biocompatible and biodegradable polymer. Chitosan is utilised for many biomedical, agriculture and environmental applications (Shahidi, et.al 1991). Nanoparticles of chitosan conjugated with certain active molecules and their applications gained immense importance recently. In the present study, anti bacterial activity of Gymnemic acid was utilised against *E. coli*, which is the major contaminant of drinking water, juices and other drinks. The application of Gymnemic acid directly in to these drinks will deteriorate the quality of the product. It is also difficult to remove Gymnemic acid from water or other drinks after the treatment. Thus Gymnemic acid was conjugated with chitosan nanoparticles for maintaining the quality of the drink and also for the cost effective and efficient removal of particles after reducing the bacterial count.

Methods

Preparation and morphological characterization of Gymnemic acid – Chitosan nanoparticles

Chitosan nanoparticles were prepared by ionic gelation method (Calvo *et al*, 1997). Gymnemic acid – chitosan nanoparticles were prepared by dissolving 40mg of Gymnemic acid into chitosan solution and stirred for 30minutes at 400 rpm using magnetic stirrer. 1mg/ml concentration of pentasodium tripolyphosphate (TPP) was added drop by drop into the chitosan – Gymnemic acid solutions with constant stirring until the nanoparticles were formed. The nanoparticles were obtained by centrifugation at 10000 rpm for 30 minutes. After the centrifugation, the pellets (nanoparticles) were collected and dried on a glass slide. Stored the nanoparticles and supernatants for further studies. The morphology of the Gymnemic acid – Chitosan nanoparticles were studied by scanning electron microscopy (SEM) (JEOL Model JSM - 6390LV).

Antibacterial activity of Gymnemic acid and Gymnemic acid - chitosan nano particles against *E. coli* by well diffusion method

Petriplates containing solidified nutrient agar with five wells were swabbed with 25922 ATCC *E. coli* culture. Gymnemic acid –chitosan nanoparticles of 10.3 mg and Gymnemic acid of 10mg were dispersed in 1ml deionized water separately to prepare nanoparticles and Gymnemic acid stocks. 500µl samples from each stock were serially diluted two times with 500µl water. 100 µl from each dilution was added in to the respective wells on the nutrient agar plate. 100µl of sterile deionized water was loaded in to another well and considered as blank. After 24 hour incubation the plate was observed for the zone of inhibition (Pasha, et.al 2002).

Evaluation of antibacterial activity of Gymnemic acid – chitosan nanoparticles by time kill assay

Three sterile 2ml eppendorf tubes were taken. Samples were prepared, first sample 10.3mg of chitosan – Gymnemic acid nanoparticles and 10mg of Gymnemic acid were dispersed in 1ml deionized water to prepare nanoparticles and Gymnemic acid stocks. 500µl sample from each stock were serially diluted two times with 500µl water. Then 100µl of sample was taken from the last dilution. To that 100µl of 25922 ATCC *E. coli* culture was added. 800µl of peptone water was added to each eppendorf tube. The last sample was blank, prepared by 100µl 25922 ATCC *E. coli* culture in 900µl peptone water. 100µl sample was taken from each tube and spread on the EMB agar plate after 0 hour, 6 hour and 24 hour incubation. The plates were kept in the incubator at 37^{O}C for 24 hours. The bacterial count was taken using the samples from all the tubes (Chad, et.al 1999). The number of surviving microorganisms in the peptone water was determined by plate count method at different time intervals and enumerated. The percentage reduction of microbial population when compared with positive control for each time interval was calculated. The change was determined as follows: (Oladosu, et.al 2013).

% Reduction = count in the positive control- count at particular time interval x 100Count in the positive control

Results

Preparation and morphological chara- cterization of Gymnemic acid – Chitosan nanoparticles

Gymnemic acid-chitosan nanoparticles were prepared and the yield obtained was 82.5 % ***(fig: 1A and fig 1B)***. Needle shaped nanoparticles of 70nm width were obtained from SEM image ***(fig: 2)***

Detection of anti bacterial activity of Gymnemic acid and Gymnemic acid - chitosan nanoparticles by well diffusion method

Gymnemic acid has anti bacterial activity against commom food pathogen *E. coli.* The zone of inhibition was observed around the wells with

Gymnemic acid of two dilutions. The zone diameters were 2 cm (2.5mg/100µl) and 1.7cm (1.25mg/100µl) each. There was no zone of inhibition observed around the wells with Gymnemic acid – chitosan nanoparticles ***(fig: 3, table 1).***

Evaluation of antibacterial activity of Gymnemic acid – chitosan nanoparticles by time kill assay

Gymnemic acid – chitosan nanoparticles and Gymnemic acid showed antibacterial activity against *E. coli* in peptone water. The percentage reduction of *E. coli* count by Gymnemic acid chitosan nanoparticles when compared to positive control at zero hour was 1.8%, 6 hr was 91% and 24 hr was 99.4%. The percentage reduction of *E. coli* count by Gymnemic acid when compared to positive control at zero hr was 3.6%, 6hr was 97% and 24 hr was 99.9% **(table: 2)**.

Figures

Fig. 1A: Dried Gymnemic acid chitosan- nanoparticles

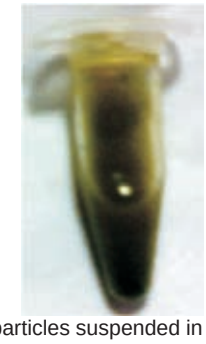


Fig.1B: Nanoparticles suspended in deionized water

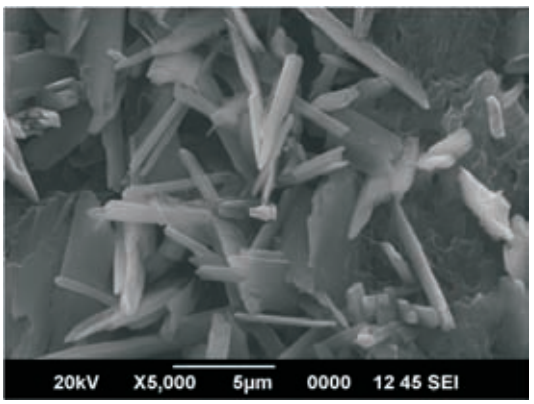
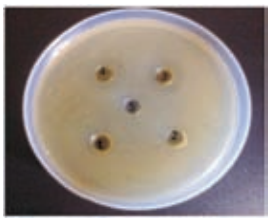


Fig. 2: Scanning electron micrograph of Gymnemic acid - chitosan nanoparticles. Scale bar =5 µm



1. Gymnemicacid chitosn nanoparticle is 2.5mg (100µl)
2. Gymnemic acid chitosan nanoparticle is 1.25mg (100µl)
3. Gymnemic acid is 2.5mg (100µl)
4. Gymnemic acid is 2.5mg (100µl)
5. Distilled water (100µl)

Fig. 3: Antibacterial activity of Gymnemic acid against E. coli

Tables:

Table 1: Antibacterial activity of Gymnemic acid and Gymnemic acid–chitosan nanoparticles against E. coli

Well no.	Samples	Zone of inhibition Diameter (mm)
1	Gymnemic acid - chitosan nanoparticle (2.5 mg/100 µl)	-------
2	Gymnemic acid – chitosan nanoparticle (1.25 mg /100 µl)	-------
3	Gymnemic acid (2.5 mg /100 µl)	1.7 cm
4	Gymnemic Acid (1.25 mg /100 µl)	2 cm
5	Distilled water	-------

Table 2: The Percentage reduction of E. coli count by Gymnemic acid and Gymnemic acid – chitosan nanoparticles compared to positive control E. coli

Positive control	Samples	% Reduction at 0hr	% Reduction at 6hr	% Reduction at 24hr
E. coli	Gymnemic acid-chitosan nanoparticles with *E. coli*	1.8	91	99.4
	Gymnemic Acid With *E. coli*	3.6	97	99.9

Discussion

E. coli is the name of a type of bacteria that lives in the intestines. Most types of *E. coli* are harmless. However, some types can make you sick and cause diarrhoea. One type causes traveller's diarrhoea. The worst type of *E. coli* causes bloody diarrhoea, and can sometimes cause kidney failure and even death. These problems are most likely to occur in children and in

adults with weak immune systems (Hudault, et.al 2001). *E. coli* spreads to the human food chain through the faeces of these animals. Bacteria in diarrhoea stools of infected people can be passed from one person to another if hygiene or hand washing habits are inadequate. This is particularly likely among toddlers, with family members and playmates of these children at high risk of becoming infected (Hudault, et.al 2001). Gymnemic acid was utilised in this study against the survival and duplication of *E. coli*.

Chitosan possesses positive charge due to the amino group present in it. Gymnemic acid has negative charge due to the -OH and -COOH group. So chitosan and Gymnemic acid bind together and form Gymnemic acid – chitosan complex. Due to this property, Gymnemic acid - chitosan nanoparticles can be prepared. This combination is applied as an antibacterial agent against common food pathogen, *E. coli*. In this work, Gymnemic acid – chitosan nanoparticles were prepared by ionic gelation method (Calvo, *et.al 1997*). The colour of the nanoparticles was green due to the Gymnemic acid present in it. The morphology of the nanoparticles was studied by scanning electron microscope (SEM). Nanoparticles of 50 nm were obtained from SEM image. 33 mg of nanoparticles were obtained when 25 mg/25 ml of chitosan solution and 40 mg of Gymnemic acid were used.

The direct addition of Gymnemic acid as an antibacterial agent will change the quality of water and also difficult to remove Gymnemic acid from drinking water or other drinks after the treatment. Gymnemic acid – chitosan nanoparticles can be directly used because these particles can be removed by centrifugation after treatment. Thus Gymnemic acid – chitosan nanoparticles maintain the quality of drinks and are not harmful to the human health (Bhavani and Nisha 2010). Chitosan is a polysaccharide, acts as a supporting material for Gymnemic acid. Gymnemic acid showed antibacterial activity against *E. coli* in well diffusion method. *G. sylvestre* can be predicted to remain an essential component in the new secondary metabolites and its pharmacological activities. Its leaf extracts exhibit broad spectra of antimicrobial activity (Gupta and Singh 2014). The zone of inhibition was seen around the wells in which Gymnemic acid of 2.5mg in 100 µl (2cm) and 1.25 mg in 100 µl (1.7cm) but no zone of inhibition was obtained for Gymnemic acid – chitosan nanoparticles. This was because the nanoparticles cannot and pure Gymnemic acid can diffuse out through solid agar media. Earlier studies stated that Gymnemic acid showed antibacterial activity against different strains. The petroleum benzene, ethanol, and aqueous leaf extract of *Gymnema sylvestre* were assayed *in vitro* searching for antimicrobial activity against human pathogenic microorganism (*Escherichia coli, Vibrio cholera, Streptococcus mutans, Staphylococcus aureus, Candida albicans* and *Aspergillus niger).* Different solvents Extract of Gymnema leaf and isolated Gymnemic acid were assayed by *in vitro* screening for antimicrobial activity on human pathogen by using the well diffusion method (Gupta and Singh 2014).

When the nanoparticles suspended in peptone water, chitosan absorbs water and pores on the surface of nanoparticles will be wide opened. The antibacterial potential of various nanoparticles was reported against *Pseudomonas aeruginosa, Klebsiella sp. Streptococcus pneumoniae, Staphylococcus aureus* and *Streptococcus sp* (Gokulakrishnan et.al 2012). This nanoparticulate system is favourable for the interaction of Gymnemic acid with bacteria. The antibacterial activity of plant extract might be related to the action of its antibiotic compounds or to the presence of metabolic toxins include gallocatechins, delphinidin, cyanidin, gallic acid, ellagic acid, pelargonidin and sitosterol, which are very well known for their therapeutic properties (Choi *et al.,* 2011). The antibacterial activity of nanoparticles by time kill assay was increased at different time intervals such as 0hour, 6 hour and 24 hour when compared to *E. coli* control. The bacterial reduction by Gymnemic acid and Gymnemic acid chitosan nanoparticles was 99.9% and 99.4% at 24 hr incubation, that states the efficiency of nanoparticles in suspension than solid agar media. Eventhough, the percentage reduction of bacterial count was equal during both treatments, non conjugated Gymnemic acid introduces a green colour and alters the taste of the drinks that deteriorates the quality. The separation of non conjugated Gymnemic acid from the media requires several tedious and toxic precipitation procedures that can be avoided in Gymnemic acid chitosan nanoparticulate systems.

The antimicrobial activity of triterpene saponins was found to be mainly dependent on their olefinic structures and the number of sugars, depending on the type, their linkage to each other, and location within the molecule. The availability of a longer sugar chain and the number of hydroxyl groups lead to an increase in activity. On the other hand, methylation of at least one of the hydroxyl groups may abolish the activity as evidenced by the observation that methoxylated derivative ilwensisaponin C may lose its activity. In addition, monodesmosidic saponins, in which the sugar units are attached to the aglycone at the C-3 position, are more potent in this antimicrobial system (Tatli and Akdemir 2005). In the present study, Gymnemic acid and Gymnemic acid – chitosan nanoparticles showed the antibacterial activity against common food pathogen *E. coli.* These nanoparticles can be used as an antibacterial agent in drinking water and other fruits juices and soft drinks for killing the fecal contaminant, *E. coli.*

Conclusion

Gymnemic acid – chitosan nanoparticles have the antibacterial activity against common food pathogen *E. coli.* These nanoparticles can be used as an antibacterial agent in drinking water and other soft

drinks for killing fecal contaminant, *E. coli.* Gymnemic acid can be directly added in to drinking water for treatment but it changes the colour and odour of the water. This Gymnemic acid can be removed by chemicals after treatment but it is more toxic and difficult to separate. So the Gymnemic acid – chitosan nanoparticles can be used directly because these nanoparticles will not be dissolved in water and will not change the pH, colour and smell. The raw materials for nanoparticle preparation were economical and non toxic. Thus Gymnemic acid – chitosan nanoparticles maintain the quality of drinks and are not harmful to the human health.

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References

1. Beverly C, Sudarsanam G, Antimicrobial activity of *Gymnema sylvestre.* Journal of Acute Disease 2013; 52: 16-28.
2. Bhavani AL, Nisha J, Dextran the polysaccharide with versatile uses, International Journal of pharmaceutical and Biosciences. 2010, 4: 569-573.
3. Calvo P, Remuna C, Lopez JL, Alonso VJ, Novel hydrophilic chitosan - poly ethylene oxide nanoparticles as protein carriers, Journal of Applied polymer science. 1997, 63-125.
4. Chad R, Keitha A, Susan L, Modified time kill assay against multi drug-resistant Enterococcus faecium with novel antimicrobial combination, International Journal of microbiology. 1999, 3: 4-7.
5. Gokulakrishnan R, Ravikumar S, Anandha R, In vitro antibacterial potential of metal oxide nanoparticles against antibiotic resistant bacterial pathogens, Asian pacific Journal of tropical disease. 2012, 2: 411-413.
6. Gupta P, Singh P, Antimicrobial activity of Gymnemic acid on pathogens – *Gymnema sylvestre*, International Journal of current microbiology and applied science. 2014, 3: 40-45.
7. Kinghorn A, Compadre M, Less Common High-Potency Sweeteners, In Nabors, Lyn O'Brien, Science of *Alternative Sweeteners.* 2001, 209-33.
8. Naidu KG, Naidu CS, Sujatha B, In vitro antibacterial activity and phyto chemical analysis of leaves of Gymnema sylvestre, International Journal of pharma technology. 2013, 5: 1316.
9. Oladosu P, Isu NR, Ibrahim K, Okolo P, Oladepo DK, Time kill – kinetic antibacterial study of Acacia nilotica, African journal of microbiology Research. 2013, 7: 5248-5252.
10. Pasha C, Sayeed S, Ali S, Khan Z. Medical microbiology, a guide to microbial infections, pathogenesis, immunity, laboratory diagnosis and control 2009, 33: 59-64.
11. Takikawa, Akiko, Abe K, Yamamoto M, Medical microbiology, a guide to microbial infections, pathogenesis, immunity, laboratory diagnosis and control. **2009,** 33: 59-64.
12. Tatli I and Akdemir ZS, Antimicrobial and antimalarial activities of secondary metabolites from some *Turkish verbascum* species, Journal of pharmaceutical science. 2005, 39: 84-92.
13. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS, Systematic review of herbs and dietary supplements for glycemic control in diabetes. 2003, 26: 77–94.

PUSHPAGIRI MEDICAL JOURNAL

✪ ORIGINAL ARTICLE

Clinical Profile of Attention deficit hyperactivity disorder in children attending Child Development clinic

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Abstract

Aims: To study 1) the clinical profile of attention deficit hyperactivity disorder (ADHD) in children attending child development clinic(CDC) and 2) the relationship between ADHD and sociodemograpic and cultural factors. Design: Cross sectional study. Setting: CDC of the Department of Pediatrics, Pushpagiri Institute of Medical sciences and Research Centre - a tertiary care medical college hospital. Methodology: Children 7yrs to 15 yrs referred to the Child Development Clinic of the Department of Pediatrics for symptoms of hyperactivity, inattention and impulsivity were taken as subjects after careful analysis. Conners' Parent Rating Scale - revised (s) was used for selection. Control group was taken from the children visiting the Pediatric outpatient department for minor diseases and immunization. 52 children were analysed during a period of one year (March 2010 - Feb 2011). Results: All children belonged to the combined group of ADHD. Statistically significant factors promoting ADHD were nuclear families, children living abroad, family disharmony, and substance abuse in parents. Excessive television viewing and sibling rivalry, junk food consumptionwere observed in affected children.Neonatal hyperbilirubinemia with phototherapy and pregnancy induced hypertension were the other significant factors observed. Conclusion: All children had combined ADHD. Children from nuclear families and non resident Indians were significantly affected with ADHD. Pregnancy induced hypertension and neonatal hyperbilirubinemia requiring phototherapy were other significant factors observed.

Keywords: ADHD, Hyperactive children, Nuclear families, Non resident Indians.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood, mainly affecting school aged children worldwide(1). It is the most extensively studied chronic mental disorder of childhood leading to academic under achievement, poor interpersonal relationship and low selfesteem. In spite of improved living conditions and high literacy rate in Kerala the disorder is found to be increasing, the reasons for which have not been adequately studied. The aim of the study was to find out the clinical profile of ADHD in children attending Child Development Clinic and its relationship between sociodemograpic and cultural factors.

Methods

This was a cross sectional study conducted in the child development clinic of the Department of Pediatrics of Pushpagiri Medical College Hospital during a period of one year(March 2010 to Feb 2011).The study group consisted of children showing features of hyperac tivity,impulsivity and in attention in the age group of 7 to 15 years.The inclusion criteria were childrenwith normal neurological and health status with features of ADHD for a period of at least 6 months.Children less than 7years (for the ease of sample selection) and above 15 years(since the upper limit of pediatric population of the institute is 15 years),those with hearing and or visual impairment, mental retardation, chronic systemic diseases,gross neurological abnormali ties,epilepsy, autism and other pervasive developmental disorders, long term drug therapy, physical or sexual abuse, and substance abuse were excluded from the study .

The controls for the study group were selected age and sex matched from the pediatric outpatient department.

During the various continuing medical education programmes conducted by the department in the previous two months prior to the starting of the study, an awareness was created among the attending medical officers of private and government sector regarding ADHD and the study. Personal letters were sent requesting to direct children showing hyper activity, impulsivity and inattention to the pediatric department of the medical college. After detailed history and physical examination to exclude chronic illnesses, sleep impairment and child abuse, the study group was selected. For all children investigations to exclude anemia, tuberculosis and thyroid disorders were carried out. Relevant investigations were done to selected group as needed. Screening for vision and hearing was carried out for all and specialists, help was sought in doubtful cases.

Of the sixty children selected, two had hearing impairment, three were anemic and three of them lost follow-up. The remaining52 children were evaluated by the clinical psychologist. Of these five children already diagnosed to have ADHD and were on treatment, were continued in the study.

The parents of the study group childrenwere provided by using Conners' Parent Rating Scale - Revised (S),a four page form, the first page of which consisted of twenty seven questions. (2) They were asked to rate each question according to the child's behavior in the last month and to circle the best answer for each one as 0,1,2,3. The circled scores were then transferred into appropriate scales on the middle form and totals of each scale(A-oppositional,B-inattention, C -hyperactivity D- ADHD index) were calculated at the bottom of the page.

The total of each scale (A to D) was then transferred to graphical representation for boys and girls and as 5 columns age wise (3 to 5 years, 6 to 8 years, 9 to 11 yrs,12 to 14 years, 15 to 17 years as column 1,2,3,4,5 respectively). Each of these columns were then converted to standardized T scores, the value above65 was calculated to be significant.

The socioeconomic and demographic variables were collected from parents on pretested proforma. Statistical significance was derived using Chisquare and Fisher extact test.

Results

The mean age of the children (total 52) in this study was 9.38 years with standard deviation of 1.87. The controls were age and sex matched and the majority belonged to upper middle class (80% study group, 75% control group) representing the population of the area. All ADHD children revealed combined type of involvement. Conners' rating scale of the study group was above 65 and of the control group was <40 for hyperactivity, inattention and impulsivity. For disorganization 100% of study group revealed value >65 compared to 6(11.5%) of control group (value <40). 27(52%) of ADHD were in the age group 7 to 9 yrs, 23(44.3%) between 10 to 12 yrs and 2(3.8%) between 13 and 15 yrs. Male to female ratio was 2.3:1(36 boys,16 girls). 31 (59.6%) of the study group were in the primary grade in school and 19 (36.5%) in the upper primary compared to 26 (50%) and 23(44.2%) respectively in the control group (p value0.00). Poor scholastic performance was observed in 25(48%) children with ADHD compared to none in the control group. Average scholastic performance was observed in 22 (42.3%) and good performance in 5(9.6%) in the ADHD group. The corresponding values for controls were 16(30.7%) and 36(69.2%) all these revealing statistically significant poor scholastic performance in ADHD children (p value 0.000). 45(86.5%) of the study group were creating school problems like classroom inattention, disturbing and bullying other children as against 3(5.76%) in the control group (p value 0.000). Excessive television watching for 6 to 8 hrs was observed in 51(98%) of the ADHD group compared to 24(46%) of the control group.(p value 0.000).45(86.5%) of the study group children had sibling rivalry (none among the control)(p value 0.000).

Table I reveals the statistically significant problems in ADHD children comparedto controls.

Table I: Problems of ADHD children (n=52

Problem	ADHD group	Control group	p value
• **Class room**			
Primary (1 to 4 std)	31(59.6%)	26(50%)	
Upper primary (5 to7 std)	19(36.5%)	24(46.1%)	0.00
• Poor School performance	25(48%)	Nil(0%)	0.000
• School problems	45(86.5%)	3(5.76%)	0.000
• Excessive TV watching	51(98%)	24(46.1%)	0.00
• Junk food eating	45(86.5%)	32(61.5%)	0.000
• sibling rivalry	45(86.5%)	Nil(0%)	0.000

36 (69.2%) of the ADHD group had nuclear family compared to 18 (34.6%) of the controls which was significant. Parenting patterns (both parents available at station, one parent care with the other abroad or cared only by grandparents) did not reveal any significance. On analyzing the place of living, 30(57.6%) of ADHD group were living abroad in contrast to 6(11.5%) from the control group (p=0.000) Educational status of the parents, working mother's as well as fathers, occupational status were not at all significant in perpetuating ADHD.But substance abuse among fathers as smoking and alcoholism (63.4% in ADHD, 11.5% in control group) revealed significant relation in ADHD (p= 0.000).

Family disharmony was observed in 40(76.9%) children of ADHD group but only 3.8% in the control group (p=0.000). Statistical significance was observed with antenatal complications mainly pregnancy induced hypertension.The mode of delivery whether normal or

caesarian was not a significant factor. Among the post natal events 13 (25%) in the study group had neonatal hyper bilirubinemia requiring phototherapy as against none in the control group (p= 0.000).Regarding past medical history there was no significant difference between the two groups.

Table II reveals the statistically significant socio-economic and demographic factors influencing ADHD.

Table II:Socioeconomic &demographic factors influenzing ADHD

No	Factors	ADHD group	Control group	P value
1	Nuclear family	36(69.2%)	18(34.6%)	0.000
2	Children living abroad	30(57.6%)	6(11.5%)	0.000
3	Substance abuse (father)	33(63.4%)	6(11.5%)	0.000
4	Family disharmony	40(76.9%)	2(3.8 %)	0.000
5	Mothers with PIH	16(30.6%)	5(9.6%)	0.02
6	Neonatal hyperbilirubinemia	13(25%)	Nil(0%)	0.000

Follow up though advised could be possible in only three children who reveled some improvement with behavioral therapy. In the lost follow up group 57.6 % children were nonresidentIndians.

Discussion

Attention deficit hyperactivity disorder is defined as developmentally inappropriate poor attention span or age inappropriate hyperactivity and impulsivity or both (2). Increasing rate in ADHD is observed world wide in recent years.The problems of ADHD children are poor scholastic performance and social maladjustment. About 60% of ADHD children will carry some of these problems into adult life manifested as substance abuse, family disharmony and impulsivity (4,5).

In spite of the high literacy rate, Kerala is now progressing to the suicide capital of India with increasing rates of alcoholism and divorce.In this context of maladjustment among adults ADHD in children merits detailed study,appropriate management and follow-up.

In the last decade western literature on ADHD has grown (6,7) and few studies are available from India (7, 8, 9) but none from Kerala.

Pathogenesis ofADHD isconsidered to be disturbances in the dopamine system of brain in genetically predisposed individuals perpetuated by environmental factors(1) Hence if the environmental factors are detected, preventive and corrective strategies can be implemented.

This study reveals a higher mean age of ADHD children (9.38yrs) compared to the Indian studies by Venkatesh and Malhi P in which the mean ages were 5.7 yrs and 6 yrs respectively (9,10) The male preponderance observed in our study (M.F.=2.3:1)is reported from world wide(1). The Indian studies by Venkatesh,Malhi, Mukhopadhyay and Qureshi from Pakistan revealed higher male preponderance than the present study(9,10,11,12).Only a single study by Yang. P on Taiwan children reveals female preponderance (13). Combined from of ADHD is seen in all children in this study indicating that they all require medication. Varying forms have been observed in different studies (3,5).Isolated inattention type is easier to treat by behavior therapy alone. Suicidal tendency is more with hyperkinetic variety(5).

Poor scholastic performance in ADHD children as revealed in this study has been reported in a Bangkok study. Socioeconomic status in this study group included only the upper middle economic group mainly attending our hospital. Bhatia has observed that hyperactivity was more in the low socioeconomic group (8).

Sibling rivalry, school problems, excessive junk food eating and prolonged television viewing are significant factors observed among ADHD group in the present study which are observed in various studies. (15, 16, 17, 18,19).

The single significant problem in pregnancy was pregnancy induced hypertension. Bhatia has observed different pregnancy problems, not hypertension alone(8). The significant problem during the neonatal period was hyperbilirubinemia requiring phototherapy. Studies regarding the role of neonatal hyperbilirubinemia or phototherapy in ADHD could not be traced.

Our study has revealed that significant number of children are those living abroad. This is because the migrating population from Kerala especially from central Travancore is very high. Children living abroad are left alone at home for long hours and they choose television viewing as their entertainment. The commercials on television play a negative impact on these children and increase behavioral problems in them since adult supervision isvirtually nil (19,20,21). Studies on such a population is not available from literature.

This study has limitations of being conducted in a small selected group of children in higher age group and representingmainly the upper middle income group. Study on larger group of children involving wider age range from all socioeconomic groups needed.

Contributors

SAS: selected the topic, conducted the study, collected the literature and prepared the manuscript.

SS: Designed the study, revised the manuscript critically for important intellectual comments.

VCL: Modified the subject selection criteria and helped in the clinical diagnostic work up.

What is already known?

ADHD in children has significant association with family disharmony, parental substance abuse, pregnancy related problems, excessive television viewing and junk food consumption. ADHD children reveal sibling rivalry, poor scholastic performance and school problems with peer group.

What this study adds?

Non resident Indian children, children from nuclear families, pregnancy induced hypertension and those with neonatalhyperbilirubinemia requiring phototherapy are significantly affected with ADHD.

References

1. Raishevich N, Jenson PS,. Attention deficit hyperactivity disorder.In Nelson Textbook of Pediatrics Eds Kleigman, Berman,Jenson,Stanton 18/eElsever;Newdelhi 2008.
2. Conners' C.K 1997. Conner's Rating Scale -Revised Technical Manual - Toronto.Ontario Canada. Multi health system
3. Nair J Ehimare U, Betiman B.D, Nair SS, Lavin A. " Clinical review : evidence - based diagnosis and treatment of ADHD in children ". Mo Med 2006;103(6):617-21.
4. Rutter M Syndromes attributed to 'minimal brain dysfunction' in childhood. Am JPsychiatry 1982;139:21 -32
5. Swanson J .M Sergeant J. A, Taylor E, et al. Attention-deficit hyperactivity disorder and hyperkinetic disorder. Lancet 1998;351:429- 33
6. Morrison J. R , Stewart M.A. A study of hyperactive child synd rome .Biol Psychiatry 1971; 3:189-195
7. Ulmann R.K, Sleater E.K, Sprague R.L. ADD Children : Who is referred from the school? Psychopharmacol Bull 1984;20: 308-312.
8. Bhatia M.S, Nigam V.R,Bohra N, Malik S.C. Attention defict disorder with hyperactivity among pediatric outpatients. J Child Psychol Psychiatry 1991;32: 297-306
9. C. Venkatesh, T. Ravikumar, A . Andal, and B. S Virudhagirinathan. Attention deficit /hyperactivity disorder in children : Clinical profile and co-morbidity Indian J Psychol Med. 2012 Jan- Mar; 34(1): 34-38.
10. Malhi P, Singhi P. Spectrum of attention deficit hyperactivity disorders in children among referrals to psychology services. Indian Pediatrics. 2000;37:1256 -60
11. Mukhopadhyay M, Misra S, Mitrs T, Niyogi P. Attention deficit hyperactivity disorder.Indian journal of pediatrics . 2003 Oct;70(10) 789-92.
12. A. Qureshi, D Thaver Medical students, Aga Khan University Hospital Karachi. Cross sectional review of children with ADHD presenting to an outpatient Psychiatric institute in Pakistan. Journal of Pakistan Medical Association vol. 53,No. 9, Sep.2003
13. PINCHEN Yang md, YUH-JYH JONG md, phd, LI-CHEN CHUNG, CHENG- SHENG CHEN Gender difference in a clinic referred sample of Taiwanese attention - deficit /hyperactivity disorder children . DOL 10.1111/ j. 1440 -1819. 2004.01312.
14. Benjasuwantep, B., Ruangdarayanon, N.,Visudhiphan, P., 2004 , prevalence and clinical characteristics of attention deficit hyperactivity disorder among primary school students in Bangkok. j. Attention Disorder, 18(3): 120- 126.
15. Barkley RA .Hyperactivity girls and boys : Stimulant drug effects on mother - child interactions. 1 Child Psychol Psychiatry 1989;30:379-390.
16. Merrell, C. & Tymms, P. (2001) inattention, hyperactivity and impulsiveness: their impact on academic achievement and progress. British journal of Educational Psychology 71.43-56.
17. McGee, R., Prior, M., Williams, S., et al. (2002) The long term significance of teacher - rated hyperactivity and reading ability in childhood: findings from two longitudinal studies. The journal of Child Psychiatry,43, 1004- 1017.
18. Kleinman RE, Brown RT, Cutter GR, Dupal G J, Clydesdale FM, Source Department of Pediatrics. A research model for investigating the effects of artificial food colorings on children with ADHD 2011 Jun; 127(6); e 1575-84
19. Dimitri A. Chiristakis, MD,MPH, Frederick J.Zimmerman, PhD David L. DiGiuseppe, MSc, Carolyn A. McCarty, PhD Early television exposure and subsequent attentional problems in children copy right © 2004 by the American Academy of Pediatrics
20. Acevedo- Polakovich ID,Lorch EP, Milich R. TVor not T V:questions and answers regarding television and ADHD .ADHD Rep 2005;13:6-11
21. Christakis DA Zimmerman FJ, DiGiuseppe DL,MoCarthy CA. Early television exposure and subsequent attentional problems in children. Pediatrics 2004;113:708-713

PUSHPAGIRI MEDICAL JOURNAL

✪ ORIGINAL ARTICLE

Study on the clinical profile of paediatric tuberculosis and comparison with adult tuberculosis: Experience from a tertiary care centre in South India

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Abstract

Objectives: To find out the clinical profile of children diagnosed with tuberculosis and to compare the same with adult patients with tuberculosis in the same period. Methods: Retrospecitve analysis of the RNTCP registers and the necessary case files from June 2010 to Dec 2013 was done to collect data. Results: total of 440 cases were there, with 68 paediatric cases. Among the latter, 58.8%was boys. 92.7% were 'new' and 7.4% 'treated' previously. Overall contact history was there for 39.2%. BCG vaccination coverage was high; prevalence of PEM was 68.8%. 76.5% had pulmonary disease and 23.5% had extrapulmonary disease. Main symptom was cough and fever in pulmonary tuberculosis (83.3%). 12(23%) of pulmonary tuberculosis had sputum positivity; consolidation was the commonest chest X ray finding (55.8%). Overall 82.6% had positive Mantoux, and high correlation was seen with positive Mantoux and pulmonary tuberculosis than extrapulmonary (p=0.04). Commonest extrapulmonary site in children was lymph node. Supportive tests like adenosine deaminase were utilized to diagnose tuberculous pleural effusion and meningitis. Among adult tuberculosis cases (n=372), male predominance (65.9%) was higher than children (58.8%). More likelihood of sputum positivity seen (p=0.00, significant). Commonest extrapulmonary TB in adults was pleural effusion. Paediatric: adult ratio was 18.2%. Most cases opted for treatment from RNTCP only, but 13.4% went for non DOTS therapy. Conclusions: Contact tracing is very important in paediatric tuberculosis. Mantoux is more likely to be positive in pulmonary than extrapulmonary tuberculosis in children. Commonest extrapulmonary site was lymph node in children and pleura in adults. Adults are more likely to be sputum positive than children. There is still significant number of patients opting for non DOTS therapy.

Keywords: tuberculosis, paediatric, adult, pulmonary, extrapulmonary

Introduction

Even though there are studies about tuberculosis, almost all of them concentrate on adult disease. Paediatric tuberculosis is relatively neglected area, firstly because of the difficulty in diagnosis and secondly because of the paucibacillary nature, which makes it less communicable. The same reasons have given it less importance in national programs too, but paediatric tuberculosis can be very devastating leading to long term sequel especially if not diagnosed early and also when it happens in the early years. Children younger than 15 years contribute to 15-20% of the global TB disease burden1. Childhood tuberculosis not only indicates inadequate control of the disease in the community, but creates a pool of latent tuberculosis which may flare up at a later age.

Subjects and methods

Children up to 14 years diagnosed as tuberculosis and registered in our RNTCP unit between June 2010 and December 2013 were included in the study. The age cut off was chosen as 14 years, according to the age cut off given by RNTCP. Since all the tuberculosis cases were being registered in RNTCP in our institution, no one was excluded. Patients' case files and RNTCP registers were used to collect the relevant data. Age and sex was noted. Detailed information was collected with regard to sputum smear positivity, category, exact diagnosis-

whether pulmonary or extrapulmonary and if extrapulmonary, the site of involvement. Available information about history of contact in the family, BCG vaccination, Mantoux report and presence of malnutrition (weight for age < 2SD according to WHO), use of any other diagnostic tests also was gathered from the medical records. Mantoux reading more than 10mm was taken as positive. Clinical data of adults diagnosed as tuberculosis and registered in RNTCP in the same period also was analyzed for comparison.

Results

Total number of cases was 440 and the paediatric to adult tuberculosis ratio was 18.2%. There were 68 paediatric tuberculosis cases. The age distribution is shown in Table 1.

Table 1: Age distribution of children with tuberculosis

Age	No. of cases of tuberculosis(n=68)	%
<1 year	8	11.8
1 -5years	22	32.4
5 -10years	14	20.5
10 -14 years	24	35.3

The mean age of diagnosis being 7 ½ years. 40 (58.8%) were boys and 28 (41.2%) girls. 63 (92.7%) were new cases and 5(7.3%) were treated cases. 30 were below 5 years of age and 38 above that. Contact history was recorded in 51 cases and positive contact history was there in 16 (31.3%). 4 additional adult contacts diagnosed through contact tracing. Overall sputum positivity was 17.6%. BCG vaccination status could be obtained from 37 case records, all of whom were vaccinated. Among the treated cases, 2 were categorized as 'relapse' (smear positive pulmonary relapse) and 3 as 'other' (smear negative relapse) according to RNTCP with 1 case each of lymph node, meningeal and hip joint disease. Nutritional status was recorded in 39 cases. 27 had PEM (68.8%). 52 children (76.5%) were having pulmonary tuberculosis while 16 (23.5%) had extra pulmonary tuberculosis. Among children with pulmonary tuberculosis, records about the symptoms were available in 42 only and the symptoms were cough with or without fever in 35(83.3%) and fever alone in 7(16.7%). Diagnosis of pulmonary tuberculosis was made based on suggestive symptoms, chest X ray and positive Mantoux. 12 had sputum positivity (23%). Chest X ay finding was recorded in altogether 43 pulmonary tuberculosis cases. 24 cases had consolidation (55.8%), 14 had infiltrates (32.6%) and 5 had hilar adenopathy (11.6%). Mantoux reading was obtainable in 46 cases, of which 38 were positive (82.6%) (Table 2).

Table 2: Association of positive Mantoux with site of involvement in paediatric tuberculosis

Site of involvement	Total no. of cases	No. of cases were Mx reading is available	Positive reading	Comment
Total case	68	49	44	
Pulmonary	52	34	34	(p=0.04, significant)
Lymph node	7	6	6	
Pleural effusion	4	4	2	
Bone and joint	3	2	2	
neurotuberculosis	2	3	0	

Mantoux positivity was significantly associated with pulmonary than extra pulmonary tuberculosis.

Lymph node tuberculosis (n=7, 43.8%) predominated extra pulmonary tuberculosis (Table 3)

Table 3: Paediatric extrapulmonary tuberculosis according to sites of involvement (n=16)

Site	No. (n=16)	%
Lymph node	7	43.8%
Pleural effusion	4	25%
Bone& joint	3	18.7%
neurotuberculosis	2	12.5%

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Diagnosis in all lymph node tuberculosis was made pathologically by FNAC/biopsy demonstrating the granulomas. Mx positivity also supported the diagnosis. Mantoux was positive in only 2 out of 4 pleural effusion cases and so diagnosis was made by the pleural fluid analysis report, including adenosine deaminase level (>60 IU/L positive) when Mantoux was negative. AFB staining and culture was negative in these cases. Neurotuberculosis was diagnosed by suggestive cytological and biochemical findings in CSF, if needed adenosine deaminase levels in CSF (>10 IU/L positive) and neuro imaging. These cases did not have identifiable primary pulmonary focus or positive Mantoux. Both these cases were above 10 years and did not have contact history. Among bone and joint tuberculosis, two were tuberculous arthritis and one was osteomyelitis involving the mandible. The latter was a 2 year old girl from Mumbai possibly having primary tuberculosis at this unusual site. Her HIV status was negative. IGRA (Interferon gamma release assay) was never used to diagnose any case of tuberculosis.

Among the adult tuberculosis (n=372), there were 245 (65.9%) males and 127(34.1%) females. 53% were sputum positive. 338(90.9%) were 'new' cases and the rest 'treated' (9.1%). Overall comparison of adult and paediatric tuberculosis is shown in Table 4.

Table 4: Overall comparison of adult and paediatric tuberculosis

Parameter	Adult (n=372)	%	Paediatric (n=68)	%	Comment
Males	245	65.9	40	58.8	
Females	127	34.1	28	41.2	
Sputum +ve	197	53	12	17.6	P=0.00, significant
Treated cases	34	9.1	5	7.4	
Pulmonary	254	68.2	52	76.5	
Extra pulmonary	118	31.8	16	23.5	

Data about the extra pulmonary tuberculosis cases and the 'treated' cases in both groups also was compared separately (Table 5 and 6 respectively).

Table 5: Comparison of extrapulmonary tuberculosis in adults and children

Site	Adult (n=118)	%	Paediatric (n=16)	%
Lymph node	33	27.9	7	44
Pleural effusion	51	43.2	4	25
Neurotuberculosis	9	7.6	2	12.5
Abdominal	9	7.6	0	0
Genito urinary	5	4.2	0	0
Spinal	3	2.6	0	0
Skin	3	2.6	0	0
Disseminated	2	1.6	0	0
bone	1	0.8	1	6.25
Vocal cord	1	0.8	0	0
Joint	0	0	2	12.5
Pericardial effusion	1	0.8	0	0

Table 6: Comparison of clinical profile of 'treated' cases in adults and children

Site	Adults (n=34)	%	Paediatric(n=5)	%
Pulmonary	33	61.8	7	40
Pleural effusion	51	14.7	4	0
Lymph node	9	11.8	2	20
Meningitis	9	0	0	20
Spinal	5	5.9	0	0
Genitor urinary	3	2.9	0	0
Skin	3	2.9	0	0
Joint	2	0	0	20
Others	1	0	1	0

There were no statistically significant differences in the clinical profile of tuberculosis in adults and children except the chance of sputum positivity which was significantly more in the adults (p=0.00).

Among the total 440 cases of tuberculosis, 94 (21.4%) took therapy from our RNTCP unit, 269(61.1%) were transferred to other local DOTS centres or medical college, 59(13.4%) opted for non DOTS therapy for convenience or because of going abroad, 5 (1.1%) were transferred outside the state and 13(3%) expired during hospital stay.

Discussion

The child to adult ratio of 18.2% found in the study probably reflects high endemicity in our place or higher case detection rate in paediatrics, as the national average is 7% as of 20112. Mukherjee AA et al3 has reported a ratio of 3.4% from West Bengal. Regarding paediatric tuberculosis, cases were comparatively more in adolescence. This trend was observed by Marais BJ et al4 also. There was apparent male preponderance. Even though it was not statistically significant in the present study, similar observation was made by Mukherjee et al5 also. Shrestha S et al6 reported a contact history of 36.6% and Seth et al7 33.7% where we got 31.3%. We got additional 4 contacts, by screening the adults in the family, thus increasing the overall contact rate to 39.2%. We wish to stress the importance of contact tracing, though it had been very difficult practically mainly because of the reluctance from the side of the adult relatives. BCG scar was noted in 48.8% by Shrestha S et al6 which could not be obtained from the present study because of lack of record about this in the files. Vaccination status was 100% from the available reports, which is in keeping with the high BCG vaccination status of Kerala and also because of high literacy rate and health care awareness of the people of this region. Seth V et al7 from Delhi has reported BCG coverage of only 41.3%. 7.4% were relapsed cases in our study. 3.9% of retreatment was reported by Mukherjee et al3 and 10% by Puwar B et al8. Presence of malnutrition was 61% in the study by Seth V et al7 where as we got 68.8%. The former study had taken different reference standards and had included grade III and IV as malnutrition whereas we took WHO cut-off of <2 SD. Pulmonary tuberculosis (76.5%) predominated all the paediatric cases and most of them were sputum negative which is explainable by the paucibacillary nature. Seth V et al7 and Shrestha S et al6 also had reported relatively higher prevalence of 82.1% and 53.6% respectively for pulmonary tuberculosis. In contrast, some studies had shown higher prevalence of extrapulmonary tuberculosis 9,10,11 in childhood. Commonest symptoms were fever and cough which was reported by other studies by Shrestha V et al6 and Seth V et al7 also. Extrapulmonary tuberculosis was more seen in age group of 1-5 years and above 10 years. Higher prevalence above 4 years was reported by Sreeramareddy CT et al12. Lymph node was the commonest extrapulmonary site. The same pattern is shown in study by Maltezou HC et al11, Satyanarayana S et al12 and Sreeramareddy CT etal13. There was high rate of Mx positivity in our study, significantly associated with pulmonary tuberculosis (Table2). Shrestha et al6 has reported only 39% overall Mx positivity in childhood tuberculosis.

Confirmed bacteriological diagnosis (smear positivity) could be made only in 12 cases (17.6%). Shrestha S et al6 reported confirmed diagnosis in 14.6% which was comparable and the reason being

paucibacillary nature of the disease in childhood. Lymph node tuberculosis was diagnosed by positive Mantoux and suggestive pathology whereas pleural effusion was more difficult because half of them had negative Mantoux, so we took into account the values of adenosine deaminase levels. In tuberculous meningitis also diagnostic difficulty was experienced. This shows the difficulty in diagnosing paediatric tuberculosis in general. Many children had to undergo an array of investigation, some of which are often repeated to reach a diagnosis of tuberculosis.

Comparing paediatric with adult tuberculosis, it was found that, chance of sputum positivity was significantly higher in the adults (p=0.00). Extrapulmonary site most commonly involved in children had been lymph node whereas it was pleural effusion in the adults. This pattern was observed in other studies also13,14. Also, proportion of neuro tuberculosis had been higher in children. Genitourinary, abdominal, skin, vocal cord and pericardial effusion were not seen in childhood. The proportion of 'treated' cases was higher in adults (10.5%) compared to children (7.4%). Ramos et al15 reported a significantly higher number of relapses in adult TB cases compared to cases from the childhood patients from a rural hospital in Ethiopia.

The registration of cases and the follow up strategy was working well in the institution. 13.4% who went for non DOTS therapy could not be tracked. This may be significant as such cases may become defaulters and contribute to the burden of drug resistant cases in the community.

Conclusion

Contact tracing is very important in paediatric tuberculosis. Mantoux is more likely to be positive in pulmonary than extrapulmonary tuberculosis in children. Commonest extrapulmonary site was lymph node in children and pleura in adults. Adults are more likely to be sputum positive than children. There is still significant number of patients opting for non DOTS therapy.

Limitations

Study was not community based. Data entry in the case files was not perfect and the number of cases also was limited.

Recommendations

A coordinated multi centric study involving different RNTCP units may be conducted to get a clearer picture about the clinical profile of paediatric tuberculosis. There should be some method to ensure the contact tracing in all paediatric tuberculosis cases. There should be uniformity in the strength of PPD used for Mantoux in every child.

References

1. Marais BJ, Gupta A, Starke JR, El Sony A. Tuberculosis in women and children. Lancet.2010;375:2057-9
2. Central TB Division. Tuberculosis India 2012. Annual Report of the Revised National Tuberculosis Control Programme, Directorate of General Health Services, Ministry of Health and Family Welfare, Government of India; 2012.
3. Mukherjee A, Chowdhury R, Singla R, Saha I, Dutta R, Das T. Comparison between childhood and adult tuberculosis in a rural tuberculosis unit of West Bengal: A retrospective study. Lung India 2014;31:116-20
4. Marais BJ, Gie RP, Schaaf HS, et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004 Mar;8(3):278–85.
5. Mukherjee A, Saha I, Sarkar A, Chowdhury R. Gender differences in notification rates, clinical forms and treatment outcome of tuberculosis patients under the RNTCP. Lung India 2012; 29:120-2.
6. Shrestha S, Bichha RP, Sharma A, Upadhyay S, Rijal P. Clinical profile of tuberculosis in children. Nepal Med Coll J. 2011;13(2):119-22.
7. Seth V, Singhal PK, Semwal OP, Kabra SK, Jain Y. Childhood tuberculosis in a referral centre: clinical profile and risk factors. Indian Pediatr. 1993; 30(4):479-85.
8. Puwar B, Patel V, Puwar T. A record based study on paediatric tuberculosis in Ahmedabad city, India. Nat J Com Med 2012;3:153-6
9. Shrestha S, Marahatta SB, Poudyal P, Shrestha SM. Clinical profile and outcome of childhood tuberculosis in Dhulikel hospital. J Nep Paediatr Soc. 2010;31(1):11-16
10. Phongsamart W, Kitai I, Gardam M, Wang J,Khan K. A population based study of tuberculosis in children and adolescents in Ontario. Paediatr Inf Dis J 2009;28(5):416-9
11. Maltezou HC, Spyridis P, Kafetzis DA. Extrapulmonary tuberculosis in children. Arch Dis Child 2000;83:342-46
12. Satyanarayana S, Shivashankar R, Vashist RP, Chauhan LS, Chadha SS, Dewan PK, et al. Characteristics and programme-defined treatment outcomes among childhood tuberculosis (TB) patients under the national TB programme in delhi. PLoS One. 2010;5: e13338.
13. Sreeramareddy CT,Panduru KV, Verma Sc, Joshi HS, Bates MN. Comparison of pulmonary and extrapulmonary tuberculosis-a hospital based retrospective study.BMC Infect Dis 2008; 8:8.
14. Ozvaran MK, Baran R, Tor M, Dilek I, Demiryontar D et al. Ann Thorac Med. 2007 Jul-Sep; 2(3): 118–121.
15. Ramos JM, Reyes F, Tesfamariam A. Childhood and adult tuberculosis in a rural hospital in Southeast Ethiopia: A ten-year retrospective study. BMC Public Health 2010; 10:215.

✪ ORIGINAL ARTICLE

The diagnostic value of first EEG in children suspected with epilepsy

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Abstract

Epilepsy is one of the most common neurological illness in childhood. The Electroencehalogram (EEG) is the most important tool to support diagnosis and classification of epilepsy. In India, studies looking into the utility of EEG for diagnosis and prognostication of pediatric epilepsy are sparse and the results inconsistent. Aims and objectives: 1. to identify the diagnostic value of first EEG in children having clinically probable epilepsy, in order to support a correct diagnosis and early treatment. 2. to analyze the necessity and yield of sleep EEG, activation procedures like hyperventilation and intermittent photic stimulation, the feasibility of classification into a specific electro-clinical syndrome, the need of neuroimaging in identifying etiology and prognostication. Methods: study conducted in the Pediatric Epilepsy Clinic, in a tertiary care medical college in kerala, India. Children aged between 1 month - 15 years, with history of clinically probable epilepsy with strict inclusion and exclusion criteria. Detailed history, examination, EEG using standard protocol, careful interpretation and analysis of data were done. Results and Conclusions: The diagnostic yield of first EEG was 57%. As number of seizures increased, yield increased to two times.The difference in EEG yield between children in epilepsy group and first seizure group was significant (p< 0.00001). The yield of combined awake and sleep EEG was 62%, only awake 17%, only sleep 21%, Hyperventilation 13%, and intermittent photic stimulation 4%. Focal epileptiform discharges were the most common EEG abnormality 70.5%. Significant associations were found between symptomatic etiology and epilepsy (p<0.001) and abnormal EEG findings (p < 0.00003), and also between abnormal neuro-imaging findings and epilepsy (p < 0.007). Cerebral Palsy was the most common cause of symptomatic epilepsy ie 43%, and 20% of them had West Syndrome. Hence we conclude that a well taken first EEG in children suspected with epilepsy will help in early treatment thereby reducing the burden of neuro morbidity in a resource poor country like India.

Keywords: Electroencephalogram (EEG), Epilepsy, Epileptiform discharges

Introduction

Epilepsy has been defined as recurrent (two or more) unprovoked seizures. It is one of the common childhood neurological illnesses occurring in about 4-6 per 1000 children in the general population.1 It is important to determine the type of seizure, and whether it constitutes part of a specific epilepsy syndrome for purpose of further evaluation, treatment and prognosis. The correct diagnosis of epilepsy is indeed difficult but possible with thorough history taking, physical and neurological examination and laboratory tests including EEG and neuroimaging. The EEG is the most important tool for epilepsy diagnosis and classification. There have been many prior studies looking into the utility of EEG for diagnosis and prognostication of epilepsies. But studies in pediatric population, especially in India, are sparse and the results inconsistent. The demonstration of interictal epileptiform discharges (IEDs) in the EEGs of patients with seizures supports the diagnosis and is helpful in the classification of epilepsy. 2It is shown that the sensitivity of IEDs on the first EEG varies from 29 to 56 %.[3,4,5]

Aims and Objectives

1. To identify the diagnostic value of first EEG in children having clinically probable epilepsy, in order to support a correct diagnosis and early treatment in a resource poor nation like India, where the treatment burden of chronic diseases are solely on the affected family.

2. The necessity and yield of sleep EEG and activation procedures like hyperventilation (HV) and intermittent photic stimulation (IPS) in pediatric age group is also analyzed. 3. The feasibility of classification into a specific electro-clinical syndrome and the need of neuroimaging in prognostication are also assessed in this study. 4. An attempt is also made to identify the etiology.

Methods

This study is conducted in the Pediatric Epilepsy Clinic, of a tertiary care medical college, kerala, India Children aged between one month and fifteen years, who attended the clinic between September 2011 to August 2012, both inclusive, with history suggestive of clinically probable epilepsy were included in the study. Excluded fromthe study were, neonatal and acute symptomatic seizures, children with febrile seizures, breath holding spells,already with a diagnosis of epilepsy, those on antiepileptics, and who have a previous EEG done elsewhere. A detailed history followed by clinical and neurological examination was carried out on all children and entered into a standard proforma.

Children were classified into “epilepsy group” when there were two or more episodes and “first seizure group” when they had only a single unprovoked event.

EEG Recording Protocol:

Scalp EEG recordings were obtained using silver-chloride electrodes placed according to the 10–20 International system, with measured impedances of less than 10 k Ohms at all electrodes. All studies utilized both bipolar and average referential montages. Initial signal conditioning included a 1 Hz low pass filter, a 70 Hz high pass filter and a 50 Hz notch filter. EEG recordings varied from 25-60 minutes, with the majority of recordings lasting 30 minutes. All EEGs were done under sleep deprivation, for which children are advised to be made to sleep less than 5 hours the previous night. An awake EEG was done on all co-operative children and activation techniques like IPS and HV were performed from 5 years and above.

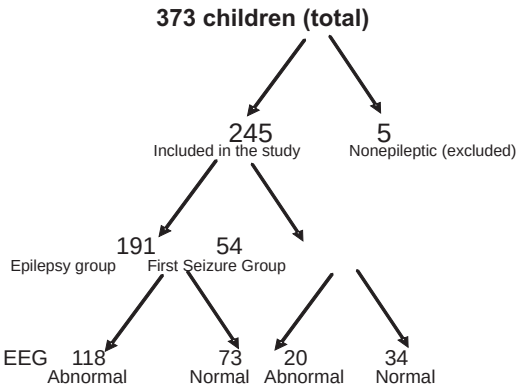
All EEGs were carefully analysed and classified into normal or abnormal. EEG abnormalities were classified as nonspecific or epileptiform. After making a diagnosis of epilepsy, an attempt to classify into specific epilepsy syndromes was made according to the ILAE classification system of 2009. Appropriate treatment and further work up was then initiated. A statistical analysis was made using Chi-square test for significance where ever appropriate.

Results

A total of 373 children attended the clinic during the period of study of which 123 were omitted according to the exclusion criteria. The remaining 250 children were included in the study.

The mean age of the study group was 4.9 years. Two-thirds (62%) of the children were boys. There were 97 (39%) children between 1 and 5 years, which was the largest group where as there were only 30(12%) children between 10 and 15 years. The other two groups i.e. children between one month and one year and children between 5 and 10 years were 62 (25%) and 61 (24%) respectively.

After the EEG, reviewing the history and neuroimaging findings, 10 children were found to have paroxysmal disorders other than epilepsy and were excluded from the study. They included 2 with breath holding spells, 1 with syncope, 2 with situation related seizures due to CNS granuloma. The results of the rest of the 245 children included in the study are further discussed in detail below.



191 children (78%) were classified in the epilepsy group and 54 (22%) in the first seizure group. In both groups the maximum children were between 1 and 5 years, which was 38% and 42% respectively and minimum between 10 and 15 years, which was 13% and 8% respectively in the two groups. In both the epileptic as well as the first seizure groups boys predominated (63%).

Diagnostic value of first EEG: Of the total 245 children, 138(57%) had an abnormal EEG. Among the children in epilepsy group, 118(62%) had an abnormal EEG. Among the 54 children in first seizure group, only 20 (38%) had an abnormal EEG.

Table no.1

Diagnosis	Epilepsy Group	First seizure group	Total
EEG normal	73(38%)	34 (62%)	107 (43%)
EEG Abnormal	118(62%)	20(38%)	138 (57%)
Total	191	54	245

Type of EEG Abnormalities: Of the total 138 abnormal EEGs, 98 (70%) had focal epileptiform discharges (EDs) of which 10 showed secondary generalization. 20 (15%) showed generalized EDs of which 5 showed hypsarrythmia, and 3 showed modified hypsarrythmia. There were 20 (15%) EEGs with nonspecific findings of which 13(10%) had asymmetry and 7(5%) had slow background activity.

Yield of activation techniques: There were 82 children who were 5 years and above in whom an awake EEG and activation techniques of HV and IPS were performed. 31 of them had a normal EEG. The remaining 51 EEGs were evaluated to see the utility of sleep, awake, HV, and IPS separately.

31of 51 (62%) had epileptiform discharges during awake as well as sleep, in which 11(21%) had exaggerated EDs during sleep. 9 (17%) had EDs only during awake state and 6(12%) had EDs only during sleep state. Seven (13%) had EDs during HV and 2 (4%) during IPS.

Clinical Diagnosis of type of seizures: Among the 191children in epilepsy group, as per history, a clinical evaluation of the type of epilepsy was made initially before the EEG was done. It was found that 113(59%) had generalised seizures, 46 (24%) had focal onset with secondary generalisation, 19(10%) had focal seizures and 13 (7%) had seizures which were undetermined as to focal or generalized. Among the first seizure group, 28 (52%) had generalised seizures, 15 (28%) had focal onset with secondary generalisation, 7 (12%) had focal seizures and 4 (8%) had seizures which were undetermined as to focal or generalised.

Electroclinical Diagnosis of Epilepsy syndromes and Epilepsies: Among the 191 children in the epilepsy group, EEG helped in an electro-clinical diagnosis in 121(63%).Table 2.

It was found that 30 children(15.7%) had a specific epilepsy syndrome, the details of which are given in Table 2.

After separating epilepsy syndromes, the rest of the children were classified according to the type of seizures using EEG findings. There were 91 (48%) children with focal seizures. In the remaining 70 (37%) children whose EEG was normal, the clinical diagnosis was retained for further management.

Table no. 2. Electro-clinical Diagnosis

A	**Epilepsy syndromes**	**30(15%)**
	West Syndrome (WS)	8
	Idiopathic Generalized Epilepsy of adolescence (IGE)	1
	Childhood Absence Epilepsy (CAE)	3
	Benign Infantile Seizures (BIS)	3
	Rolandic (BECTS)	5
	Juvenile Myoclonic Epliepsy (JME)	2
	Juvenile Absence Epilepsy (JAE)	1
	Lennox Gastaut Syndrome (LGS)	1
	Landau Kleffner Syndrome (LKS)	1
	Continuous Spike wave Slow Wave Sleep (CSWS)	1
	Epilepsy with myoclonic Atonic seizures (EMAS)	1
	Dravet Syndrome	1
	Early Infantile Epileptic Encephalopathy	1
	Myoclonic epilepsy of Infancy	1
B	**Focal Seizures**	**91(48%)**
C	**Seizures unclassified**	**70(37%)**

Among the First seizure group 20 out of 54 (38%) had an abnormal EEG, of which 16 (80%) had focal EDs, 3 (15%) had generalized discharges and 1 (5%) had focal EDs going into secondary generalization.

Etiology: Among the total 245 children, 150 (61%) children had normal neurodevelopment and no risk factors for epilepsy, however the exact etiology could not be ascertained as neuro-imaging was not done due to financial constraints. Of the remaining 95 children, 61(64%) had symptomatic epilepsy with a definite etiology for seizures of which 41 (43%) were having Cerebral Palsy. 34 (36%) were found to have idiopathic epilepsy.

EEG findings according to etiology: Of the 61 children with symptomatic epilepsy, 49 (80%) had an abnormal EEG. Among the 34 with idiopathic epilepsy 17(50%) had abnormal EEG.Among the remaining 150 children whose etiology was undetermined as to symptomatic or idiopathic, 78 (52%) had a normal EEG.

Neuro-imaging: Neuro-imaging was done among 74 children, out of which MRI was done on 42 children and CT on 32 children. 2 children had findings of neurocysticercosis and were excluded from the study.38 (53%) children had abnormal findings on neuro-imaging. Of these, 36 were epileptic children and 2 belonged to the first seizure group.

EEG findings according to neuro-imaging: Among the total 72 children who underwent neuro-imaging, 60(83%) had abnormal EEG findings and 12 (16%) had a normal EEG. Among the 60 who had abnormal EEG, 35 (58%) had abnormal neuro-imaging findings and 25(42%) had normal neuro-imaging findings. Among the 12 who had normal EEG, 1 (8%) had abnormal neuro-imaging findings and 11 (92%) had normal neuro-imaging findings.

Discussion

The diagnosis of epilepsy has serious medical and social implications and hence must be made very carefully. Except in the rare situation where the patient has a seizure while undergoing the recording of EEG, the diagnosis of epilepsy is made on the basis of clinical history, best if taken from the patient and an eye witness. Even where a good eye witness account is available, neurologists may differ in their diagnosis, as shown by van Donseelar et al.6 The inter ictal EEG provides information that aids in diagnosis and management of epilepsy. One must remember that the EEG is merely a tool, and its usefulness depends largely upon the skill of the individual who wields it. Like all diagnostic tests, it has significant limitations and cannot substitute for a careful history and exercise of good judgment. Nonetheless, in skilled hands, it provides unique and vital information in many patients, and enhances our understanding of their condition.7 The sensitivity of routine EEG in confirming the diagnosis of epilepsy has varied from 29 to 56% among various studies.4,5 However, the appearance of EDs in circumstances suggestive of a seizure is helpful in confirming the diagnosis, since only around 0.5 to 2 % of people without epilepsy exhibit them.8.9.10

250 children between the age of 1 month and 15 years were studied and the results of 245 first EEGs are described. Children between 1 and 5 years constituted 39%, which was the largest group and those between 10 and 15 years constituted 12%. The low percentage of older children in our study may be a biased observation as older children in their teens may be visiting adult outpatient departments.

In our study the diagnostic yield of first EEG was found to be 57% which is comparable with the above mentioned studies. There was a significant difference in the EEG results between children in epilepsy group and children in first seizure group. ($p< 0.00001$). In the epilepsy group, the first EEG yield was 62% when compared to 38% in the first seizure group.

Yield of activation procedures: Records including both awake and sleep tracings were available in 82 (33.4%) cases. Among the 51(62%) abnormal EEGs, 62% had EDs in awake and sleep, 17% only in awake, 21% only in sleep, 13% in HV and 4% during photic stimulation. Shinnar S et al11 have shown that 15 out of 50 (30%) demonstrated abnormality either only while awake (n=8) or only while asleep (n=7) and that obtaining a combined awake and sleep EEG significantly increased the yield of EEG abnormalities (40%). In another study by Raybarman C, hyperventilation revealed increased EDs only in 11.6%, when compared with the baseline EEG and in 0.7% ictal epileptiform discharges without clinical seizure. 12

Clinical Diagnosis: According to the clinical diagnosis of type of seizures, our study showed that 59% had generalised, 10% had focal, 24 % had focal seizures with secondary generalisation. In 7%, it was undetermined as to generalised or focal seizures. In a study done by Shinnar S et al 11 56% patients had partial and 35% had generalised seizures. In the study by K N Shah, SBR et al 13 partial seizures were seen in 53.6%, generalised in 40.4% and unclassified in 6%. King et al 14 studied 300 consecutive adults and children over the age of 5 years presenting with unexplained seizures. They were able to diagnose a generalized or partial epilepsy syndrome clinically in 141 patients (47%), with only three of these clinical diagnoses later being proved incorrect.

Among the first seizure group, our study showed that 28 (52%) had generalised seizures, 15 (28%) had focal onset with secondary generalisation, 7 (12%) had focal seizures and 4 (8%) had seizures which were undetermined as to focal or generalised.

Electroclinical Diagnosis: Syndromic classification of epilepsy was put forward in 1989. It utilizes the clinical presentation as well as the EEG correlates in a given patient in order to classify them into a specific syndrome from a list of accepted epilepsy syndromes. But it must be understood that syndromic diagnosis may not be always possible. The EEG may be helpful in classifying the seizure type, particularly in the case of generalized tonic clonic seizures where it is not clear if they are due to idiopathic generalized epilepsy or are secondarily generalized. The extent to which it is possible to identify the syndromes precisely at the time of initial diagnosis is debatable.

In our study among the 191 children in the epilepsy group, EEG helped in an electro-clinical diagnosis in 121(63%).15% had a specific epilepsy syndrome, 93 (48.6%) children had focal seizures. According to the study by K N Shah, SBR et al13 partial syndromes were seen in 54%, generalised syndromes in 26.4% and undetermined in 15.5% and 4% had special syndromes like West syndrome, Lennox Gastaut syndrome and childhood absence epilepsy. In a study by Freitag CM et al 15 focal epilepsy and epileptic syndrome were seen in 58%, generalised in 39% and 3% had undetermined syndromes. In Our study the high proportion of unclassified cases may be because of the use of only the first EEG which when repeated will increase the yield and better delineation of the specific syndrome. The discordance in the classification pattern is also due to the fact that different studies have used different classification system.

Etiology and epilepsy: There were many constraints to identify etiology because of the cost of neuro-imaging. Symptomatic epilepsy was proved in only 25% of cases, out of which 93% belonged to epilepsy group. This association between symptomatic etiology and epilepsy was statistically significant ($p<0.001$). Among the symptomatic epilepsy group 80% had abnormal EEG findings thus it showed that idiopathic epilepsy was more often associated with normal EEG than was symptomatic epilepsy. This association was also statistically highly significant. ($p < 0.00003$)

Neuro-imaging and epilepsy: In the present study EEG was supplemented with CT scan or MRI in only 74 (29.6%) children. 38 (53%) had abnormal findings out of which 78% of imaging findings were suggestive of perinatal damage with evident neurological manifestations like cerebral palsy, mental retardation, Tuberous Sclerosis, etc.

Two children who had situation related epileptic seizures (neurocysticercosis, and excluded from the study). Among the 38(53%) children, 95% were in epilepsy group. This association between abnormal imaging finding and epilepsy was statistically significant ($p < 0.007$).

Among the 74 children who underwent neuro-imaging, 60 (83%) had abnormal EEG and the major type of EEG abnormality was focal EDs with secondary generalisation in 69%. Among the 83% who had abnormal EEG, 58.8% were having abnormal findings in neuro-imaging. A significant association was also found between abnormal EEG finding and abnormal Neuro-imaging ($p< 0.003$)

In a study done by U C Weishmann in UK 16 to study clinical application of neuro-imaging in epilepsy, 919 patients were studied out of which 677 patients had epilepsy and others had single attack or epilepsy inremission or non epileptic seizure. CT scan could detect abnormality in 28 out of 93(30%) and MRI in 69 out of 142 (49%) patients. Though this study comprises of all age groups, it is in concordance with the present study.

Conclusion

The diagnostic utility of first EEG in children suspected with epilepsy was found to be 57%. The yield increased to two times when the number of seizures increased. There was a significant difference in the EEG results between children in epilepsy group and children in first seizure group. ($p< 0.00001$). The yield of combined awake and sleep EEG was 62%, only awake EEG was 17%, only sleep EEG was 21%, 13% for hyperventilation, and 4% for intermittent photic stimulation. Focal epileptiform discharges were the most common EEG abnormality in 70.5%. According to a clinical diagnosis, in the epilepsy group, 59% had generalised seizures, 24% had focal onset with secondary generalisation, 10% had focal seizures and 7% had undetermined seizures as to focal or generalised.

Symptomatic epilepsy was proved in 25%, in which 78% had evidence of perinatal damage. A highly significant association was found between symptomatic etiology and epilepsy ($p<0.001$) and abnormal EEG findings ($p < 0.00003$). A highly significant association was found between abnormal neuro-imaging findings and epilepsy ($p < 0.007$) as well as with abnormal EEG findings ($p< 0.003$). This clearly showed that neuro-imaging should be considered as an important adjunct in the diagnostic work up of epilepsy. Cerebral Palsy was the most common cause of symptomatic epilepsy ie 43%, and 20% of them had West Syndrome. Hence we conclude that a well taken first EEG in children suspected with epilepsy will help in early treatment thereby reducing the burden of neuro morbidity in a resource poor country like India.

The limitations of the study were that activation procedures could be done only in 82 children who were above five years and hence the results were not truly representative of the original sample size. Neuro-imaging could be done only in 74 children due to financial constraints and hence a symptomatic etiology could not be ascertained using this facility in the rest of the children where it was suspected.

References

1. Cowan L, Bodeasteiner J, Leviton A. Prevelance of epilepsies in children and adolescents. Epilepsia 1989; 30: 94-100.
2. Hart YM. Management of newly diagnosed epilepsy. In: Shorvon S, Perucca E, Fish D, Dodson E, eds: Treatment of epilepsy. 2nd ed, Oxford: Blackwell, 2004;161-73.
3. Carpay JA, Weerd AW, Schimsheimer RJ, et al. The diagnostic yield of a second EEG after partial sleep deprivation: A prospective study in children with newly diagnosed seizures. Epilepsia,1997; 38(5): 595-99.
4. Marsan CA, Zivin LS. Factors related to the occurrence of typical paroxysmal abnormalities in the EEG records of epileptic patients. Epilepsia. 1970; 11(4):361-81.
5. Salinsky M, Kanter R, Dasheiff RM. Effectiveness of multiple EEGs in supporting the diagnosis of epilepsy:an operational curve. Epilepsia 1987; 28: 331-4.
6. Pillai J, Sperling MR. Interictal EEG and the diagnosis of epilepsy. Epilepsia. 2006; 47 Suppl 1:14.
7. Van Donseelar CA, Geerts AT, Meulstee J, Habbema JDF, Staal A. Reliability of the diagnosis of a first seizure. Neurology 1989; 39: 267-71.
8. Zivin L, Marsan CA. Incidence and prognostic significance of 'epileptiform' activity in the EEG of non-epileptic subjects. Bain 1968; 91: 751-78.
9. Gregory RP, Oates T, Merry T. Electroencephalogram epileptiform abnormalities in candidates of aircrew training. Electroencephalogr Clin Neurophysiol 1993; 86: 75-7.
10. Goodin DS, Aminoff MJ. Does the interictal EEG have a role in the diagnosis of epilepsy? Lancet 1984;1: 837-8.
11. Shinnar S, Kang H, Berg AT, Goldensohn ES, et al. EEG Abnormalities in Children with a First Unprovoked Seizure. Epilepsia 1994;35(3): 471–76.
12. Raybarman C. Is hyperventilation an effective "activating" procedure in routine clinical EEG studies in children? J Child Neurol. 2009; 24(10):1294.
13. KN Shah, SB Rajadhyakhsha, VS Shah, VG Desai. Experience with international League against epilepsy classification of epileptic seizures (1981) and epilepsies and epileptic syndromes (1989) in epileptic children in a developing country. Epilepsia 1992; 33(6): 1072-77.
14. King MA, Newton MR, Jackson GD et al. Epileptology of the first seizure presentation: A clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. Lancet 1998; 352: 1007-11.
15. Freitag CM, Theodor WM, Pfafflin M, et al. Incidence of epilepsies and epileptic syndromes in children and adolescents: A population based prospective study in Germany. Epilepsia 2001; 42(8): 979-82.
16. UC Weishmann; Clinical application of neuroimaging in epilepsy. Journal of Neurology, Neurosurgery and Psychiatry 2003; 74: 466-70.

PUSHPAGIRI MEDICAL JOURNAL

✪ ORIGINAL ARTICLE

Anti-HBS antibody status of healthcare workers in Pushpagiri Institute of Medical sciences and Research Centre

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Abstract

Background: Health care workers (HCW) are at risk of infection with hepatitis B virus (HBV). HCWs can occupationally become infected with HBV through needle prick or exposure to HBV infected blood and other body fluids. Currently, there are more than 240 million people infected and approximately 600,000 people die every year due to Hepatitis B virus (HBV). Though vaccination is considered to be the best solution to this problem, it is fraught with the issue of non-responders. Objectives: To evaluate anti-HBs antibody titre in previously vaccinated clinicians, laboratory personnel and nursing staff of Pushpagiri Medical College Hospital, Tiruvalla. Materials and Methods:90 participants who had a history of previous HBV vaccination and no known past history of Hepatitis B infection were included in the present study. Participant's data collected included vaccination date, number of doses of vaccine, job description, and age at the time of study. Hepatitis B surface antibody (anti-HBs) titres were measured by Enzyme-Linked Immunosorbent Assay (ELISA) (DiaSorin, Saluggia, Italy) to investigate the immune response against the vaccine. Results: 90 Samples were taken from different age groups ranging from seventeen to sixty two years. Among the population studied the Hepatitis B vaccine induced immune response in HCWs were good (93.34%) with some of the participants in our study having an anti- HBs level >100 IU/ml even 15 years after the last dose of HBV vaccination. 6.6% were non-responders. Conclusions: Anti-HBs levels should be tested in all HCW following HBsAg vaccination so that necessary post-exposure precautions can be taken for the non-responders.

Introduction

Hepatitis B Virus (HBV) is classified as a member of Hepadnaviridae family. HBV infection is responsible for chronic liver disease and may ultimately lead to cirrhosis and liver cancer. Currently, there are more than 240 million people infected with HBV and approximately 600,000 people die every year due to the disease (1). The population prevalence of HBV infection is 3.4% in India (2). Health care workers (HCWs) are at an increased risk of hepatitis infection due to occupational exposure to blood and infectious body fluids. In some studies it is shown that the frequency of transmission of HBV infection after a single needlestick exposure to contaminated blood is estimated to range between 7 and 30% (3), far more than Human Immunodeficiency virus or Hepatitis C infections.

The immunity to HBV infection is directly related to the development of anti-HBs antibodies, the protective antibodies with a minimum level of 10 IU/L after 3 doses of Hepatitis B vaccination (4). Most people develop anti-HBs titer >100 IU/L within 6-8 weeks after completing the vaccination schedule (5). But some individuals do not show an anti-HBs antibody response or respond poorly to the Hepatitis B vaccination; they are labelled as non-responders or hyporesponders (antibody titer <10 IU/L) (6). It is estimated that about 5-15% of the people who are vaccinated may be non-responders (7). There are several factors like dose, storage, sex, genetic factor, obesity, diabetes and immunosuppressionthat can adversely affect the immune response in an individual. Therefore within 1 to 2 months after completion of vaccination series testing for antibody titre is recommended to detect a non-responder or a hyporesponder (8). Although antibody titre declines over the course of time among vaccinated

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individuals but it should be above 10 IU/L for ensuring the immunoprotection (4).

The information about the anti-HBs response to HBV vaccination is not available in Central Travancore region of Kerala, although HBV vaccination in HCWs is been practiced for more than 20 years. The studies on the HBV markers for HCWs in Kerala are rare. Therefore, the present study was carried out in Pushpagiri Medical College, Tiruvalla, initiated to determine the seroprevalence of anti-HBs in HCWs from Central Travancore region of Kerala.

Materials and Methods

A total of 90 HCWs working at Pushpagiri Institute of Medical Sciences and Research Centre, which is a 1200 bedded tertiary care hospital located in Central Travancore region of Kerala participated in the study. A detailed questionnaire about their vaccination history and an informed consent was obtained from all the participants of the study before sample collection. The blood samples collected was allowed to clot for 20 minutes and followed by centrifugation at 3000rpm for 10 minutes. The serum was aliquoted and stored at -20° C till the samples were tested. Anti-HBs antibodies were detected by ELISA using commercial Kits (DiaSorin, Italy).

DiaSorin Anti-HBs enzyme immunoassay

The method for qualitative/quantitative anti-HBs determination is a direct, non-competitive sandwich assay, based on the ELISA technique (Enzyme-linked Immunosorbent Assay). The presence of anti-HBs allows the enzyme tracer to bind to the solid phase. The enzyme activity is therefore proportional to the concentration of anti-HBs present in samples or calibrators. Enzyme activity is measured by adding a colourless chromogen/substrate solution. The enzyme action on chromogen/substrate produces a colour which is measured with a photometer. The absorbance was measured at 450/620 nm within 10 minutes in an ELISA reader. The result of the ELISA was calculated by correlation to a standard curve and expressed in international units IU/L.

All statistical analysis was done using SPSS for Window software, version 11.5. The standard graph and sample results were interpreted by using the graph PRISM® version 5.1

Results

In this study, a total of 90 individuals working in various departments of Pushpagiri Medical College Hospital were studied. The study population comprised 74 (82.22%) females and 16 (17.78%) males. All the participants had received Hepatitis B vaccination and had no known past history of Hepatitis B infection. The participant distribution according to age, sex and occupations are listed in Table 1.

Table 1: Participant distributions according to age, gender and occupation

	No: of Participants (%) according to age (year)						
	15-20	20-29	30-39	40- 49	50-59	>60	Total
Gender							
Male		10 (62.50%)	3 (18.77%)	1 (6.25 %)	2 (12.50%)		16
Female	11 (14.86%)	37 (50%)	18 (24.32%)	7 (9.45%)		1 (1.35%)	74
Occupation							
Physician		14 (58.33%)	8 (33.33 %)		1 (4.16%)	1 (4.16%)	24
Nurses		18 (72%)	7 (30.43%)				25
Paramedical Staff		15 (50%)	7 (23.34%)	7 (23.34%)	1 (3.34%)		30
Students	11 (100%)						11
Total	11 (12.22%)	47 (52.24%)	22 (24.45%)	7 (7.77%)	2 (2.22%)	1 (1.11%)	90

Based on the measurement of their anti-HBs titres, the population was categorized in four groups: category A (<10 IU/L), category B (11-100 IU/L), category C (101- 500 IU/L) and category D (>500 IU/L). The results are summarized in the following table 2.

Table 2: Serum Concentration of HBsAb

Category	HBsAb level IU/L	Number of persons (%)
A	< 10	6 (6.6%)
B	11 - 100	11(12.22%)
C	101 - 500	26 (28.88%)
D	500 - 1000	47 (52.22%)
Total		90

Analysis of association between HBs antibody titers and occupational factors were categorized in the table3.

Table 3: Serum concentration of HBsAb (IU/ml) and profession.

Category	HBsAb level IU/ml	Profession (%)			
		Physician	Nurse	Paramedical Staff	Students
A	< 10	2 (8.33%)	1 (4%)	1 (3.34%)	
B	11 - 100	2 (8.33%)	2 (8%)	6 (20%)	2 (18.18%)
C	101 - 500	9 (37.50%)	4 (16%)	10 (33.34%)	5 (45.45%)
D	500 - 1000	11 (45.83%)	18 (72%)	13 (43.34%)	4 (36.36%)

Thirty four (37.78 %) participants mentioned that they received vaccination less than five years before, while more than 56 participants (62.24%) stated that they were vaccinated more than five years before. Mean Anti-Hbs titre according to the year of vaccination is summarized in the table 4. From the results it was evident that immunity against HBV had not reduced significantly over the time but it is mainly depends upon each individual immune response.

Table 4: Time elapsed between vaccination and the time of assessment for immunity

Time elapsed	Number of Individuals	Mean anti-HBs antibody titre (IU/L)
< 5 years	35 (38.88%)	510.60
5 - 10 years	30 (33.34%)	509.30
10 – 15 years	21 (23.34%)	449.81
> 15 years	4 (4.45%)	404.02

Discussion

Hepatitis B Virus infection is responsible for chronic liver disease and may ultimately lead to cirrhosis and liver cancer. Currently, there are more than 240 million people infected and approximately 600,000 people die every year due to HBV infection worldwide (1). Studies suggest that mortality related to HBV infection will continue to increase over the next two decades. Various therapies for persistent HBV infection such as: interferon-á, pegylated interferon-á, lamivudine, adefovir (dipivoxil), entecavir, telbivudine and tenofovir (disoproxilfumarate) exist but the goal of eradicating HBV worldwide mainly depends upon prevention of new infection (9). In this context in 1991 the WHO recommended that Hepatitis B vaccine should be integrated into national immunization programs by the year 1997 (10). Hepatitis B vaccine induces anti-HBs immune response which can prevent HBV infection and decrease the risk of chronic infection and its subsequent complications. Studies have suggested that childhood vaccination significantly reduces the rate of chronic HBV infection (11).

All HCWs should have serologic testing 1–2 months following the final dose of the 3 dose hepatitis B vaccine series. An anti-HBs serologic test result of >10 mIU/mL indicates immunity. Periodic testing or boosting of HCWs if titres of >10 mIU/mL is demonstrated is not required (12). If the titres are below 10 mIU/mL the HCW should repeat the 3-dose series again and re-test for anti-HBs as before. If the HCW is still negative after the second vaccine series, the HCW is considered a nonresponder. The Hepatitis B vaccine induced immune response was seen in 93.34% of HCWs in our study and is similar to that observed in HCWs in other parts of the world. However, there were 6.6% non-responders who remain susceptible to HBV infection in our study. A non-responder should be counselled that he is susceptible to HBV infection. He should be educated on the post-prophylaxis to be taken in view of a needle-stick injury from a known HBsAg positive patient. HBIG has to be administered as early as possible to such HCWs. Hence lack of prior knowledge of anti-HBs titres can lead to delay in decision making on HBIG administration pending availability of anti-HBs reports.

It is also possible that the non-responder is chronically infected with HBV and hence testing for HBsAg should be done in such cases. We tested our non-responders for HBsAg and they were found to be negative.

Our findings also show that the immunity against HBV does not decline with time. Therefore the need for a booster after 10–15 years is not necessary in healthy adults, as reported (13). In agreement with the findings of the recent studies, some of the participants in our study had an anti-HBs level >100 mIU/ml even 15 years after the last dose of HBV vaccine. 72% of the nurses showed a higher level of titres in the 500-1000mIU/mL range over other staff, suggesting a possibility that as they come in close contact to patients more often than doctors, students or para-medical staff boosting of immune response may have occurred due to unrecognized exposures. Recent data suggests even if anti-HBs titres decline over time, immune memory remains and an exposure augments the immune response and hence these individuals are protected (12). Thus, once an anti-HBs response is demonstrated after vaccination booster doses are not recommended.

The findings of our study provide a base for testing for anti-HBs in vaccinees in Kerala. The seroprevalence survey of vaccine- preventable disease among HCWs, will help to develop policies for the management of employee vaccination programs and preventive healthcare at our institution.We recommend not just vaccination of susceptible HCWs to prevent disease transmissions, limit outbreaks, and reduce the resulting costs incurred (ie, worker compensation, lost work days, and economic burden on the healthcare facility) but also testing for anti-HBs titres post-vaccination to rule out the possibility of a non-responder so that immediate decisions can be taken on post-exposure prophylaxis.

Reference

1. Zuckerman J.N., Zuckerman A.J.Current topics in hepatitis. J.Infect. 2000; 41(2):130-136.
2. Acharya SK, Madan K, Dattagupta S, Panda SK. Viral hepatitis in India. Natl Med J India 2006; 19: 203-217.
3. Kane MA, Holleran C, Andre F. The epidemiology and control of hepatitis B as an occupational hazard in the health professionals. Proceedings of the European Conference on Hepatitis B as an Occupational Hazard. Geneva,Switzerland, 11–12 December 1990. 1991; 10–14.
4. Mahoney, F. J. Update on diagnosis, management, and prevention of hepatitis B virus infection. ClinMicrobiol Rev.1999; 12:351-366.
5. Siebert, D. and S. Locarnini. Hepatitis B: issues in laboratory diagnosis and vaccination. AustPrescr. 1998; 21:72-5.
6. Zuckerman, J. N., et al. Immune response to a new hepatitis B vaccine in healthcare workers who had not responded to standard vaccine: randomised blind dose- response study. Br Med J. 1997; 314:329-33.
7. Zuckerman, A. J. Hepatitis Viruses. In Baron S et al. (ed.),Baron's Medical Microbiology, 4th ed. Univ of Texas Medical Branch.1996.
8. Ronald, W. E. Hepatitis B vaccine in clinical practice. Taylor & Francis, New York.1993.
9. Clercq ED., et al. Antiviral Treatment of Chronic Hepatitis B Virus (HBV) Infections. Viruses. 2010; 2: 1279-1305
10. World Health Organization. WHO expanded programme on immunization. Report of 14th Global Advisory Group (Antalya, Turkey, Oct 14-18, 1991). Geneva: WHO.1991.
11. Harpaz, R., B. J. MacMohan, and H. S. Margolis. Elimination of new chronic hepatitis B virus infection: results of the Alaska immunization program. J Infect Dis.2000; 181:413-4.
12. Hepatitis B and the health care worker. CDC answers frequently asked questions about how to protect health care workers. Available at http://www.who.int/occupational_health/activities/3hepatiti.pdf
13. Leuridan E, Van Damme P. Hepatitis B and the need for a booster dose. Clin infect Dis. 2011; 53: 68-75.

✪ ORIGINAL ARTICLE

Clinical profile of sarcoidosis – A case series from Central Kerala

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Abstract

Sarcoidosis has been traditionally thought to be uncommon in tropical countries like India and remained unreported from India till the late 1950. Because of the remarkable resemblance to tuberculosis and lack of facilities to perform invasive diagnostic procedures and lack of awareness among physicians and pathologists regarding the disease have all been the reasons for underreporting of the disease. Some also argue that in all cases of Sarcoidosis, which is a disease of unknown origin, because of the high prevalence of tuberculosis in our country, empirical antituberculous treatment should be administered along with Sarcoidosis.[9]

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology. [1,2] Although the frequency and clinical presentation of Sarcoidosis vary among geographic locations, there are more similarities than differences throughout the world.[1]The prevalence of Sarcoidosis is particularly difficult to estimate in regions such as India where tuberculosis is common. In India, Sarcoidosis is an under diagnosed disease [3,4,5,6,7]. Recently we are identifying more and more cases of Sarcoidosis, may be due to the availability of diagnostic modalities such as CT thorax, VATS, fiberoptic bronchoscopy. In our experience, most of the patients with Sarcoidosis are males, and a majority of them present in their fourth or fifth decade of life. Few patients with Sarcoidosis are asymptomatic with incidental findings on the chest radiograph. Among males, most of them are non-smokers. The only co-morbidity noted was diabetes mellitus. Patients with Sarcoidosis mostly presented with symptoms due to pulmonary component. Rest of the patients presented in the dermatology department with skin lesions. Lymphadenopathy especially bilateral hilar was present in all our cases. The systems involved in our cases were pulmonary, followedby dermatology, ophthalmology and finally renal systems. Sarcoidosis with asymptomatic bilateral hilar adenopathy or acute erythema nodosum have favourable prognosis. Diagnosis is often delayed because of the usual nonspecific presentation. Diagnosis is based on compatible clinical and/or radiological picture, histological proof of non caseating granulomas and exclusion of similar diseases. [8,9]

Burden of Sarcoidosis

The true burden of Sarcoidosis in India is not clearly known as reliable epidemiological data are not available[4,5]. In our department of pulmonology 11 cases were identified within a period of eight months.

Clinical presentation

Sarcoidosis is predomin antly a disease of adults and seldom seems to affect children. While more than 70 percent of the Sarcoidosis in the west were less than 40 years of age[1, 2]. Sarcoidosis in our experience has a late onset by nearly a decade as shown in the Fig 1

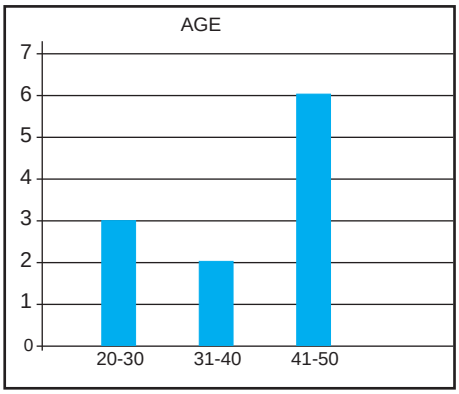

Fig. 1 : Age distribution of Sarcoidosis

While the diseases has a slight female preponderance globally (1, 2), Sarcoidosis is commoner in males in our profile(Fig 2)

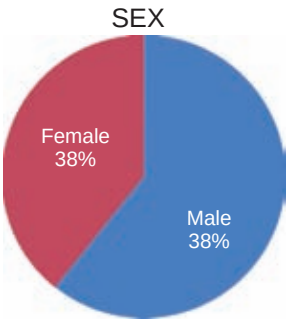

Fig. 2 : Sex distribution of Sarcoidosis

Acute presentation in the form of lofgren's syndrome and heerfordt's syndrome was not noted in any of our patients thoughtwo had acute erythema nodosum and bilateral hilar adenopathy. Familial Sarcoidosis has occasionally been reported from India also. In the series reported by us no familial involvement was noted.

The constitutional symptoms such as fever, fatigue, and malaise and weight loss have been reported to occur more often in Indian patients than in patients from the west. In our series constitutional symptoms were present in three of nine symptomatic patients.

Pulmonary involvement was noted in all our patients. Eight out of nine symptomatic patients had cough which was commonly non-productive, dyspnoea and one had chest pain. Haemoptysis and clubbing were absent. Chest signs on auscultation such as creps were noted in two patients. Cutaneous involvement was noted in five out of eleven patients. These include erythema nodosum (in two cases), plaques, maculopapular lesions, subcutaneous nodules, alopecia and hypo and hyper pigmented areas. Sarcoidosis skin lesions seldom produce itching or pain and they do not ulcerate. Ocular involvement was noticed in two patients of Sarcoidosis. Though all the parts of the eye or orbit can be affected nonspecific uveitis was the ocular manifestation in both cases. Peripheral Lymphadenopathy was observed in four patients, among which supraclavicular was the most common.

Hypercalcaemia and hypercalciuria was encountered in two patients with Sarcoidosis. Nephrocalcinosis that can occur secondary to persistent Hypercalcaemia and hypercalciuria was present in those two cases.

Radiological manifestation

The chest radiographs revealed abnormalities in all our patients with Sarcoidosis at presentation. The characteristic radiological finding encountered in all our patients was bilateral hilar Lymphadenopathy. Pulmonary Sarcoidosis staged by the traditional radiographic criteria is as follows [1,2]

Stage 0 Normal chest radiograph
Stage 1 Bilateral hilar adenopathy without Parenchymal infiltrates
Stage 2 Bilateral hilar adenopathy with Parenchymal nfiltrates
Stage 3 Parenchymal infiltrates without hilar adenopathy
Stage 4 Advanced fibrosis

In the western literature, most of the patients had stage 1 disease, while most of the Indian patients with Sarcoidosis presented with Stage 2 disease. In Indian patients with Sarcoidosis, it has been observed that while the chest radiographs may look startling, patients may manifest minimal symptoms and this has been termed clinicoradiographicdissociation.In our series, seven patients had bilateral hilar lymphadenopathy and four had Stage 2 Sarcoidosis at the time of presentation. Clinicoradiographic dissociation was present in two cases of Sarcoidosis.

Parenchymal infiltrates that are often bilateral and symmetricalreticular, reticulonodular, focal alveolar opacities, milliary mottling of ground glass appearance were the patterns observed in cases with stage 2 Sarcoidosis. Pleural involvement was absent in all patients.

While computerized tomographic scan of the chest is not routinely required for diagnostic evaluation or follow up of patients with Sarcoidosis, it was useful in detecting enlarged lymph nodes or parenchymal infiltrates that were not evident on the conventional chest X ray and was therefore useful in patients with atypical or uncommon manifestations. Characteristic features of Sarcoidosis on CT scan included central bronchovascular thickening and nodularity, milliary nodules, thickening of interlobular septae, luminal irregularity, ground glass attenuation, architectural distortion, honey combing. The lesions were most commonly located along the peribronchovascular sheath lymphatics and sometimes in sub pleural and interlobular septal lymphatics.

Laboratory investigations

Cutaneous anergy is considered to be a cardinal feature of Sarcoidosis.[1,2] Tuberculin skin test was negative in all of our patients with Sarcoidosis. Hypercalcaemia and hypercalciuria was present in two patients with Sarcoidosis. Elevated levels of serum ACE had been observed in three of five patients with Sarcoidosis. Rest of them can't afford it. Elevated levels of serum ACE have been observed in 40 to 90% of patients with Sarcoidosis and areconsidered to be a marker of disease activity in reports from the west.[8] Experience with this expensive test in the Indian context has been controversial.Gupta et al[3] observed elevated serum ACE levels in three-fourths of their Indian

Pulmonary function

Pulmonary function abnormalities were present in about 14.2% of patients with stage 1 Sarcoidosis, 75% of patients with Sarcoidosis. Restrictive pattern was present in six cases of Sarcoidosis. Obstructive

defect was noticed. Exercise induced desaturation was present in two cases of stage 2 Sarcoidosis. However pulmonary function abnormalities are not specific for Sarcoidosis are typical for ILD of any aetiology.[1,2] Review of published evidence suggests that the physiological abnormalities poorly correlate with the pathological findings.

Bronchoscopy

Flexible fiberoptic bronchoscopy and bronchoscopic techniques such as transbronchial lung biopsy (TBLB) and bronchoalveolar lavage (BAL) had been found to be useful for studying the disease and procuring tissue for the confirmation of a diagnosis of Sarcoidosis. BAL has very little practical clinical or prognostic utility and has been utilized as a research tool. BAL revealed lymphocytic alveolitis in eight out of eleven cases.

Diagnosis

As there is no definitive gold standard for the diagnosis, Sarcoidosis is essentially a diagnosis of exclusion . The antigen required for kveim-slitzbach test is not widely available in India, not well standardized, and not approved for general use Thus all suspected cases of Sarcoidosis must be confirmed by tissue biopsy to exclude mycobacterial, fungal, and other granulomatous infections or malignant conditions. Specimens were procured for histopathological examination from the most accessible site with the least invasive method. TBLB and video assisted thoracoscopic surgery (VATS) had been found to be useful in procuring lung as well as intra thoracic lymph node material. Presence of non caseatingepithelioid cell granulomas in tissue biopsy specimens confirmed the diagnosis of Sarcoidosis. A complete and thorough history of occupational and environmental exposure, medication use and medical history was obtained and other known causes of granulomatous inflammation were excluded before a patient was labelled as having Sarcoidosis. Histopathological sample was obtained by lymph node biopsy in eight cases. Peripheral lymph node biopsy in four and VATS guided intrathoracic lymph node biopsy in four cases. Skin biopsy in three cases. Lung biopsy in two cases, transbronchial lung biopsy in one and VATS guided in other.

Management

Decision to treat Sarcoidosis depended on the presence of symptoms and stage of the disease[10,11,12,13,14]. No treatment was given for patients with stage 1 disease. For three patients with stage 2 who had symptomatic pulmonary disease, systemic steroids were started. These patients also had extensive extra pulmonary vasculitis in one of them and Hypercalcaemia in two of them. Topical steroids for eye lesions were given in 2 patients. Corticosteroids had been the mainstay of therapy in patients with Sarcoidosis.[10,11,13]

Sarcoidosis patients were monitored regularly. Monitoring included a review of symptoms, physical examination, chest x-ray and spirometry. Patients with stage 1 Sarcoidosis were monitored initially every six months then once a year for next three years, if stable. Patients with stage 2 were monitored initially every 3-6 months and to be monitored indefinitely once a year if stable. Prednisolone treatment resulted in significant improvement in pulmonary functions. If the response to the treatment was considered appropriate, steroids were gradually tapered while following the patients clinically, radio graphically and physiologically.

Conclusions

In India, Sarcoidosis is an under diagnosed disease. With the availability of VATS, FOB and HRCT newer and newer cases are detecting. Most of the patients with Sarcoidosis in our series are males, the majority presenting in the fourth or fifth decade of their life. Mean age noted was higher. In our patients with Sarcoidosis, clinicoradiographic dissociation was seen. Presence of hilar adenopathy may speed up the diagnostic process. Evidence of multiorgan involvement is supportive of a diagnosis of Sarcoidosis. The organ most affected by Sarcoidosis was lung and intrathoracic lymph node. Pulmonary function abnormalities were suggestive of a restrictive ventilatory defect. Treatment should be tailored to suit the needs of the individual patient under close clinical monitoring.

References

1. Newman LS, Rose CS, Maier LA. Statement on Sarcoidosis. AmJ RespirCrit Care Med 1999;160:736-55.
2. Nunes H, Soler P, Valeyre D. Pulmonary sarcoidosis.Allergy 2005;60:565-82
3. Gupta SK, Dutta SK. Diagnostic delay and difficulties insarcoidosis in Eastern India. Lung India 1999;17:107-11.
4. Sharma SK, Mohan A. Sarcoidosis: global scenario andIndian perspective. Indian J Med Res 2002;116:221-47.
5. Singh RB, Babu KS. Pulmonary sarcoidosis in a SouthIndian hospital: clinical and lung function profile. Indian JChest Dis Allied Sci 1999;4:145-51.
6. Sharma SK, Mohan A. Sarcoidosis in India: not so rare! J Indian AcadClin Med 2004;5:12-21.
7. Sharma SK, Mohan A, Guleria JS. Clinical characteristics,pulmonary function abnormalities and outcome ofprednisolone treatment in 106 patients with sarcoidosis.JAssoc Physicians India 2001;49:697-704
8. DeRemee RA. Sarcoidosis. Mayo ClinProc 1995; 70:177
9. Sulavik SB, Spencer RP, Palestro CJ, et al. Specificity and sensitivity of distinctive chest radiographic and/or 67Ga images in the noninvasive diagnosis of sarcoidosis. Chest 1993; 103:403.
10. Lannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357:2153.
11. Du Bois RM. Corticosteroids in sarcoidosis: friend or foe? EurRespir J 1994; 7:1203.
12. Judson MA. The diagnosis of sarcoidosis.Clin Chest Med 2008; 29:415.
13. Baughman RP, Costabel U, du Bois RM. Treatment of sarcoidosis. Clin Chest Med 2008; 29:533.
14. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008; 63 Suppl 5:v1. 50
15. Winterbauer RH, Lammert J, Selland M, et al. Bronchoalveolar lavage cell populations in the diagnosis of sarcoidosis. Chest 1993; 104:352.

✪ CASE SERIES ARTICLE

Unusuals in Uterine Pathology
Part II: Clear cell adenocarcinoma of endometrium: A rare uterine neoplasm

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Abstract

In the second part of this series article we are discussing a case of clear cell endometrial cancer (CCE) which is a rare but important neoplasm because of its aggressive behaviour. It also has got a high recurrence rate. A fifty two year old postmenopausal lady was detected to have a suspicious growth in the uterine cavity on radiological investigations. Pap smears showed the presence of atypical cells of possible endometrial origin. Both dilatation and curettage and hysterectomy specimens showed a neoplasm with cells having a clear cell morphology. The findings were consistent with CCE carcinoma. This case is reported because of its rarity.

Keywords: Clear cell endometrial cancer, hobnail, tubulocystic, serous.

Introduction

Clear cell endometrial cancer is recognized and defined on the basis of clearing of cytoplasm of neoplastic cells which can grow in any pattern namely solid, glandular, tubulocystic , papillary or a combination of these. It is a rare neoplasm forming about1-5% of all endometrial carcinomas and occurs almost exclusively in postmenopausal

Case Report

A 52 year old postmenopausal female presented with complaints of spotting per vaginum since four years. She is a known diabetic, hypertensive and hypothyroid. Per vaginal examination revealed a bulky and anteverted uterus. Ultrasonogram showed endometrial thickness of 1.5cm with indistinct endomyometrial junction. MRI revealed an enhancing lobulated lesion within endometrial cavity with breech of endomyometrial interface and invasion of greater than 50% of myometrium. Multiple enlarged lymphnodes were also noted.

Pathology

Pap smear cytology showed atypical cells in three dimensional clusters with hobnailing of the nuclei which showed pleomorphism (Fig 1a and 1b) . The smear was reported as Atypical Glandular Cells Of Undetermined Significance (AGUS) - possibly of endometrial origin. This was followed by dilatation and curettage which showed a neoplasm composed of clear and hobnail cells arranged in solid, tubulocystic, glandular and occasional papillary pattern(Fig 2a & 2b). A cervical polyp was also present.

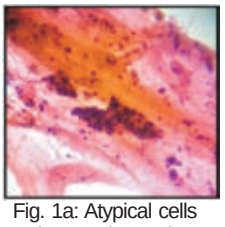

Fig. 1a: Atypical cells (Pap stain100X)

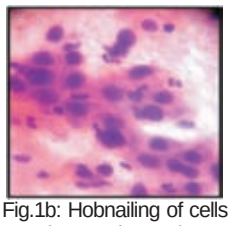

Fig.1b: Hobnailing of cells (Pap stain400X)

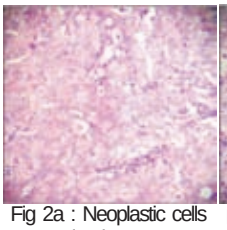

Fig 2a : Neoplastic cells in sheets (H&E 100X)

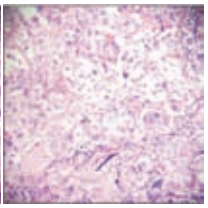

Fig 2b: Neoplastic cells with clear cytoplasm (H&E 100X)

She underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, lymphadenectomy and omentectomy. The specimen we received was an irregularly enlarged uterus. The endometrial cavity showed a

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polypoidal growth measuring 2x1x0.8cm with granular cut surface (Fig 3). Cut section of both the ovaries showed well defined and diffuse whitish areas. All the other structures appeared unremarkable.

Fig 3: Polypoidalgrowth in endometrial cavity

The H&E stained sections from the uterus showed a neoplasm arising from the endometrium and infiltrating upto the serosa. The neoplasm was composed of cells arranged in sheets, tubulocystic (Fig 4a) and papillary pattern with many psammoma bodies (Fig 4b). The cells were large polygonal with clear/ pale eosinophilic cytoplasm (Fig 4c), pleomorphic vesicular nucleus and numerous mitotic figures. The stroma showed many vascular emboli (Fig 4d) and dense lymphoplasmacytic infiltration. The cervix, both the ovaries and fallopian tubes showed infiltration by neoplastic cells.The lymph nodes showed no neoplastic deposits.

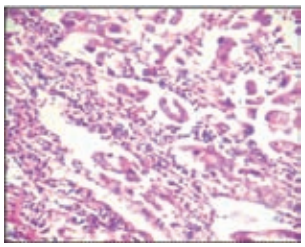

Fig 4a: Cells in tubulocystic pattern (H&E 100X)

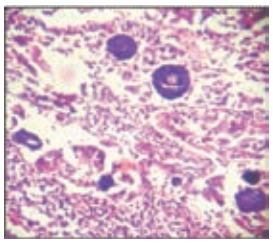

Fig 4b: Psammoma bodies (H&E 100X)

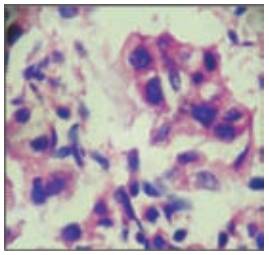

Fig 4c: Large cells with clear/pale eosinophilic cytoplasm (H&E 400X)

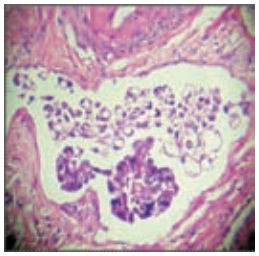

Fig 4d: Vascular emboli (H&E 100X)

Discussion

Clear cell adenocarcinoma is a rare neoplasm of the endometrium comprising only about 1-5 % of the endometrial malignancies. According to WHO, CCE is defined as an adenocarcinoma composed mainly of clear or hobnail cells arranged in solid, tubulocystic and papillary patterns or a combination of these. It is a type II tumour (estrogen independent) arising from the atrophic endometrium similar to serous carcinoma and is seen exclusively in post menopausal females.

The lesion is found in patients who present typically with abnormal or postmenopausal bleeding or discharge. Such bleeding is followed by further evaluation leading to a tissue diagnosis, usually done by a dilatation and curettage (D&C). Histologicales the lesion may coexist with classical endometrial cancer. Clear cell endometrial cancer has no characteristic gross features. Histologically, it can show any of the following patterns namely papillary, tubulocystic or solid, solid pattern being the most common . The papillae may be filiform and regular or irregular in size and shape . The constituent cells can be one or more of 5 types: (1) polygonal with clear, glycogen-rich cytoplasm and eccentric nuclei; (2) hobnail; (3) polygonal with oxyphilic cytoplasm; (4) flattened; and (5) cuboidal. The nuclear features are typically grade 2 or 3. Highly pleomorphic nuclei with bizarre and multinucleated forms may also be seen. Other common features include intraluminal mucin, focal presence of intracytoplasmic vacuoles containing eosinophilic hyaline mucin droplets and stromal hyalinization and deposition of basement membrane material.

CCE differ slightly from serous tumours by presence of two fetures : (1) glands or papillae lined by single layer of polyhedral cells with uniform nuclei and prominent nucleoli, (2) in contrast to serous carcinomas, prominent exfoliation is not present.

Patients with CCE are usually diagnosed in advanced clinical stages. These tumours are very aggressive neoplasms and have a very poor prognosis. But tumours confined to the uterine corpus have a considerably better prognosis when compared to serous adenocarcinomas of same stage[1]. According to the FIGO Annual Report 2006, 5-year overall survival was 62.5% for patients with this histological type compared with 83.2% for those with endometrioid carcinoma of the endometrium[6,7].

Treatment for clear cell endometrial cancer incorporates surgery, chemotherapy, and/or radiotherapy, often in combination. Literature data on the pattern of failures and the optimal treatment modalities of the clear cell carcinoma are not well defined, largely because most papers have assessed clear cell carcinoma and serous adenocarcinomas together because of their rarity. But at present the primary treatment is considered surgical. FIGO-cancer staging is done at the time of surgery which consists of peritoneal cytology, total hysterectomy, bilateral salpingo-oophorectomy, pelvic/para-aortic lymphadenectomy, and omentectomy. Relapse in the pelvis, in para-aortic nodes and at distant sites have also been reported in these rare tumours[8].

References

1. Haines and Taylor. Endometrial hyperplasia and cancer. Harold Fox, Michael Wells, editors. Obstetrical and Gynecological Pathology. 5th edition. Elsevier Science;2003. Pg .469-471

2. WHO Classification of Tumours. Tumours of breast and female genital organs. Tumours of uterine corpus. Editors , Fattaneh.A, Tavassoli, Peter Devilee. IARC press, 2003. Pp 225-226.

3. Trope.C, Kristensen GB, Abeler VM. Clear cell and papillary serous carcinoma – Treatment options. Best Practice Res Clin Obstet Gynecol. 2001; June:15(3) 433-446.

4. Olawaiye AB, Boruta.D, Management of women with clear cell endometrial carcinoma. GynecolOncol (2009), doi 10.1016/j.ygyno.200902.003.

5. Christopher D.M Fletcher. Diagnostic histopathology of tumours. Tumours of female genital tract. 4th edition. Pp. 773-774.

6. Gadducci.A, Cosio.S, Spirito.N, Cionini.L. Clear cell carcinoma endometrium – A biological and clinical enigma. Anticancer research. 2010 April; 30(4):1327-34.

7. Hamilton .A, Cheung MK. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to Gr 3 endometrioid corpus cancers. British journal of cancer. 2006 March, 13; 94(5) 642-6.

8. Joyce Varughese, Pei Hui,LingengLu,Herbert Yu. Clear cell cancer of uterine corpus : The association of clinicopathological parameters and treatment on disease progression. Journal of oncology. Vol 2011(2011).

✪ CASE REPORT

Condylar Hyperplasia

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Eapen Thomas

Abstract

Condylar hyperplasia is a rare disorder characterized by unilateral enlargement of the mandibular condyle leading to gross facial asymmetry. The exact aetiology or pathogenesis of condylar hyperplasia is unknown. Various classifications and treatment modalities have been proposed for the same. Female patients are more commonly affected than males. Here we report management of condylar hyperplasia in a patient who reported to our department with a complaint of facial asymmetry and inability to chew on the right side of her face. The treatment planning and execution were carried out based on an available literature search and taking into consideration patient's concerns and fears. Though the primary treatment was correction of the hyperplasia through condylectomy, she required a postoperative maxillo-mandibular fixation for corrective occlusal guidance.

Keywords:

Condylar hyperplasia, Condylectomy, Mandibular condyle, enlarged condyle

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Introduction

Condylar hyperplasia is a rare disorder which is characterised by a unilateral enlargement of the mandibular condyle leading to facial asymmetry. It may occur in the age group of 10 – 30 years. In childhood forms, compensatory mechanisms leads to an almost normal appearance. If it occurs in late growing phase, it leads to facial deformity.Treatment options are many namely Conservative management, high condylectomy, condyloplasty, complex mandibular

Case Presentation

A 42 year old female presented with a complaint of a progressive shift of lower jaw towards the left side for the past 6 months. She also had severe pain on the right side of the temporomandibular joint which was getting referred to the right side of the face. She also had difficulty in chewing and pain increased on talking. There was frequent tongue biting and ulceration in the tongue due to altered movements of the jaw.

On examination, there was a deviation of chin to left side. The angle of mandible at right side was at a lower position when compared to the left. Lips were competent. The right side of labial commissure was at a lower level when compared to left (Figure 1 & 2).

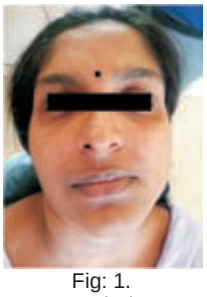

Fig: 1.
Frontal View

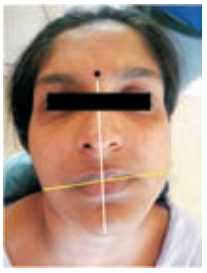

Fig: 2.
Superimposition showing asymmetry

The mandibular midline was shifted to left side. A Class III occlusion on right side and class I relation on left. Right posterior openbite and a contralateral crossbite was seen. Cond ylar movements could be palpated. Tenderness in relation to right TMJ was elicited and patient had difficulty in opening the mouth (Figure 3).

However, no ulceration could be seen on the tongue which was part of her presenting complaint.OPG revealed an enlarged right mandibular condylar head and neck. Vertical

ramus height was increased on right side. Class III molar relation on right side and a class I on left (Figure 4).

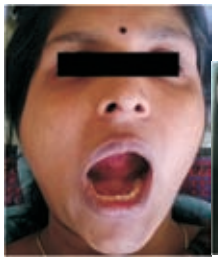

Fig: 3. Restricted mouth opening

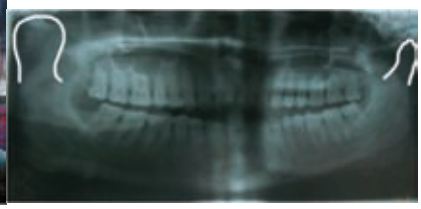

Fig: 4. Superimposition in OPG showing enlarged condyle on right side.

3D CT scan was taken to know the medial extent of the hyperplastic growth. It showed an enlarged right condyle along the anteroposterior as well as in the medial plane (Figure 5&6).

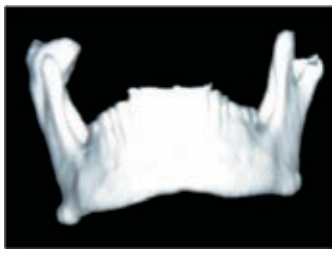

Fig: 5. Medial extent in 3D CT

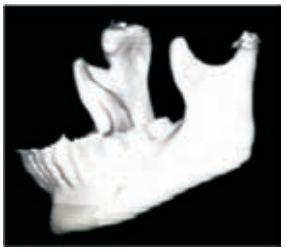

Fig: 6. Anteroposterior extent in 3D CT

Subsequent Course

Treatment was planned as a two stage procedure – Condylectomy followed by esthetic surgery if the need arose.

A pre-auricular incision with a Blair's hockey stick extension was marked.Local anesthetic with adrenaline was infiltrated along the incision line since the preauricular area is highly vascular. Incision was placed and temporalis fascia was exposed and the flap was retracted anteriorly. Temporalis fascia was incised and blunt dissection was carried inferiorly over the zygomatic arch. The condyle was exposed. Since the maxillary artery is in close proximity to neck of the condyle, the ostectomy was done as multiple segments. A 2 cm gap was achieved between ramus and glenoid fossa to avoid ankyloses (Figure 7, 8, 9).

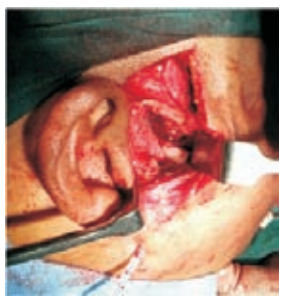

Fig: 7. Defect

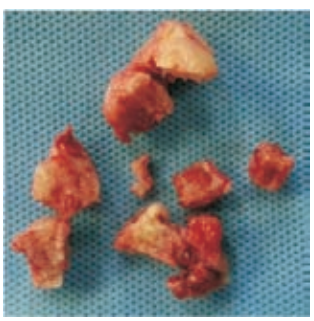

Fig: 8. Resected Condyle

A negative suction drain was placed and the surgical site was closed in layers. Upper and lower eyelets were placed to facilitate guidance and cross-bite correction in the postoperative period.On the 3rd post-operative day, she was placed on inter-maxillary fixation for a period of 2 weeks. At the end of 2 weeks, patient had a restriction in opening the mouth, which improved progressively over time with active mouth opening exercises. At the end of 4 weeks after surgery, she had full range of movement (Figure 10) and wasnot interested in undergoing further cosmetic corrections.

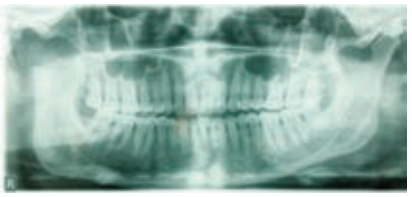

Fig: 9. Post OP OPG

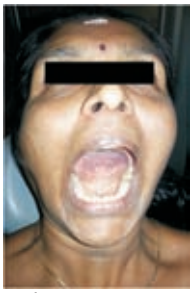

Fig: 10. Post OP Mouth Opening

Histopathological section showed mature lamellar trabeculae, some showing widening, separated by marrow elements and fibro-fatty tissues. One of the sections showed ossification of the marrow tissue. No cartilaginous tissue is seen. These were consistent with Osteomyelosclerosis which is an increased density of cancellous bone while the cortical bone remains unaffected.

Discussion:

Condylar hyperplasia is a rare condition characterized by unilateral enlargement of the mandibular condyle leading to various degrees of facial asymmetry depending upon age of onset. Various classifications have been described for the same.

Obwegeser & Makek proposed a classification system in 1986 describing 2 different types of Condylar hyperplasia. Hemimandibular elongationdescribed as a deformity created by horizontal displacement of the mandible and chin toward the unaffected side without significant vertical elongation. They stated this entity can be bilateral or unilateral. The other anomaly was hemimandibular hyperplasia that included enlargement on one side of the mandible as a tri-dimensional anomaly, involving the condyle, ramus, and body, creating a unilateral vertical elongation deformity with the maxilla usually following the mandible, creating a transverse cant in the occlusion and jaws.

Wolford Classification–CH type 1: Onset usually occurs during puberty; an accelerated and prolonged growth aberration of the “normal” condylar growth mechanism causes condylar and mandibular elongation (prognathism); 60% of patients are female; growth is self-limiting, usually ending by the early to mid-20s, and can occur bilaterally (CH type 1A) or

unilaterally (CH type 1B).CH type 2: A unilateral condylar enlarging pathology is caused by an osteochondroma; it can develop at any age (although 68% are initiated during the second decade): it occurs predominantly in female patients (76%) and with a vertical overgrowth of the mandible. One growth vector causes predominantly vertical elongation and enlargement of the condylar head and neck (CH type 2A) and the other form also has a horizontal exophytic tumor growth off of the condyle (CH type 2B).CH type 3: These are other benign tumors causing CH.CH type 4: These are malignant tumors that originate in the condyle, causing enlargement.

In a series of 61 patients, Nitzan et al, it was observed that CH may occur at any age, it does not stop at the end of the growth period, it is more prevalent in females, and its laterality is gender-dependent. Patient's primary complaint is almost always facial asymmetry, though varying degrees of TMJ signs and symptoms may be present.

It has an uncertain aetiology, but there is a consensus that the growth in one of the condyles in adults may be accelerated, or that the growth may be prolonged by persistent activity of the condyle after the end of general skeletal growth. However, there are additional factors such as hormonal influences, hyper-vascularity, heredity, infection, or trauma.

In most patients with this anomaly, the mandibular arch form remains approximately symmetric with the maxillary arch, and there is no major compensatory alveolar modifications, and that except for the condylar enlargement and increased length of the condylar neck causing deviation of mandible and the chin to the opposite side and cross-bite, the general contour of the displaced mandible is symmetric .

Condylar hyperplasia is usually self-limiting, but the longer it persists the greater the developing asymmetry and associated changes .

Treatment consists of removal of the growth centre by a partial condylectomy and secondly, correction of the facial asymmetry by orthodontics and surgery. Published articles have demonstrated the effectiveness of condylectomy only, in managing adult patients with active condylar hyperplasia. Condylectomy in association with bimaxillary surgery has been shown to produce good clinical results in terms of facial symmetry and unimpaired joint function. Same study reveals that all these joints have signs of arthrosis in some form.A recent study evaluated condylar function in patients with active CH who underwent condylectomy.

They found a good condylar function, if the patients followed a postoperative physiotherapy schedule and they suggested that condylectomies must be considered in treatment of active CH in adults as well as growing children with CH .

Conclusion

Condylar hyperplasia is an over development of the condyle leading to facial asymmetry and malocclusion. Early diagnosis and surgical intervention can improve the aesthetic and functional outcome even without cosmetic correction.

References

1. Angiero, F.; Farronato, G.; Benedicenti, S.; Vinci, R.; Farronato, D.; Magistro, S.; Stefani, M. Mandibular condylar hyperplasia: clinical, histopathological, and treatment considerations. Cranio**2009**,27(1), 24-32.
2. Wolford, L.;Movahed, R.;Perez, D. A Classification System for Conditions Causing Condylar Hyperplasia. J Oral Maxillofacial Surg**2014**,72 (3), 567-595.
3. Verhoeven, T.; Nolte, J.; Maal, T.;Berge, S.; Becking, A. Unilateral condylar hyperplasia: a 3- dimensional quantification of asymmetry. PLoS One**2013**,8(3).
4. Bartl, R.; Frisch, B. Biopsy of Bone in, Internal Medicine: An Atlas and Sourcebook;, 1993;Vol. 21,pp 187-193.
5. Obwegeser, H.; Makek, M. Hemimandibular hyperplasia-Hemimandibular elongation. J Maxillofac Surg1986,14(4), 183-208.
6. Nitzan, D.; Katsnelson, A.; Bermanis, I.; Brin, I.; Casap, N. The clinical characteristics of condylar hyperplasia: with 61 patients. J Oral Maxillofac Surg**2008**,66 (22), 312-318.
7. Gray, R.; Sloan, P.; Quayle, A.; Carter, D. Histopathological and scintigraphic features of condylar hyperplasia. Int J Oral Maxillofac Oral Surg**1990**,19 (2), 65-71.
8. Mehrotra, D.; Dhasmana, S.; Kamboj, M.; Gambhir, G. Condylar hyperplasia and facial asymmetry: report of five cases. J Maxillofac Oral Surg**2011**,10(1), 50-56
9. Butt, F.; Guthua, S.; Nganga, P.; Edalia, M.; Dimba, E. One- stage treatment of acquired facial deformity caused by severe unilateral condylar hyperplasia. J Craniofac Surg**2011**,22 (5), 1966-1968.
10. Alyamani, A.; Abuzinada, S. Management of patients with condylar hyperplasia: A diverse experience with 18 patients. Ann Maxillofac Surg**2012**,2 (1), 17-23.
11. Lippold, C.; Kruse-Losler, B.; Danesh, G.; Joos, U.; Meyer, U. Treatment of hemimandibular hyperplasia: the biological basis of condylectomy. Br J Oral Maxillofac Surg**2007**, 45 (5), 353-360.
12. Olate, S.; Martinez, F.; Uribe, F.; Pozzer, L.; Cavalieri-Pereira, L.; de Moraes, M. TMJ function after partial condylectomy in active mandibular condylar hyperplasia. Int J Clin Exp Med**2014**,7(3), 775-779.
13. Saridin, C.; Gilijamse, M.; Kuik, D.; te Veldhuis, E.; Tuinzing, D.; Lobbezoo, F.; Becking, A. Evaluation of temporomandibular function after high partial condylectomy because of condylar hyperactivity. J Oral Maxillofac Surg2010,68 (5), 1094-1099.

✪ CASE REPORT

An unusual presentation of Mucormycosis

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Abstract

Mucormycosis is a rare opportunistic fungal infection most frequently caused by mucor and rhizopus species. Depending on the immune status of the patient the disease may manifest in several different ways. Patients with diabetes mellitus usually have rhinocerebral and pulmonary type of mucormycosis. The management of mucormycosis includes surgical debridement and administration of antifungal drugs including Amphotericin B. Here we report a case of mucormycosis which coexisted with osteomyelitis and carcinomatous changes in maxilla.

Keywords:

Mucormycosis, Fungal infection, Fungal Osteomyelitis

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Introduction

Invasive fungal infections are uncommon, and are usually severe and devastating to the patients once it occurs. They are opportunistic infections occurring when the host defence mechanism decreases. Mucormycosis is a saprophytic aerobic fungus found in the environment. They are frequently isolated from oral mucosa, nasal mucosa, paranasal air sinuses and pharyngeal mucosa of healthy individuals. However, it can cause serious tissue loss in immunocompromised patients. This is a case presentation about a patient who reported with a suspected periodontal infection of teeth leading to mobility, which turned out to be osteomyelitis secondary to mucormycosis.

Case Presentation

A 61 year old male patient was referred to department of maxillofacial surgery for extraction of mobile teeth. His complaint was pain in gums of upper front teeth since two weeks. He had undergone a coronary artery bypass graft and was on antiplatelet drugs. He was an uncontrolled diabetic under insulin treatment for the past 6 years. He was an occasional pan chewer. He had undergone an extraction of maxillary right molar one year back, following which he had cellulitis and treated for the same. On examination, he had missing – maxillary right molars; Generalised Grade I Mobility of almost all remaining teeth and periodontal abscess in relation to 13, 12, 11 (maxillary right canine, lateral incisor and central incisor). Intraoral Periapical radiograph revealed bone loss, widening of periodontal space in relation to 13, 12, and 11. A diagnosis of Chronic Generalised Periodontitis with Periodontal abscess in relation to 13, 12, and 11 made and it was planned to extract 13, 12, and 11 under LA.

Following institutional protocol, the Patient was referred to Cardiologist & Endocrinologist for fitness, following which the patient reported back after 5 days. Re-examination revealed a swelling measuring 5 X 2 cm on palatal &5 X 1 cm on buccal Side in relation to 15 (Maxillary right 2nd Premolar), 14 (Maxillary right 1st Premolar), 13, 12, 11 region. There was also multiple draining abscess in buccal aspect. The right maxillary dentoalveolar complex was mobile. (Fig. 01)

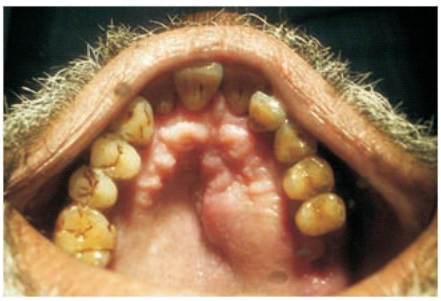

Figure 01 Palatal Swelling

OPG revealed bone loss in relation to 15, 14, 13, 12, 11 region and also exhibited a marked haziness of the right maxillary antrum. CT PNS revealed extensive bony erosions involving inferior and lateral walls of right maxillary sinus, alveolar process of maxilla involving the right half upto the midline and the hard palate on right side.Bony defects were noted involving inferior and lateral walls of right maxillary sinus (Fig. 02 &03).

Mucosal thickening of right maxillary sinus was seen – suggestive of sinusitis. Soft tissue thickening was seen involving the right half of hard palate extending to pterygopalatine fossa. CT was suggestive of a neoplastic change.

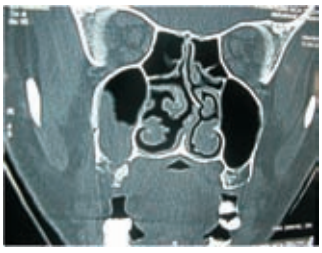

Fig: 02. CT showing bony erosions

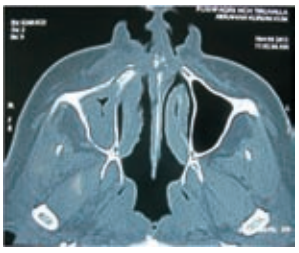

Fig: 03. CT Showing complete obliteration of Maxillary antrum

MRI – Maxilla with contrast was done and it revealedbony erosion of bilateral palatine bone and premaxillary bone. Adjacent maxillary mucosal thickening with a few non-enhancing areas were noted suggestive of necrosis. There was no significant lymph node enlargement. MRI was suggestive of chronic osteomyelitis involving floor of right maxilla with erosion of premaxilla, palatine process of maxilla and horizontal palatine bone with extension into the alveolar margin.An incisional biopsy was done, which was inconclusive.

Based on MRI findings it was decided to do a curettageunder GA for controlling the spread of osteomyelitis though incision biopsy was inconclusive. A crevicular incision from 15 to 11 was placed. Mucoperiosteal flap raised and the necrotic bone was removed (Fig. 04).

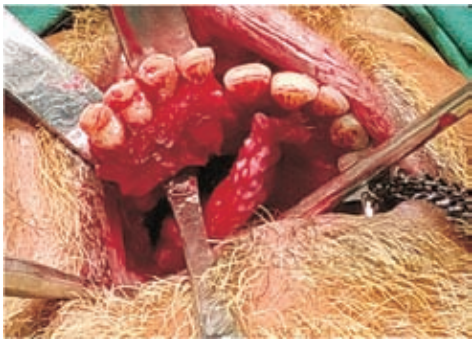

Fig: 4. Necrotic bone removed

Sequestrectomy removed the alveolus, palatine bone, part of lateral wall and medial wall of maxillary antrum. Curettage was done until normal bleeding borders were seen in bone. Intraoperatively the features were like Osteomyelitis. The flap was approximated primarily. On day two an obturator was placed.

The Histopathological picture of the excised specimen revealed presence of bony tissue composed mostly of necrotic bony trabeculae. The marrow spaces showed varying morphological findings. Most areas showed collections of neutrophils and granulation tissue surrounded by chronic inflammatory cells, occasional small epithelioid cell granulomas and few scattered multinucleated giant cells. Sheets of well differentiated squamous epithelium were seen infiltrating the marrow spaces. There were extensive areas showing coagulative necrosis with scattered broad, non-septate, basophilic fungal hyphae. The Histopathological picture was suggestive of squamous cell carcinoma infiltrating maxilla with chronic osteomyelitis and fungal infection by mucormycosis.Since Histopathological examination showed carcinomatous changes, he was referred to oncologist for further evaluation and management. He remains symptom free at the last follow up in our institution.

Discussion:

Mucormycosis (Zygomycosis, phycomycosis) is an acute opportunistic infection caused by a saprophytic fungus. In 90% of the cases of rhino-cerebral mucormycosis, rhizopus is the main pathogen. This microbe may be cultured from the oral cavity, nasal passages, throat, and stool of healthy patients without clinical signs of infection. Predisposing factors for mucormycosis are uncontrolled diabetes mellitus, renal failure, cirrhosis, malignancies, long-term corticosteroid and immunosuppressive therapy, and AIDS. 60 % of reported cases of mucormycosis occurs in diabetic patients . Our patient had uncontrolled diabetes, history of cellulitis, osteomyelitis and also malignancy.

In Diabetic patients there is a decreased granulocyte phagocytic ability with altered polymorphonuclear leukocyte response. Peripheral vascular disease seen is diabetics also causes local

tissue ischemia and increases the susceptibility to infections; therefore, thrombosis of the internal maxillary artery or descending palatine artery caused by mucormycotic infection results in necrosis of the maxilla.

The fungus invades the arteries, forms thrombi within the blood vessels. These thrombi leads to necrosis of the surrounding structures. Based on clinical presentation and the involvement of a particular anatomic site, mucormycosis can be divided into six clinical categories: a. rhinocerebral, b. pulmonary, c. cutaneous, d. gastrointestinal, e. disseminated, and f. miscellaneous.Although mucormycosisis commonly seen affecting other parts of body, mucormycosisof maxilla without orbital involvement is a relatively rare condition.Only 6 such cases have been reported so far. The infection usually presents as acute sinusitis with fever, nasal congestion, purulent nasal discharge, and headache. However, our patient had none of these.A clinical suspicion of mucormycosis requires confirmation by radiological examination, preferably a CT scan of the maxilla, showing membrane or periosteal thickening and bony disruption. In our case, there was extensive bony erosions involving inferior and lateral walls of right maxillary sinus, alveolar process of maxilla involving the right half up to the midline and the hard palate on right side. Bony defects were noted involving inferior and lateral walls of right maxillary sinus.

The general impression of intra-operative finding in our case was similar to that of Osteomyelitis as well as clinical/radiological features. There was necrotic bone with sequestrum, with some granulation tissue with pus discharge in the structures involved.

Surgical debridement is fundamental for the successful management of most cases of Mucormycosis.

In our case, since histopathology revealed osteomyelitis, mucomycosis and squamous cell carcinoma, the patient was referred to oncologist for further management. Ideally Mucormycosis should simultaneously be treated with Amphotericin- B. The usual starting dose is 5 mg/kg daily, and the dosage sometimes will increase up to as high as 10 mg/kg daily in an attempt to control the infection. Antifungal therapy should continue until all signs of infection have been resolved, that might often extends for months .

Conclusion

Mucormycosis can lead to wide spread tissue damage in susceptible individuals. Early recognition and aggressive treatment is required to completely eradicate the condition. This paper also stresses on the importance of maintaining oral health especially in diabetic patients.

References

1. Bhansali, A.; Bhadada, S.; Sharma, A.; Suresh, V.; Gupta, A.; Singh, P.; Chakarbarti, A.; Dash, R. Presentation and outcome of rhino-orbital-cerebral mucormycosis in patients with diabetes. Postgrad Med J**2004**,80 (949), 670-674.
2. Leitner, C.; Hoffmann, J.; Zerfowski, M.; Reinert, S. Mucormy cosis: Necrotizing soft tissue lesion of the face. J Oral Maxillofac Surg**2003**,61, 1354-1358.
3. Pogrel, M.; Miller, C. A case of maxillary necrosis. J Oral Maxillofac Surg2003,61, 489-493.
4. Jones, A.; Bentsen, T.; Freedman, P. Mucormycosis of the oral cavity. Oral Surg Oral Med Oral Pathol**1993**, 75, 455-460.
5. Islam, M.; Cohen, D.; Celestina, L.; Ojha, J.; Claudio, R.; Bhattacharyya, I. Rhinocerebral zygomycosis: an increasingly frequent challenge: update and favorable outcomes in two cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod**2007**,104(5), e28-e34.
6. Auluck, A. Maxillary necrosis by mucormycosis. A case report and literature review. Med Oral Patol Oral Cir Bucal**2007**, 12(5), e360-e364.
7. Fogarty, C.; Regennitter, F.;Viozzi, C. Invasive fungal infection of the maxilla following dental extractions in a patient with chronic obstructive pulmonary disease. J Can Dent Assoc2006,72(2), 149- 152.
8. Pandey, A.; George, J,; Rao, N. Mucormycosis causing extendive destruction of maxilla. Indian J D ent Res**2004**,15(2), 74-77.
9. Ramon, Y.; Oberman, M.; Horowitz, I.; Freedman, A. Extensive maxillary sequestration resulting from rhinocerebral mucormyocosis. J Oral Surg**1977**,35 (12), 989-991.
10. Harril, W.; Stewart, M.; Lee, A.; Cernoch, P. Chronic rhinocerebral mucormycosis. Laryngoscope**1996**,106, 1292-1297.
11. Pandey, A.; Bansal, V.; Asthana, A. K.; Trivedi, V.; Madan, M.; Das, A. Maxillary osteomyelitis by mucormycosis: report of four cases. International Journal of Infectious Diseases**2011**,15(1), e66-e69.
12. Dhiwaker, M.; Thakar, A.; Bahadur, S. Imporving outcomes in rhinocerebral mucormycosis—early diagnostic pointers and prognostic factors. J Laryngol Otol**2003**,117, 861-865.
13. Verma, A.; Singh, V.; Jindal, N.; Yadav, S. Necrosis of maxilla, Nasal, and frontal bone secondary to extensive rhino-cerebral mucormycosis. Natl J Maxillofac Surg**2013**, 4(2), 249-251.

PUSHPAGIRI MEDICAL JOURNAL

✪ CASE REPORT

Vacterl anomalad with fibrotic bands in the lung – Is it another association in the increasing cluster ?

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Abstract

Historically, VACTERL - Vertebral anomalies (V), Anorectal anomalies (A), Congenital Cardiac defects (C), Tracheal Esophageal fistula (TE), Renal (R) and Limb (L) anomalies was known as VATER since 1972 following coining of the term by David Smith, considered by many as the "Father of dysmorphology", as well as Linda Quan, an Emergency Room Physician[1]. It did not previously include cardiovascular or limb defects within the range of the disorder. VACTERL, as we know now, is typically defined by the presence of at least three of the congenital malformations previously described as VATER. However, over the years, case studies reporting these defects have compelled the inclusion of these other defects in the association because of their non-random, co-occurrence within a group of congenital malformations together[2]. The general incidence is quoted to be about 1 in 10000 to 1 in 40000 births[3].

Over time, different authors have found associations which have not been described before, in addition to the core features including Single Umbilical Artery[3,4,5] and Genitourinary abnormalities[5,6]. Three authors have described lung anomalies[7,8,9], all involving the Right side. We report a neonate with multiple of the above described anomalies along with another variant of lung anomaly unreported in literature elsewhere, who presented to our unit.

Keywords: VACTERL, Fibrotic lung bands, Pulmonary anomalies, Lung anomalies

Case Report

This Term, male baby with a birth weight of 2.480 kg was delivered by normal vaginal delivery to a non – consanguineously married 25 year old primigravida with no antenatal risk factors and normal antenatal ultrasound scans. The baby was referred to us for Imperforate anus at 34 hours of life. On examination, there was no abdominal distension and heart sounds were better heard on the Right side, though there was no murmur at admission. There was no obvious facial dysmorphology. No external features to suggest spinal anomaly was clinically evident. Umbilicus was shriveled at admission and the number of umbilical vessels could not be made out.

X-ray chest and abdomen showed a Dextropositioned heart with the Right lung showing haziness (?collapse consolidation), with compensatory emphysema on the Left side even at presentation.(Fig. 1)

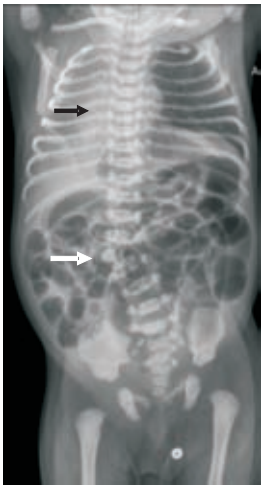
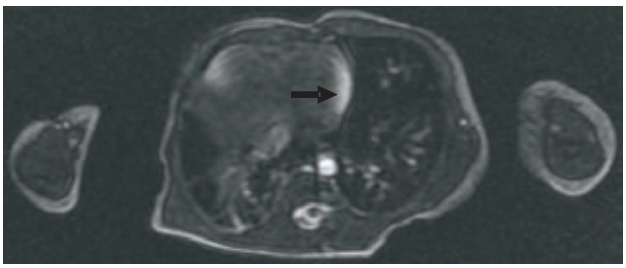


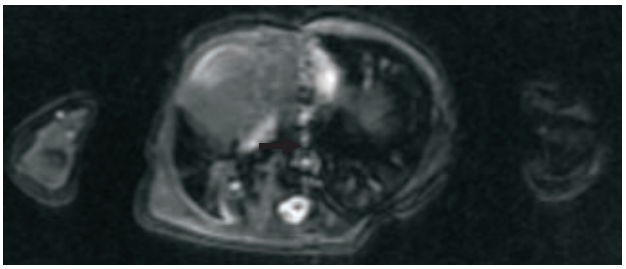
Fig 1: Chest Radiograph showing Dextropositioning of the heart (Black arrow) and Hemivertebra (White arrow). Position of the anal opening is marked on the film - Ring marker placed

Nasogastric tube placed for gastric decompression could be radiologically visualized in the stomach ruling out an Eosphageal atresia. X-ray spine showed right hemi vertebrae at the L1 level. Echocardiogram revealed a Dextropositioned heart with a small secundum ASD, a tiny Patent Ductus Arteriosus (PDA) with Left to Right shunt and moderate Pulmonary arterial hypertension and ruled out other major congenital heart defects. X-ray Cross Table Prone Lateral done confirmed a "High" Anorectal Malformation. An abdominal and transperineal sonography revealed grossly distended rectum,sigmoid and left colon with evidence of a high type of Anorectal malformation. Sonography also revealed bilateral moderate hydronephrosis with a normal bladder (?PUV obstruction). A greening tinge to the urine clinically suggested a recto-vesical fistulous communication.The baby did not show any features of respiratory distress but was started on oxygen in view of the X-ray findings. A suspicion of a lung anomaly was kept in view of the oddity of an early presentation. Paediatric surgery opinion was taken and colostomy was done, following which, the baby passed meconium via the colostomy.

Once stable, an MRI Chest was done in view of the persisting haziness of the lung on the Right side.(Fig. 2)



Sequence 1



Sequence 2

Fig 2 : MRI Chest Axial Fiesta sequences (1 & 2) showing fibrous bands on the Right side (White arrow) and cardiac image is seen towards to the Rt. side (Black arrow).

Right lung showed evidence of volume loss with normal appearance of trachea and bifurcation with few fibrotic strands in right lower lobe. Right hemi vertebra (L1) was also commented upon. (Fig. 3 & 4)

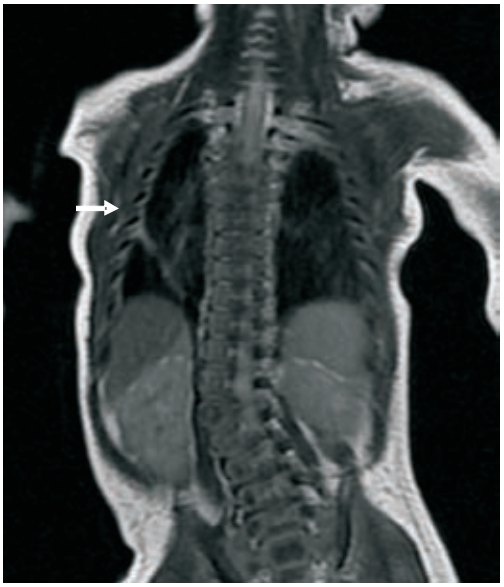


Fig 3 : MRI Chest Coronal image showing the fibrous bands on the Right side of the chest (White arrow)

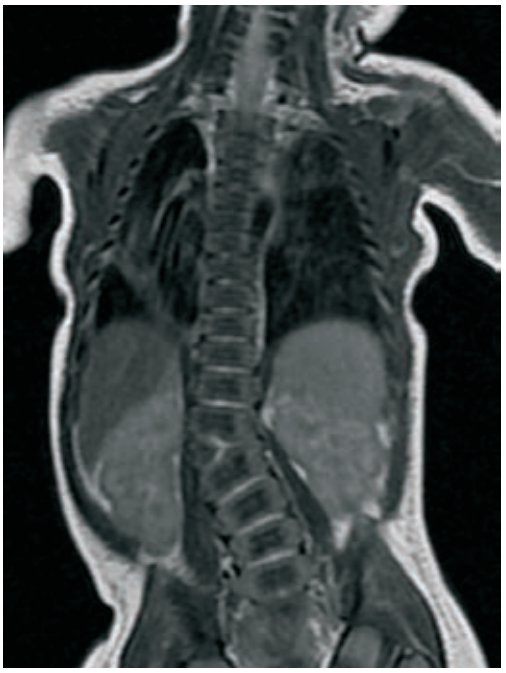


Fig 4 : MRI Chest Coronal image showing hemi-vertebra (Black arrow)

Feeds once gradually introduced were graded up tocup feeds and later Direct breast feeds prior to shifting the baby, who remained well without oxygen during the interim. The baby was discharged satisfactorily, once the mother had learnt colostomy site care and feeding. The baby continued to passstools normally and was on breast feeds without any respiratory distress.

Discussion:

Among the malformations seen as a part of VACTERL, 60-80% of patients have vertebral anomalies. The vertebral anomalies seen are hypoplastic or hemi vertebrae. Anal anomalies namely imperforate anus has been described in 55-90% patients. Forty to eighty per cent have cardiac malformations – Atrial and Ventricular Septal Defects (ASD and VSD) and Tetrology of Fallot (TOF) are among the common congenital heart defects and Truncus Arteriosus and Transposition of the Great Arteries (TGA) may be found rarely. About 25% of patients have renal anomalies like renal agenesis. Other urological and urogenital abnormalities, other than fistulous communication in presence of Ano-Rectal malformation, such as obstruction to the outflow of urine from the kidneys or severe reflux of urine into the kidneys from the bladder have been increasingly described. Forty to eighty per cent of patients may also have displaced or hypoplastic thumb, polydactly, syndactly or radial aplasia. Tracheo-eosophageal fistula (TEF) is by far the commonest association in this condition, being associated in 50 – 80%. Other anomalies of the respiratory tract other than TEF have been rarely picked up unless they were major defects which were clinically evident. Two cases of Pulmonary agenesis in association with the above have been described[8,9] while one was a patient with a Tracheal bronchus[7].

In view of other syndromes with genetic association having phenotypic resemblance to the VACTERL association being there, a genetic basis to explain the apparent non-related pattern of malformations in this condition has been attempted with limited success[3,10].

Management of these patients with VACTERL association typically centres on surgical correction of specific congenital anomalies (Anal atresia, certain types of cardiac malformations, Tracheooesophageal fistula) in the immediate post natal period. Long term medical management of the sequlae of the congenital malformations needs to continue. If optimal surgical correction is achieved, prognosis can be relatively reassuring, though some patients continue to be affected by the malformation through life. Patients with VACTERL association do not tend to have neurocognitive impairment.

Our patient was born low birth weight with Right Hemi vertebrae (L1), high anorectal malformation with fistula, Acyanotic heart disease (ASD, PDA), with bilateral hydronephrosis as a part of VACTERL association and in addition the baby was also found to have fibrosis of the right lung fields with volume loss which has not been described before with VACTERL anomalad. We propose that it may represent an increasing number of variable lung anomalies not just limited to Tracheo-Esophageal Fistula, which now need to be recognized as the new cluster association with the VACTERL anomalad.

Our patient is doing well on follow up, with adequate weight gain, no delay in achievement of milestones this far and is due for an elective colostomy closure and primary repair. Follow up ultrasounds have not shown any worsening of the bilateral pyelectasis.

References:

1. Quan L, Smith DW: The VATER association: Vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, radial dysplasia. In the clinical delineation of birth defects. Volume XII. G.I. tract including liver and pancreas. Edited by: Bergsma D. Baltimore: The Williams and Wilkins company; 1972:75-78.

2. Rittler M, Paz JE, Castilla EE: **VACTERL association, epidemiologic definition and delineation.** *Am J Med Genet* 1996, **63:**529-536.

3. Solomon B D. VACTERL/VATER Association. Orphanet Journal of Rare Diseases 2011, 6:56. Available at http://www.ojrd.com/content/6/1/56. Accessed June 16, 2014.

4. Tongsong T, Wanapirak C, Piyamongkol W, Sudasana J: Prenatal sonographic diagnosis of VATER association. *J Clin Ultrasound* 1999, **27:**378-384.

5. Weaver DD, Mapstone CL, Yu PL: The VATER association. Analy sis of 46 patients.*Am J Dis Child*1986, **140:**225-229.

6. Solomon BD, Pineda-Alvarez DE, Raam MS, Bous SM, Keaton A A, Vélez JI, Cummings DA: Analysis of component findings in 79 patients diagnosed with VACTERL association.*Am J Med Genet A* 2010, 152A:2236-2244.

7. Kanu A, Tegay D, Scriven R: Bronchial anomalies in VACTERL association.*PediatrPulmonol*2008, **43:**930-932.

8. Chen CP, Shih JC, Chang JH, Lin YH, Wang W: Prenatal diagnosis of right pulmonary agenesis associated with VACTERL sequence.*PrenatDiagn* 2003, 23:515-518.

9. Avcu S, Akgun C, Temel H, Arslan S, Akbayram S, Unal O: Report of a girl with VACTERL syndrome and right pulmonary agenesis. *Genet Couns* 2009, 20:379-383.

10 Shaw-Smith C: Oesophageal atresia, tracheooesophageal fistula, and the VACTERL association: Review of Genetics and Epidemiology.J Med Genet 2006;43:545–554.

✪ CASE REPORT

A case of Laryngeal Haematoma following a RTA

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Abstract

51 year old male presented with dysphagia and hoarseness of voice following a road traffic accident (RTA). Clinical examination and investigations revealed presence of laryngeal haematoma. Timely diagnosis helped in management of the case conservatively. This case emphasizes the significance of high index of suspicion in the case of road traffic accidents even in the absence of obvious external injuries and the need of early diagnosis and prompt management.

Keywords: Road traffic accidents, laryngeal haematoma, blunt trauma

Case Report

51 year old male presented to ENT outpatient department with complaints of dysphagia, hoarseness of voice and pain on the left side of neck following a road traffic accident (RTA). He was riding on a motorbike which collided with an auto rickshaw and his neck hit to the handle of the bike. After sometime he developed difficulty in swallowing followed by hoarseness of voice. There was no history of difficulty in breathing or loss of consciousness, or ENT bleed or history suggestive of head injury.

The otorhinolaryngological examination revealed tenderness over the left side of cricoid cartilage and minimal tenderness of left alae of thyroid cartilage. No external neck bruises, swelling or subcutaneous emphysema was found. Laryngeal crepitus was absent. Indirect laryngoscopic examination revealed enlarged left arytenoid and aryepiglottic fold with restricted mobility of left vocal cords.

X-ray of soft tissue neck and cervical spine, both AP and lateral view and chest X-ray were normal. CT neck showed assymmetry between two vocal cords (figure 1). Left vocal cord appeared bulky and oedematous. Thickened aryepiglottic fold with air pockets suggestive of supraglottic haematoma and laryngeal injury was also seen (figure 2). Retropharyngeal air pockets presence of retro was suggestive of pharyngeal injury. Video laryngoscope revealed haematoma of left arytenoids and aryepiglottic fold was seen overhanging into the gloth's. Multiple haemorrhagic spots were present on left vocal cord with impaired mobility of the vocal cord on left side. Both vocal cords were at the same level and there was no evidence suggestive of dislocation. From the examination and investigation laryngeal haematoma extending to supraglottic region was diagnosed. He was treated conservatively with oral steroids, oral antibiotics and anti inflammatory drugs for five days under observation in the hospital. He was discharged on low dose of prednisolone for one week. On subsequent follow up he was found to be asymptomatic and the haematoma found to be completely resolved.

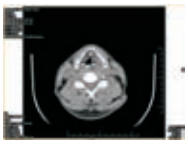

Fig. 1: CT Neck Axial view showing assymmetry of vocal cords. Left vocal cord appears bulky and edematous

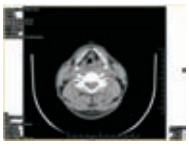

Fig. 2: CT Neck axial view showing thickened aryepiglottic fold with air pockets suggestive of supra glottic haem atoma and laryngeal injury

Discussion:

Blunt trauma to larynx is sustained mainly during motor vehicle accidents, personal assaults, or sports injuries. Although the mandible and sternum normally protect the larynx; hyperextension of neck during the

trauma, which allows the laryngeal skeleton to be crushed between the impinging object and the cervical vertebral column leads to the complications. With a moderate blow to the larynx, the momentum of the vocal folds causes a shearing effect between the vocalis muscle and the internal perichondrium. This results in injuries such as endolaryngeal mucosal tears, edema or hematoma. This case is blunt trauma of low velocity. More severe trauma or of high velocity produces fractures of the laryngeal cartilages and disruption of the laryngeal ligaments[1].

It is of the utmost importance to realize that whilst patients with significant blunt laryngeal trauma are often relatively asymptomatic on initial presentation, they can rapidly develop debilitating stridor and subsequent respiratory compromise. Furthermore, it has been reported that early recognition and treatment of these injuries improves the long-term prognosis .[2, 3]

A high index of suspicion, careful attention to signs and symptoms, thorough physical examination and judicious use of ancillary procedures and radiological examination are essential for prompt identification of the disorder. Dysphonia ranging from mild hoarseness to aphonia, dyspnea and stridor are the common presenting symptoms of laryngeal injury. Other symptoms include haemoptysis, dysphagia, and odynophagia.[4,5] A careful physical examination should be performed to identify associated neurovascular injuries. Attention should be paid to signs like ecchymoses, laryngeal tenderness, subcutaneous emphysema, and palpable cartilage fractures.[1]

The management of this clinical entity poses a particular challenge to the managing physician due to the significant risk of concomitant injury to other vital structures in close proximity to the larynx.[2] If the patient is breathing well and there is no respiratory compromise, observation may be all that are indicated – remembering that all injuries in this region carry a propensity for airway compromise. Injudicious maneuvers such as forceful neck examination, hypopharyngeal suctioning, changing the patient's position from sitting to supine, and nasogastric tube insertion should be avoided during the initial stages of trauma as they may precipitate airway obstruction.

Definitive diagnosis of suspected laryngeo-tracheal injury is made by radiological and endoscopic studies. Soft tissue anterio-posterior and lateral neck X–rays are usually done to identify oedema, subcutaneous emphysema and bony injuries. CT scan neck may detect an unsuspected injury, confirm diagnosis of a laryngotracheal fracture and assess the severity of a fracture preoperatively.[6] Patients with a stable airway should be evaluated with flexible laryngoscopy in the first instance after which, microlaryngoscopy and bronchoscopy can be performed if indicated[2]. However care should be taken in a non intubated patient as the insignificant trauma associated with the insertion of the fiberoscope may precipitate an airway emergency.[6]

Management is divided into medical and surgical treatment depending on the severity of injury as determined at physical examination and radiological assessment. The decision to treat a patient medically or surgically is determined by the likelihood that the injury will resolve without surgical intervention. The following conditions are likely to resolve spontaneously without serious sequelae: edema, small hematoma with intact mucosal coverage, small glottic or supraglottic lacerations without exposed cartilage, and single non displaced thyroid cartilage fractures in a stable larynx[7, 8]. Traditional management of these patients consists of measures including voice rest, humidification, prophylactic antibiotics, proton pump inhibitor therapy, and steroids [2].

The goals of adjuvant therapy are to eliminate further injury and to promote rapid healing. Hospitalization and monitoring for at least 24 hours is recommended to observe for signs of progressive airway compromise. Preparations are made for possible emergency tracheotomy. Bed rest with elevation of the head of the bed for several days helps resolve laryngeal edema. A period of voice rest can minimize further edema or reduce the progression of a hematoma or subcutaneous emphysema. The use of cool, humidified room air helps prevent crust formation in the presence of mucosal damage and transient ciliary paralysis. Additional oxygen is usually not needed unless evidence exists of oxygen desaturation, the advent of which should prompt further investigation.

Corticosteroids, if use, are most likely to be of benefit in the first few hours after injury. If evidence of a mucosal tear or laceration is found, antibiotics can be useful as prophylaxis against infection.

A patient with a laryngeal injury is restricted at first to a clear liquid diet with intravenous supplementation, as necessitated by other injuries. Nasogastric feedings usually are unnecessary, and passage of a nasogastric tube can worsen the injury. Prolonged use of a nasogastric tube can traumatize the posterior larynx and promote gastric acid reflux. The use of H_2 blocking agents and proton-pump inhibitors can help prevent the development of reflux laryngitis, which may be important in preventing scar formation in the instance of laryngeal mucosal injury.

Surgical treatment in blunt trauma to larynx is often required due to associated structural damages. Small mucosal damage could be corrected using endoscope.

Injuries likely to necessitate open laryngeal exploration and repair include lacerations involving the free margin of the vocal fold, large mucosal lacerations, exposed cartilage, multiple and displaced cartilage fractures, avulsed or dislocated arytenoid cartilages, and vocal fold immobility[7,8,9].

Surgical management includes open reduction and internal fixation of laryngeal fractures and endolaryngeal stent insertion.

Success is measured in terms of restoration of the voice and the airway. Among patients with edema, hematoma, or minor lacerations, excellent recovery of both voice and airway usually can be achieved without surgery or with minimal surgical intervention, such as tracheotomy or endoscopy. With severe lacerations and cartilaginous fractures, good results can be achieved with early primary repair of lacerations and internal fixation of fractures.[1]

An estimated early mortality rate is as high as 30% in laryngeal injuries due to airway obstruction and associated injuries[10]. In patients who survive, residua include laryngotracheal fibrosis and contusions, breathing difficulties, dysphonia and recurrent pulmonary aspiration. Delay of immediate treatment beyond 24 hours appears to contribute to development of late complications.[15]

Conclusion:

Timely proper management of injury to the larynx is essential to preserve the patient's life, airway and voice. A high index of suspicion is the most valuable aid to early diagnosis. Restricted injury and early quality care play an important part in restoration of patient's respiratory and phonatory ability.

References

1. JR Jordan, Scott PS. Laryngeal Trauma.In:Byron JB, Jonas TJ, Shawn DN, editors.Head & Neck Surgery – Otolaryngology. 4th ed. Philadelphia: Lippincott Williams & Wilkins;2006.Pp.950-960.

2. J. C.Oosthuizen, P. Burns, J. D. Russell. Endoscopic management of posttraumatic supraglottic stenosis in the pediatric population. *The American Journal of Otolaryngology* 2011; 32(5) :426–9.

3. M. Kurien , N. Zachariah. External laryngotracheal trauma in children.*International Journal of Pediatric Otorhinolaryngology* 1999; 49, (2): 115–9.

4. *Camnitz PS, Shepherd SM, Handerson RA*. Acute blunt laryngeal and tracheal trauma. Am J Emerg Med 1987; 5: 157.

5. *Hermon A, Segal K, Har El G*. Complete cricotracheal separation following blunt trauma of the neck. J Trauma 1987;27: 1365-8.

6. Dr. KohliA,Dr. Bhadoria P, Dr. Bhalotra A.,Dr. AnandR,Dr. Goyal. An unusual laryngeal injury.Indian j. anaesth2007; 51(1):57-59.

7. Hwang SY, Yeak SCL. Management dilemmas in laryngeal trauma.*JLaryngolOtol* 2004;118:325.

8. Gussack GS, Jurkovich GJ, Luterman A. Laryngotracheal trauma: a protocol approach to a rare injury. *Laryngoscope.* 1986;96:660.

9. Yen PT, Lee HY, Tsai MH, et al. Clinical analysis of external laryngeal trauma. *J Laryngol. Otol.* 1994;108:221.

10. *Bhojani RA, Rosen baun DH, Dikmen E*. Contemporary assessment of laryngotracheal trauma. J Thorac Cardiovasc Surg. 2005; 130(2): 426-32.

✪ CASE REPORT

Unusual Response to Pancuronium

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Abstract

Anaphylactic shock happens very rarely under general anesthesia.In the literature there are some reports of anaphylactic reaction to muscle relaxants. However, there are very few reports of hypersensitivity to pancuronium bromide 1,2. This communication reports a probable anaphylactic reaction in a patient to pancuronium bromide.

Keywords: Anaphylactic reaction, Pancuronium bromide

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Introduction

Although anaphylactic reactions happens very rarely in general anaesthesia, theanaes thesiologist must be familier with the correct diagnosis and measures that must be undertaken immediately to resuscitate the patient.Pancuronium Bromide is a longacting(>50 min) non depolarizing neuromuscular blocking agent. Anaphylaxis to steroid is very rare and pancuronium is a steroid with no significant histamine release.The side effect of histamine release is most often noted after administration of benzylisoquinolinium class of muscle relaxants3.

Clinical presentation

A 52 yr old gentleman was scheduled for open reduction & internal fixation of fracture of right radius & tibia under general anesthesia. He had no history of atopy or previous general anesthesia. He was a known diabetic & hypertensive since 2 years . He was on oral hypoglycemic agents& anti-hypertensive drugs.Preoperative investigations included blood chemistry, electrocardiography and chest X-ray, which were all within normal limits.

On physical examination, the patient is a well developed healthy looking male , with noevidence of distress.On arrival in the operating room an ECG, pulse oximeter and automated blood pressure.His initial blood pressure was 130/80 mmHg, pulse rate 78/min and Spo2 was 99%. Patient was adequately premedicated. Inj .Ondansetron 4mg , Inj. Midazolam 1 mg , Inj. Fentanyl 100 mcg , Inj. Xylocard 60 mg, Inj. Propofol 120mg, Inj. Scoline 100 mg i/v. Intubation was done with 8.5mm ID OCETT , B/L air entry was confirmed & fixed at 21 cm & connected to ventilator. Maintainance was done with O2 , N2O &1% Sevoflurane. Till then all vitals were within normal limits & SpO2 was 100%. After giving Inj. Pancuronium 5mg i/v for continuing muscle relaxation , the airway pressures started to increase & the reservoir bag became tight & patient was not ventilatable.On auscultation B/L airentry was diminished & after 1 minute chest became silent.

Oxygen saturation started falling which was associated with tachycardia & hypotension. Pulse was not palpable.Inj. Hydrocortisone 100 mg i/v , Inj. Deriphyllin 100mg i/v , Inj. Dexona 8 mg i/v and incremental doses of adrenaline were given. The patient was ventilated with 100% oxygen manually.There was no evidence of ECG changes on electrocardiogram. Gradually B/L air entry was regained & SpO2 started picking up.

Surgery was done after stabilizing the patient & muscle relaxation thereafter was maintained with Inj. Vecuronium. Postoperatively patient was extubated& vitals were stable.

Discussion:

Anaphylaxis to muscle relaxants occurs by recognition of the complex of ammonium ions group present in many of muscle relaxants by IgE antibodies4.Pancuronium bromide is a long acting neuromuscular blocker with minimal or no histamine release. Bronchospasm following use of pancuronium is rare although bronchospasm in asthmatics were reported3.

Release of histamine by other muscle relaxants are well known but pancuronium was considered to be relatively ineffective in this regard possibly because it's a steroidal compound.

In this case an anaphylactic reaction with histamine release is considered. But patient had no known drug allergy or bronchial asthma. The rapid development of bronchospasm , hypotension and saturation fall after giving pancuronium for maintainance of muscle relaxation and immediate alleviation of symptoms after giving steroids and deriphyllin supports it.

Conclusion

Intraoperative anaphylaxis is a rare and unpredictable event , but nonetheless a significant problem and is complicated by significant morbidity and a reported mortality of between 3.5% and 10%5. The class of drugs most commonly implicated are the neuromuscular blocking drug.

References:

1. Brauer F.S and Ananthanarayanan, Histamine release by pancuronium, Anaesthesiology 1978;49:434-435.
2. Conil C, Bornet JL, Jean- Noel M, Conil JM, Brouchet A: anaphylactic shock caused by pancuronium and vecuronium. Ann Fr AnesthReanim. 1985;4(2):241-3.
3. Mohamed Naguib, Cynthua A. Liew Chapter 29 Miller's Anaesthesia 7thEdn.,Churchill Livingstone Elsevier 2010;Pp882-884.
4. BaldoB.A ,Fisher M.M substituted ammonium ions as allergenic determinents in drug allergy. Nature 198; 306:262-264
5. MertesPM ,Aimone-Gastin I, Gueant-Rodriguez RM, et al. Hypersensitivity reactions to neuromuscular blocking agents. Curr Pharm Des 2008;14:2809-25

✪ CASE REPORT

Polymicrogyria in a case of Neurofibromatosis 1

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Abstract

Anecdotal cases of polymicrogyria in patients with neurofibromatosis type 1 (NF1) have been described; however, the cases were unilateral and had negative NF1 genetic testing. Here we report the case of bilateral; polymicrogyria in a 13 year old boy. It is notable that, given the key role played by the NF1 gene product, neurofibromin, in normal brain development, and the relatively high frequency of other brain findings in NF1, there are not more NF1 cases with brain malformations manifesting as PMG

Keywords: Neufibromatosis, Polymicrogyria

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Introduction

Cerebral cortical malformations occurring in individuals with neurofibromatosis type 1(NF1), especially polymicrogyria is rarely reported. We report a case of bilateral polymicrogyria, in a boy who clinically has NF1 with learning disability.

Case Report

A 13 year old boy was admitted with headache and upper respiratory infection. On detailed history, the boy had history of multiple falls leading to trivial injuries since childhood and poor scholastic performance.He was born to nonconsanguinous parents with a normal birth and development history. On examination he had a large head (OFC 56cm) with flat occiput,multiple café au lait spots (>10 nos) over the trunk, back, arms and face ranging from 5to40mm in size (fig1 & 2) and scars of injuries over his forehead.

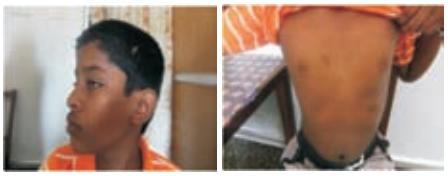

Fig.1&2: multiple café au lait spots over face and trunk

His system examinations were within normal limits without any neurological deficits or cardiac defects. Considering the possibility of seizures leading to falls, an EEG was done which was normal except for slowing of back ground activity over the parietooccipital regions. An evaluation for poor scholastic performance was done which showed that the boy had specific learning disability. Psychometry revealed an IQ of 82 with difficulties in working memory.Ophthalmological evaluation revealed Lisch nodules in his Iris (fig 3).

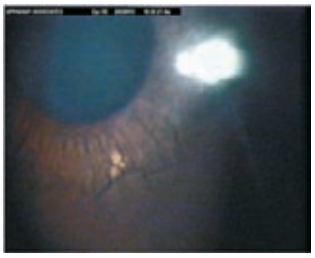

Fig 3: Lisch nodules in Iris

A provisional diagnosis of Neurofi bromatosis 1 was made. His MRI brain showed bilateral polymicrogyria over theposterior parietal regions (fig 4) more prominently over the right side.

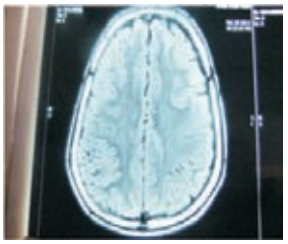

Fig 4: Polymicrogyria over both posterior parietal lobes

The boy was treated for his respiratory infection and was advised remedial training for improving scholastics and discharged. A screening for family members is also advised.

Discussion:

NF-I is the commonest of all the phakomatoses (one in 2000 to 3000 live births), formerly known as von Recklinghausen's disease, named after the German physician who recognized the neurological component of the disorder. It is usually inherited as an autosomal dominant disorder. The National Institute of Health (NIH) has created specific criteria for the diagnosis of NF-1. Two of these seven "Cardinal Clinical Features" are required for positive diagnosis. (1)

- 6 or more café-au-lait spots over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals. Note that multiple café-au-lait spots alone are not a definitive diagnosis of NF-1 as these spots can be caused by a number of other conditions.
- 2 or more neurofibromas of any type or 1 plexifor mneurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- 2 or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis
- A first degree relative (parent, sibling, or offspring) with NF-1 by the above criteria
- Discovered mutations of the NF1 gene, which is located at chromosome 17q11.2

CNS manifestations usually associated with NF-I are gliomas (opticochiasmatic, hypothalamic, brainstem), non-neoplastic hamartomas of white matter and basal ganglia, macrocephaly, hydrocephalus, skull and meningeal dysplasias, plexiform neurofibromatosis, and neurofibromas of spinal nerves.(2)

Anecdotal cases of polymicrogyria (PMG; a malformation of cortical development consisting of an excessive number of small gyri with abnormal lamination) in patients with neurofibromatosis type 1 (NF1) have been described; however, the cases were mostly unilateral and had negative NF1 genetic testing.(3)Ruggieri M et al has described an 11-year-old girl with Nf1 manifesting as a complex epileptic syndrome, including partial seizures, secondarily generalized and status epilepticus, who had in association, bilateral, asymmetrical (opercular and paracentral lobular) PMG. She had a 1-bp deletion (c.1862delC) in exon 12b of the NF1 gene. It is notable that, given the key role played by the NF1gene product, neurofibromin, in normal brain development, and the relatively high frequency of other brain findings in NF1, there are not more NF1 cases with brain malformations manifesting as PMG.(4)

The most common complication in patients with NF-1 is cognitive and learning disability. These cognitive problems have been shown to be present in approximately 80% of children with NF-1 and have significant effects on their schooling and everyday life. These cognitive problems have been shown to be stable into adulthood and do not get worse unlike some of the other physical symptoms of NF-1. The most common cognitive problems are with perception, executive functioning and attention. Attention deficit hyperactivity disorder has been shown to be present in approximately 38% of children with NF-1,Speech and language delays in approximately 68% of preschool children with NF1, Math deficits, motor deficits are common that are probably not cerebellar and Asperger's Syndrome.(5)

The boy in our case qualifies the criteria for diagnosis of NF 1, and is having borderline intelligence with cognitive problems. This association of polymicrogyria in our case however is rare, butseems to be increasingly recognised recently which may be due to the availability of high quality MR imaging facilities.

References:

1. Huson SM, Hughes RAC. The Neurofibromatoses. London, UK: Chapman and Hall; 1994;1.3.2:9
2. Smirniotopoulos JG & Murphy FM. The phakomatoses. AJNR 1992;13:725-46
3. A. McLellan, B. Harding, H. Cross. Familial hemi-polymicrogyria and neurofibromatosis type 1. Neuropathol and Applied Neurobiol.2002; 28(2) :158
4. Ruggieri M, Mastrangelo M, Spalice A, Mariani R, Torrente I, Polizzi A, Bottillo I, Di Biase C, Iannetti P.. Bilateral (opercular and paracentral lobular) polymicrogyria and neurofibromatosis type 1. Am J Med Genet Part A 2011; 155: 582–585.
5. Hyman SL, Shores A, North KN."The nature and frequency of cognitive deficits in children with neurofibromatosis type 1". Neurology 2005; 65 (7): 1037–44

✪ TECHNICAL REPORT

Treatable Dementias

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Abstract

Dementias are a major public health concern and become burdensome as the age of the population increases. A small proportion of dementia cases are fully or partially reversible. One of the important steps in the evaluation of any dementia syndrome is to look for reversible causes. However the search for treatable dementias should be cost effective. Most of the potentially reversible conditions are easily identified by careful clinical examination of the patient, routine laboratory tests, and brain imaging. Comorbid conditions, which may amplify the underlying dementia are easier to identify and should always be corrected.

Keywords: Dementia; Reversible; Treatable; Comorbid

Introduction

Dementias are a major public health concern and become burdensome as the age of the population increases. The majority of dementing illness is either degenerative or vascular. However 10-30% cases are fully or partially reversible. This group have two underlying mechanisms which may be present singly or in combination. Either the dementia is caused by a potentially treatable condition or there is a potentially treatable comorbid condition that may amplify the underlying dementia.[1-5] One of the important steps in the evaluation of any dementia syndrome is to look for reversible causes. The diagnoses of a treatable primary cause in a patient with dementia may need exhaustive investigations. Such investigations may be beneficial in some but in the majority with a syndrome diagnosis it may not be really cost effective. The chance of finding a treatable syndrome should always be weighed against the cost involved in investigating for it.[4] In some patients even though the basic dementia syndrome is a non-curable one, they may have comorbidities which are treatable and hence have to be recognised.

Potentially treatable dementia, treatable dementia and comorbidity

Potentially reversible condition can be defined as a condition known to be potentially reversible or arrestable, either on treatment or spontaneously, and responsible for,or contributing to, the observed cognitive symptoms or dementia.[6] Examples include depression, vitamin deficiency syndromes etc. Table 1 shows a list of commonly encountered potentially treatable dementias.

However in a majority of cases,potential reversibility does not always translate into actual clinical change.In one of the studies on reversible dementias,even though 23% of patients had potentially treatable dementias, only 3.6% of them showed improvement on follow-up. In that study, of the blood tests that constituted the typical work-up for dementia, the only one for which replacement therapy led to documented improvement in cognitive status was the thyroid profile. Vitamin B12 replacement did not result in improvement in any patient.[1]Young age group, mild cognitive impairment ,rapid progression and early intervention are factors found to favour reversiblity.[6,7]

Table- 1. Common Causes of potentially reversible cognitive impairment or dementia

CNS infections	Meningitis- Tuberculosis, fungal, malignancy Encephalitis- HIV, herpes, limbic Others- Syphilis, Lyme's disease
Space occupying lesions	Intracranial tumors Normal pressure hydrocephalus Subdural hematoma Intracranial abscess
Immune mediated	CNS Vasculitis Sarcoidosis Whipple's disease
Endocrine conditions	Hashimoto's encephalopathy[17,18] Hypo/hyperthyroidism Hypo/hyperparathyroidism Pituitary insufficiency Addison's disease Cushing's disease
Metabolic	Hypoglycemia[19] Hepatic failure Renal failure Respiratory failure Vitamin deficiencies(B1, B6, B12, folate)
Psychiatric	Depression Anxiety states
Others	Drugs and toxins Alcohol abuse Epilepsy Head trauma Sleep apnoea Limbic encephalitis-neoplastic/autoimmune[20]

Prevalence

Several factors may influence the prevalence of potentially reversible conditions in patients with possible dementia and explain the variation between studies. Firstly, the referral pattern may vary depending on the setting of the study. Secondly, a study with systematic prospective registration of a structured classification of diagnoses may yield more potentially reversible cases than a retrospective study. Thirdly, the definition of potentially reversible conditions may vary between studies.[6]

The prevalence of potentially reversible conditions in dementia was studied in several smaller studies, most of which were summarized in two major reviews. In a meta-analysis of 32 studies including 2889 patients, Clarfield found a frequency of 13.2% for potentially reversible conditions.[1] In 1995, Weytingh*et al* published a quantitative review of 16 studies, in which they found that the frequency of potentially reversible dementia varied widely from 0 to 37.5%, with an average of 15.2%.[8]

The first study to investigate potentially reversible conditions in a prospective cohort of younger as well as older memory clinic patients was by Heil et al. In 1000 consecutive patients, they found a potentially reversible aetiology in 19% and a potentially reversible concomitant condition in 23%. Among patients with symptoms meeting the criteria for dementia, a potentially reversible primary aetiology was less frequent and observed in only 4%.[6]

The prevalence of dementia in India vary from 0.84% to 3.5% in various studies.[9-14] A prospective study of reversible dementias in India, on 129 patients, who met the criteria for dementia, found that 18% had reversible causes for dementia. These reversible causes were clinically suspected in only 58% of patients. Even though the prevalence of treatable dementia was rather high the duration of follow up was too brief to arrive at a meaningful conclusion.[5]

Causes

Depression accounts for the majority of the causes for treatable dementia.[6]Some guidelines does not consider vascular dementia as potentially reversible, even though it could be argued that controlling risk factors might halt or slow the progression of disease. These risk factors however should, in any case, be controlled in most patients with dementia.[1] In the study on 1000 memory clinic patients, depression was the most common cause of potentially reversible primary etiology for the cognitive symptoms, followed by hydrocephalus and alcohol dependence. These three causes constituted 82% of the reversible primary etiologies identified. A small proportion of patients had space occupying lesions, metabolic diseases, epilepsy, post traumatic syndromes, obstructive sleep apnoea and delirium as the reversible cause for the cognitive symptoms.[6]In a study by Susan Freter and Mark Clarfield, depression was the most common etiology of potentially reversible dementia (51%) followed by medication use (22%) and vitamin B12 deficiency (18%)[2]. The other causes identified were normal pressure hydrocephalus, brain tumor, hypothyroidism and alcohol abuse.The study from India on 129 patients with dementia, 24 patients had reversible causes for dementia[5]. CNS infections were diagnosed in 11 patients, normal pressure hydrocephalus in 8 patients and vitamin B12 deficiency in 5 patients. In author's experience,420 hospital based patients were screened positive for dementia during a period of 5 years. A diagnosis of dementia could be confirmed in 283(63.78%). Of these patients, a high proportion [120(42.2%)]qualified for possible normal pressure hydrocephalus(pNPH).Studies from India[15] and Brazil[16] found neuroinfections especially neurosyphilis as a major cause for treatable dementias. CNS tuberculosis and HIV infections are other neuroinfections which can cause dementia. However large studies of reversible dementias from the west have not found CNS infections as a cause of dementia.

Investigations

Since the causes of treatable dementia are varied the investigations aimed at detecting these conditions are also varied.Table 2 shows investigations available for treatable dementia syndromes.

Table 2:

1. Neuroimaging- CT/ MRI Brain- to rule out structural lesions like tumors, hydrocephalus, abscess etc.
2. CSF study- to rule out CNS infections.
3. EEG- supports diagnosis in encephalitis and metabolic encephalopathy
4. peripheral smear- to aid in the diagnosis of vitamin deficiencies.
5. Vitamin B12 levels
6. Retroviral test- to rule out HIV infection
7. VDRL- to rule out Syphilis
8. ANA, Rheumatoid factor - to rule out vasculitis
9. Thyroid function tests
10. Thyroid antimicrosomal antibody
11. Complete blood counts including ESR
12. Liver function tests, renal function tests
13. Blood glucose, serum electrolytes including calcium.
14. Search for malignancy in case of suspected paran eoplastic limbic encephalitis- Peripheral smear, Chest Xray, CT Chest and Abdomen, Stool occult blood, Prostate specific antigen, CSF- malignant cells, Bone scan, Mammogram.

Investigating all dementia patents for all these causes may not be cost effective. Neuroimaging is obligatory and has been recommended as part of dementia evaluation.Two treatable conditions which are likely to be diagnosed by CT scan or MRI scan are brain neoplasms or subdural hematoma.A third condition,normal pressure hydrocephalus,also may be detected CT or MR and might be responsive to treatment is considered to be rare.[2]Laboratory screening with blood tests is recognized as an important integral part of the general screening of a patient presenting with cognitive disturbances. Cognitive disturbancesmay be associated with a wide range of metabolic, infectious, and toxic conditions, which should be identified and treated. For most of these conditions, there is no specific evidence from randomized controlled trials that treatment will reverse cognitive symptoms.The blood tests generally proposed as mandatory tests for all patients at first evaluation, both as a potential cause of cognitive impairment or as co-morbidity: blood sedimentation rate, complete blood cell count, electrolytes, calcium, glucose, renal and liver function tests, and thyroid stimulating hormone level.[2,3]More extensive tests will often be required,e.g. vitamin B12 and serological tests for syphilis and HIV, in individual cases.[3]

Conclusions

Potentially reversible conditions in patients with dementia syndromes are rare and so is complete reversal of the dementia syndrome with treatment of the condition. Reversible conditions are most often encountered in patients with mild cognitive disturbances and rapidly progressive dementias. An attempt should always be made to identify reversible conditions in dementia patients in a cost effective way. Most of the potentially reversible conditions are easily identified by careful clinical examination of the patient, routine laboratory tests, and brain imaging. Comorbid conditions are easier to identify and should always be identified and corrected.

References

1. Clarfield AM. The reversible dementias: do they reverse? Ann Intern Med 1988;109:476–86
2. Freter S, Bergman H, Gold S, Chertkow H, Clarfield A M. Preva lence of potentially reversible dementias and actual reversibility in a memory clinic cohort.CMAJ. 1998 ;159(6):657-62.
3. Manjari Tripathi and Deepti Vibha. Reversible dementias. Indian J Psychiatry. 2009; 51(Suppl1): S52–S55
4. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, Small GW, Miller B, Stevens JC. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology.Neurology. 2001;56(9):1143-53.
5. Srikanth S, Nagaraja AV. A prospective study of reversible dementias: Frequency, causes, clinical profile and results of treatment. Neurol India. 2005 ;53(3):291-4
6 A Hejl, P Høgh, G Waldemar. Potentially reversible conditions in 1000 consecutive memory clinic patients. J NeurolNeurosurg Psychiatry 2002; 73:390–394
7. Diagnosis and treatment of rapidly progressive dementias. Paterson RW, Takada LT, Geschwind MD. Neurol Clin Pract. 2012 ;2(3):187-200.
8. Weytingh MD, Bossuyt PM, van Crevel H. Reversible dementia: more than 10% or less than 1%? A quantitative review. J Neurol 1995; 242:466–71
9. Mathuranath PS[1], Cherian PJ, Mathew R, Kumar S, George A, Alexander A, Ranjith N, Sarma PS.Dementia in Kerala, South India: prevalence and influence of age, education and gender. Int J Geriatr Psychiatry. 2010 ;25(3):290-7
10. Shaji S, Bose S, Verghese A. Prevalence of dementia in an urban population in Kerala, India. Br J Psychiatry. 2005; 186:136-40.
11. Vas CJ, Pinto C, Panikker D, Noronha S, Deshpande N, Kulkarni L et al. Prevalence of dementia in an urban Indian population. Int Psychogeriatr. 2001; 13:439-50.
12. Chandra V, Ganguli M, Pandav R, Johnston J, Belle S. Prevalence of Alzheimer's disease and other dementias in rural India. The Indo-US study. Neurology 1998; 51:1000-1008.
13. Rajkumar S, Kumar S, Thara R. Prevalence of dementia in a rural setting. A report from India. Int J of Geriatr Psychiatry. 1997; 12:707-7.
14. Shaji S, Promodu K, Abraham T, Roy KJ, Verghese A. An epidemiological study of dementia in a rural community in Kerala, India. Br J Psychiatry 1996;168:745-9.
15. Jha S, Patel R. Some observations on the spectrum of dementia. Neurology ndia 2004; 52:213-4
16. Takada LT et al. Prevalence of potentially reversible dementias in a dementia outpatient clinic of a tertiary university affiliated hospital in Brazil. Arq Neuropsiquiatr.2003;61:925-9.
17. Amitabha Ghosh. Endocrine, metabolic, nutritional, and toxic disorders leading to dementia. Ann Indian Acad Neurol. 2010 ; 13(Suppl2): S63–S68.
18. Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, Swanson J, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol.* 2006;63:197–202
19. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA.* 2009;301:1565–72
20. Michael H. Rosenbloom, Sallie Smith, Gulden Akdal and Michael D. Geschwind. Immunologically Mediated Dementias. *Curr Neurol Neurosci Rep.* 2009 ; 9(5): 359–367.

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