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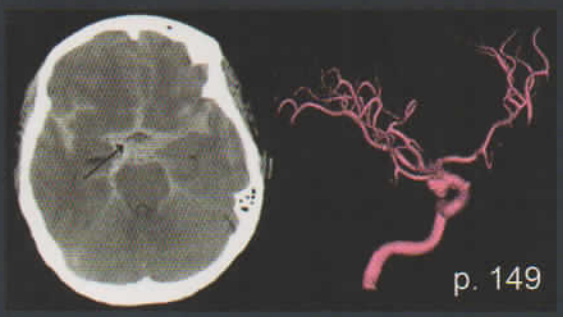
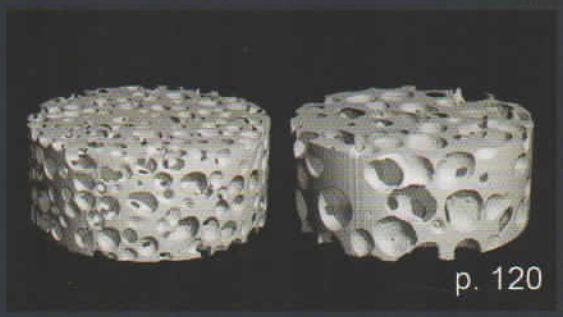
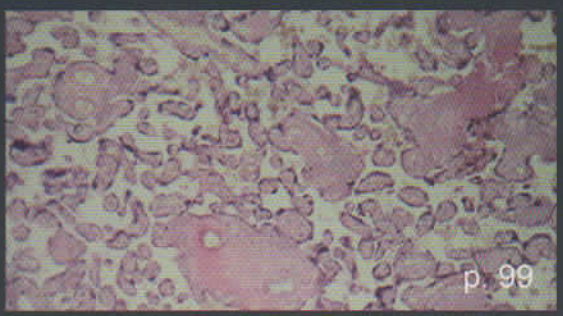

p. 149

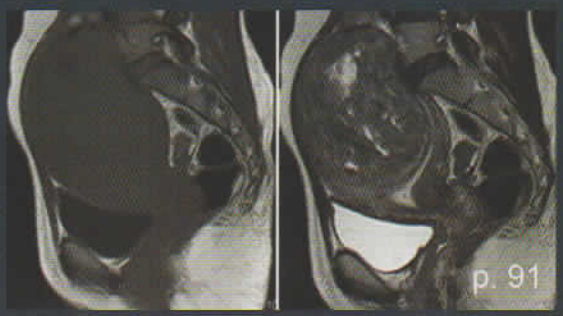
Subarachnoid haemorrhage: CT, MR angiography


p. 120

Polymer scaffold in tissue engineering


p. 99

Microscopic study of placenta


p. 91

MRI of female pelvis: Leiomyoma

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Bijo Elsy, Susan Mathew, Y M Fazil Marickar

Making Multiple choice questions useful for application of medical student knowledge 102
Rajeev A, Thomas Heming

Profile of Retinopathy of prematurity in newborns 107
Jibu Edamana, Jacob Abraham

Factitious Hyperkalemia 110
Joel Jacob, Abraham Varghese V

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Santosh Pillai

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Sara Chandy, Anand Manoharan

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✍ EDITORIAL

Challenges in writing, editing and publishing

Writing is one of the distinctive features of human civilization like speech, it is an advanced means of communication. Akin to others who write, e.g. historians and poets or journalists, scientists and those involved in medical research need to write in order to document their observations and accomplishments. Scientists and doctors in general may not be members of an *elite literati*, but it is a great advantage to be able to write clearly, succinctly and effectively.

While *doing* research it is important, *transcribing* why and how it was done, what was found, and what it meant, is far more important. Research and clinical studies, even if outstanding, are incomplete, until they have been published. A successful researcher has to be a good communicator who efficiently conveys the research findings to a chosen audience. Publication serves as a yardstick of having achieved a certain academic standard. The published work paves the way for additional opinions, criticisms, refutations and discussion from the professional colleagues and other learned members of the fraternity in due course.

In any discipline, proficiency is obtained by practice under supervision. Yet today few supervisors have enough time or sufficient experience to do this. Editors in the west have tried several methods to improve the quantity and quality of lucid scientific articles. Professional writers have been embedded in research teams or attached to large hospitals; journals have employed "rewrite specialists"; and introduced training courses in medical writing - all of which have been fruitful.

Once the written word is in, the editorial and publication processes of any nascent medical journal is often fraught with difficulties, namely review process, the liaison among the authors, reviewers and editorial board, the impact factor and last but not the least, the financial aspects. The evaluation process requires selection of suitable reviewers, erudite in the topic under consideration and capable of providing a rational and objective assessment, without bias and conflict of interest, within a specific time frame. Peer reviewing is the crucial process which enhances the status of the Journal. Although most authors are compliant with the comments of the reviewers, differing opinions between some authors and reviewers can surface, resulting from different interpretation of the available data. These aspects of the review process must be noted by the editorial board and often requires an additional opinion, which may lead to delay in the final acceptance of the submitted manuscript.

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✪ MEDICAL ETHICS

Should Aruna Shanbaug be made to die?
Should active euthanasia be legalized in India?

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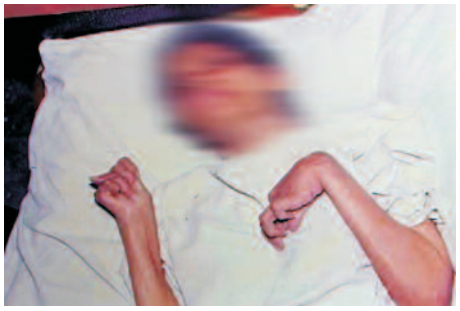
India's Supreme Court has rejected the plea to end the life of Aruna Shanbaug, previously a nurse in King Edward Memorial hospital, Mumbai, who has been in a paralyzed state since 1973, when she was attacked by a ward boy and strangulated using a dog chain. The plea had been made by a journalist Pinki Virani who had written a book on Ms Shanbaug. The Attorney General and the KEM hospital administration had opposed the euthanasia plea. The two-judge bench of justices Markandey Katju and Gyan Sudha Mishra passed the verdict after hearing the arguments by various parties on allowing euthanasia for Aruna. It being seen as a landmark case in India, where euthanasia or mercy killing had been illegal. All those who have at least a minimum respect for human life, and compassion for the sick and the helpless, would wholeheartedly welcome the verdict.



The word *euthanasia* is derived from the Greek word *"euthanatos"* meaning *well death*. In the modern context euthanasia is limited to the killing of patients by doctors, at the request of the patient/ relatives in order to free him/ her of excruciating pain, or from terminal illness.

Euthanasia can be classified into active and passive types. *Active euthanasia* means putting an end to the life of an individual by a medical practitioner by giving a lethal dose of medication to the patient. *Passive euthanasia* entails withholding artificial life support systems like ventilators, medical support, hydration, etc.

Euthanasia in various countries

In countries like Albania, Switzerland, Belgium, Luxembourg and Netherlands euthanasia/ physician-assisted suicide has been declared legal. Australia, UK, Israel, Italy, Russia, Spain, New Zealand and Mexico consider it illegal. In June 2010, the Federal Court of Justice of Germany legalized passive euthanasia with patient consent. While active euthanasia is illegal throughout the USA, assisted suicide is considered legal in three states of the US: Orgeon, Washington and Montana.

Should euthanasia be legalized in India?

At the present juncture, the debate largely revolves around active euthanasia, and not around passive euthanasia.

Arguments in favour of legalizing active euthanasia

- The society should acknowledge the rights of patients, and respect their decision to elect euthanasia.
- Not allowing euthanasia would come to forcing people to suffer against their will, which would be cruel, and a negation of human rights and dignity.
- Every person has a right to live with a minimum dignity and when the situation falls below that particular level, he must be permitted to end such torture.
- A relief from suffering (rather than preserving life) should be the primary objective of health-care providers in such cases.
- In view of the increasing demand for hospital facilities and mounting expenses, the younger and hopeful-of-recovery patients should be able to benefit from the available resources.

- A risk of misuse definitely exists; but any individual freedom carries some risk of abuse; this could be kept to a minimum by proper legal safeguards.

Arguments against active euthanasia

➢ ***Social and humanitarian concerns***

- Legalizing euthanasia accepts that some lives (disabled/ ill) are worth less than others
- Euthanasia need not necessarily be in the patient's best interests
- Compassionate palliative care makes euthanasia unnecessary
- It is impossible to regulate euthanasia strictly, and to prevent its misuse
- Allowing it will ultimately lead to insufficient care for the aged/ bedridden, and will stop the necessary treatment of the terminally ill, and emergence of new treatment modalities
- It would reduce the commitment of doctors and nurses to saving lives, and make them the authorities on determining matters of life/ death
- Ultimately euthanasia may become the best *cost-effective* way of treating the terminally ill
- It will put moral pressure on the elderly and the sick to end their lives, instead of wasting the available family resources on their care
- The elderly who are abandoned by their families will feel euthanasia as their only hope
- Voluntary euthanasia could be the start of a slippery slope that leads to involuntary euthanasia, further leading to loss of moral values

➢ ***Religious and ethical concerns***

a. Hindu doctrine

The Indian cultural views of euthanasia and suicide are grounded in the Hindu doctrines of *karma*, *moksha*, and *ahimsa*. *Karma* is the net consequence of good and bad deeds in a person's life, which then determines the nature of the next life. Ongoing accumulation of bad karma prevents *moksha*, or liberation from the cycle of rebirth, which is the ultimate goal. Suicide (physician assisted or not) is generally prohibited in Hinduism, on the basis that it disrupts the timing of the cycle of death and rebirth and therefore yields bad *karma*. Hinduism considers human life a precious opportunity to attain higher states of rebirth. Accordingly, if a person commits suicide, he neither goes to the hell nor the heaven, but remains in the earth as a bad spirit, wanders aimlessly till he completes his actual and allotted life time, thus putting his spiritual clock in reverse.

b. Buddhist teaching

Meditation and the proper use of pain killing drugs should enable a person to attain a state where they are not in mental pain, and so no longer contemplate euthanasia or suicide. Helping to end someone's life is likely to put the helper into a bad mental state, which should be avoided. Buddhism places great stress on *'nonharm'* to life - any life - so the intentional ending of life seems against Buddhist teaching.

c. Euthanasia and suicide in Islam

Muslim religion is against euthanasia. They believe that all human life is sacred because it is given by Allah, and that Allah chooses how long each person will live. Suicide and euthanasia are explicitly forbidden as per Qur'an. '*Destroy not yourselves. Surely Allah is ever merciful to you*'. Qur'an 4:29.

d. Sikh moral thinking

Sikhs have a high respect for life which they see as a gift from God; they believe that the timing of birth and death should be left in God's hands. The Sikh Gurus rejected suicide (and by extension, euthanasia) as an interference in God's plan. Suffering, they said, was part of the operation of *karma*, and human beings should not only accept it without complaint but act so as to make the best of the situation that *karma* has given them. Sikh teaching on situations where people think about euthanasia is to provide such good care that euthanasia become an unattractive option.

e. Christian teaching

Catechism of the Catholic Church gives guidelines on Assisted-Suicide in paragraphs 2276 - 80:

2277: An act or omission which, of itself or by intention, causes death in order to eliminate suffering constitutes a murder gravely contrary to the dignity of the human person and to the respect due to the living God, his Creator....

2278: Discontinuing medical procedures that are burdensome, dangerous, extraordinary, or disproportionate to the expected outcome can be legitimate; it is the refusal of "*over-zealous*" treatment....

2279: Even if death is thought imminent, the ordinary care owed to a sick person cannot be legitimately interrupted…..

2280: It is God who remains the sovereign Master of life. We are obliged to accept life gratefully and preserve it for His honour and the salvation of our souls. We are stewards, not owners, of the life God has entrusted to us. It is not ours to dispose of…….

The *Sacred Congregation for the Doctrine of the Faith Declaration on Euthanasia, Vatican,* May 5, 1980, approved by *His Holiness Pope John Paul II* stated firmly that nothing and no one can in any way permit the killing of an innocent human being, whether a fetus or an embryo, an infant or an adult, an old person, or one suffering from an incurable disease, or a person who is dying. Furthermore, no one is permitted to ask for this act of killing, either for himself or herself or for another person entrusted to his or her care, nor can he or she consent to it, either explicitly or implicitly. Nor can any authority legitimately recommend or permit such an

action. For it is a question of the violation of the Divine law, an offence against the dignity of the human person, a crime against life, and an attack on humanity. It may happen that, by reason of prolonged and barely tolerable pain, for deeply personal or other reasons, people may be led to believe that they can legitimately ask for death or obtain it for others. The pleas of gravely ill people who sometimes ask for death are not to be understood as implying a true desire for euthanasia; in fact, it is almost always a case of an anguished plea for help and love. According to Christian teaching, suffering, especially suffering during the last moments of life, has a special place in God's saving plan.

Life is a gift of God, and on the other hand death is unavoidable; it is necessary, therefore, that we, without in any way hastening the hour of death, should be able to accept it with full responsibility and dignity. It is true that death marks the end of our earthly existence, but at the same time it opens the door to immortal life. Therefore, all must prepare themselves for this event in the light of human values.

Pope Benedict XVI says, 'Euthanasia is a false solution to the drama of suffering, a solution unworthy of man. The true answer cannot be putting someone to death, however kindly, but to bear witness to the love that helps us to face pain and agony in a human way. We are certain: no tear, whether it is of those who suffer, or those who stand by them, goes un-noticed before God'.

Conclusion

Aruna is not on any life support, like the ventilator or pacemaker. She is being spoon-fed, and is not even on tube feeding. The treating doctors say that she is able to relish some of the food items like fish! She has been rejected by her family (they could not afford it); but she is so well taken care of by the nurses of the hospital, that she has not so far developed a bed sore! They have not even catheterized her; when she passes urine involuntarily, they just change the dress and bed sheets! True, part of her brain is irreversibly damaged, but should she be killed for it? What the nurses in KEM hospital are doing for Aruna should open the eyes of the entire humanity. They are teaching the Nation, and the world at large, on what should ideally be done with such patients, rather than deliberately ending their lives.

Ever since the time of Hippocrates in the fifth century B.C. the Medical profession has been guided by the concept of the worth of each individual human life, which was reaffirmed by the Geneva code in 1948, which states*, "I will show the utmost respect for human life from the time of conception".* True*,* suffering is extremely difficult, and we should take every step to mitigate or relieve it.

At the same time we should respect the unique value of human life. Scriptures says man is made in the image of God. This gives human life, its unique dignity and value, which should be respected under any circumstance, whatsoever.

As for us who work in the Medical profession, we ought not to neglect any means of making all their skill available to the sick and the dying; and should remember how much necessary it is, to provide them with the comfort of boundless kindness and heartfelt charity.

The hospital staff members who were taking care of Aruna distributed sweets, nobody can now put an end to her life deliberately. They would take care of her nursing and feeds happily. Let mother nature take its course ……...

PUSHPAGIRI MEDICAL JOURNAL

✪ ORIGINAL ARTICLE IN SERIES

Magnetic Resonance Imaging of Female Pelvis: A systematic evaluation

Part 1: Imaging of Uterine pathologies

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Abstract

Background: Since magnetic resonance imaging (MRI) offers high contrast resolution, provides good tissue characterization, and is capable of multiplanar imaging capabilities, it is becoming a useful tool for the evaluation of female pelvic pathology. Since MRI is more expensive and potentially less readily available than ultrasound, it is important to know when patients should undergo MRI. **Objective:** To evaluate the advantages of MRI in comparison with other methods of imaging ulterine pathologies. **Materials and methods:** The usefulness of MRI in the female pelvis was studied in detail, and compared it with other imaging modalities. This first part of the series article studies the significance of MR Imaging in evaluating uterine pathologies. The second part would signify evaluation of ovarian and adnexal masses and the third part, the various congenital anomalies of female genital tract (Mullerian duct anomalies). **Subjects:** Selected patients referred to the Department of Imaging, Pushpagiri Institute of Medical Sciences and Research Centre. **Results:** The situations in which MRI should be considered strongly to evaluate uterine pathologies have been delineated in depth in this series article. **Conclusion:** MRI has an established role in the pre- and post-procedural assessment for uterine artery embolization, diagnosis of adenomyosis, and staging of known cases of endometrial and cervical carcinoma.

Key words

Advantages of MRI of female pelvis, In comparison with Ultrasonography and CT scan, Leiomyoma, Adenomyosis, Endometrial and cervical carcinoma, Invasive mole, Endometrial polyp, Endometrial hyperplasia, Uterine arterio-venous malformations (AVM).

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Introduction

Ultrasound is the imaging modality of choice for the female pelvis. It is widely available, non-invasive, less expensive, and has broad acceptance by patients as a familiar test. High-resolution imaging of transvaginal ultrasound provides high diagnostic accuracy for pelvic pathologies. However, there are some shortcomings with this modality, such as the limited field of view, obscuration of pelvic organs by bowel gas, inherent limitations depending on the patient size, and its dependence on the skill and experience of the operator. USG also has limitations in displaying a global image of large tumours and in tissue characterization.

With its very high contrast resolution, ability to provide good tissue characterization, and its multiplanar imaging capabilities, MRI is increasingly used to evaluate pelvic pathologies. Lipid, fluid, haemorrhage, smooth muscle, fibrosis, any solid malignant tissue, and hydrated soft tissue (including oedema, mucin, and myxomatous tissue) have typical MR imaging properties, and their presence in a mass can often be established on MR images. Consideration of the tissue composition of the various pathologic processes in the pelvis can result in more systematic approaches to image interpretation and thus narrow the differential diagnosis.

However, the high cost and inconvenience associated with MR imaging can be prohibitive. USG thus represent a primary diagnostic tool, whereas MR imaging assumes the role of a problem-solving tool. The use of

computed tomography (CT) is mostly limited to evaluation of potential metastasis; this limitation is due to the risks associated with radiation exposure and the poor soft-tissue contrast, except for recognition of fat and calcification.

Technique

Standard protocol for MRI of the female pelvis in our 1.5 Tesla GE Signa HDxt scanner:

Sequences	TR/TE (msec)	FOV cm	Flip angle	No. of slices	Time of acquisition
T2W Sagittal FRFSE	3200/100	25x25	-	20	2.50 min
T1W Sagittal FSE	500/40	25x25	-	20	3.40 min
T2* Sagittal 2D Gradient recalled echo	520/13	25x25	25	20	4.00 min
T2W Axial FRFSE	3500/100	25x25	-	24	3.40 min
T2W Fat saturated *Axial FRFSE*	3500/100 with FAT CLASSIC	25x25	-	24	4.02 min
T2W Fat saturated coronal FRFSE	3000/70 with FAT CLASSIC	25x25	-	24	2.00 min
T1W Axial FSE	700/10	25x25	-	20	5.00 min

FRFSE - Fast recovery fast spin echo, FSE - Fast spin echo.

3D LAVA Gradient recalled echo-multiphasic dynamic contrast study is done following intravenous administration of 10 ml gadolinium contrast in some cases, with T1W Fat saturated post-contrast in all planes.

For pelvic floor imaging, dynamic 2D GRE imaging may be performed with and without the Valsalva manoeuver to detect pelvic prolapse. If artifact from the bowel is perceived as problematic on initial sequences, glucagon may be administered by intramuscular (0.8 mg) or intravenous injection (0.2 mg).

Uterine anatomy

MRI provides a comprehensive and detailed view of the anatomy of uterus. The uterine body is composed of three distinct zones on T2W images: endometrium, junctional zone and myometrium. The inner layer consists of the high signal intensity endometrium. Junctional zone or basal layer of myometrium appears as low signal intensity stripe at the interface of endometrium and myometrium. The outer zone represents the stratum vasculare of the myometrium and usually exhibits intermediate signal on T2W images. The cervix is mainly composed of dense fibrous stroma resulting in a typically cylindric or ring form of low signal intensity on T2W images.

In Fig. 1 the Sagittal T2W sequence optimally demonstrates the three distinct zones in the uterine wall.

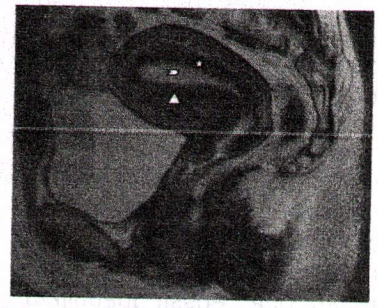


Fig.1 : Zones of uterus in sagittal T2W sequence
△ - outer myometrium (intermediate-to-high signal)
☆ - inner myometrium or junctional zone (low signal)
⊃ - endometrial complex (high signal)

Materials and methods

The usefulness of MRI in the female pelvis was studied, and compared with other imaging modalities in selected patients referred to the Department of Imaging, Pushpagiri Institute of Medical Sciences and Research Centre, Tiruvalla, Kerala.

Observations

In this part of the series we describe various uterine pathologies, as evaluated by MRI.

I. Leiomyomas

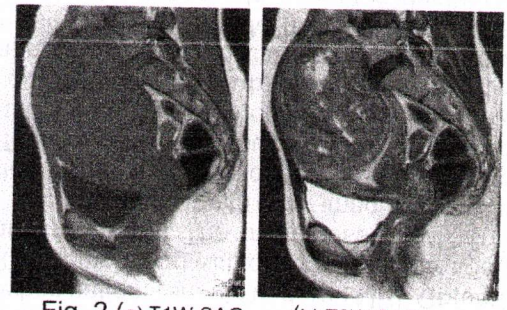
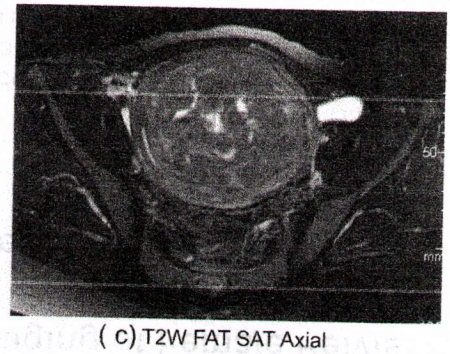


Fig. 2 (a) T1W SAG (b) T2W SAG



(c) T2W FAT SAT Axial

A large intramural fibroid is seen in the region of the fundus and anterior myometrium (Fig. 2). It appears isointense on T1WI and hypointense on T2WI. Multiple high signal area within it on T2WI suggests cystic degeneration. Low signal intensity capsule is well seen in T2W image.

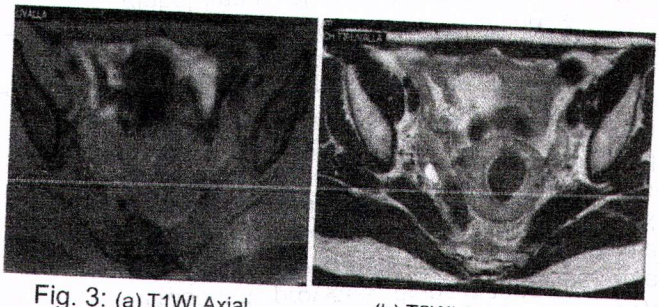


Fig. 3: (a) T1WI Axial (b) T2WI Axial

The submucosal fibroid seen anteriorly appears homogenously isointense on T1WI and hypointense on T2WI.

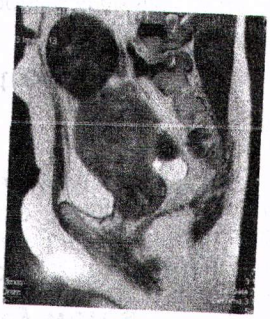


Fig.4: T2WI SAG

Uterus is bulky with exophytic subserosal fibroid in the region of fundus, showing a narrow stalk of attachment (Fig. 4). This appears predominantly hypointense on T2WI.

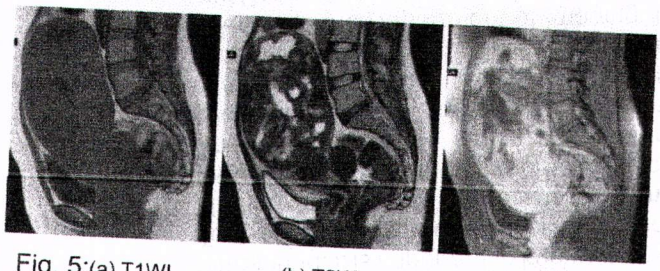


Fig. 5:(a) T1WI SAG (b) T2W SAG (c) T1W Fat sat Post contrast SAG

A large well encapsulated mass in the region of fundus is seen (Fig. 5), which exhibits heterogenous signals. It appears predominantly iso-intense on T1WI, hypointense on T2WI with intense but heterogenous enhancement, and shows non enhancing fluid intensity areas within, suggestive of cystic/ myxoid degeneration.

Discussion

Leiomyomas, benign uterine neoplasms, are the most common tumours of the female genital tract. Their classifcation is based on their location within the uterine corpus as either intramural (Fig. 2), submucosal (Fig. 3), subserosal (Fig. 4) or cervical. MRI is superior in terms of mapping individual myomas. This is especially true with larger uteri and with the presence of a large number of myomas. A uterus containing leiomyomas will be enlarged and will have an abnormal contour.

The leiomyomas can demonstrate variabi appearances due to the presence of oedema, anc hyaline, cystic (Fig 5), or red degeneration. On T2W images, leiomyomas appear as sharply marginate lesions of low signal intensity relative to the myometrium. Often, a high-signal-intensity-rim can b identified, more commonly in intramural or subserosa leiomyomas. On MRI, myomas larger than three to five centimetres are often heterogeneous because o, variable degrees of degeneration. Most myomas enhance similar to or less than the surrounding myometrium on contrast study. Calcifed myomas can cause signifcant artifact on ultrasound and can obscure adjacent tissues. While similar calcification appears as a signal void on MRI, it typically does not limit the evaluation of adjacent tissues.

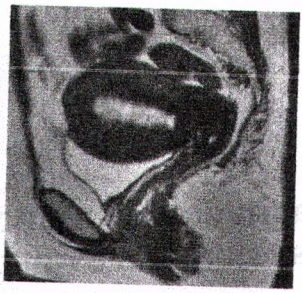
The lesion with high signal on T2W with delayed hyper-enhancement on contrast study can be categorized as atypical/ cellular leiomyoma. Fibroid with red degeneration are a subtype of cellular leiomyoma exhibiting haemorrhages within. Lipoleiomyoma contains striking amount of fat within, and shows high signal on T1W images.

MRI is the modality of choice in evaluating leiomyomas before and after treatment with uterine artery embolization (UAE). The use of MRI is optimal for pre-embolization assessment for delineating the location of leiomyoma, accurately assessing pedunculated lesion, and predicts collateral feeding vessels. It is particularly useful in providing post-embolization comparative images to assess whether there are persistent enhancing fibroids and to compare their pre- and post-therapeutic sizes. Certain pre-procedural imaging characteristics like high signal intensity on T1W sequences and complete lack of contrast enhancement may indicate pre-existing hemorrhagic infarction, resulting in poor post embolisation outcome secondary to non-viable tumorous. MRI characteristics that indicate a successful treatment include high signal intensity on T1W images and homogenously decreased T2 signal intensity. These findings are suggestive of haemorrhagic infarction and correlate with a lack of contrast enhancement.

MR imaging findings that allow distinction between leiomyoma and leiomyosarcoma have yet to be very clearly established; however, invasion, haemorrhagic necrosis, or rapid growth would be suggestive of malignancy.

II. Adenomyosis

MRI shows bulky uterus with thickened and indistinct junctional zone anteriorly, features suggestive of adenomyosis (Fig. 6). A large intramural fibroid is seen in the posterior myometrium.



(b) T2WI SAG

sound for the diagnosis
teristic appearance of
diffuse thickening (more
one. This is most evident
responds to the smooth
with the ectopic tissue. A
qual to 8 mm virtually
a width of 9 to 11 mm is
hat may suggest the
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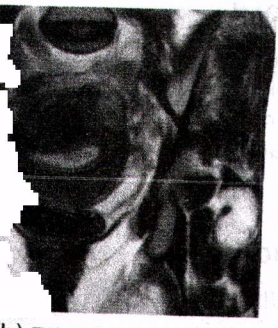


b) T2WI Coronal

shows a well-defined
nsity sessile polyp
atrium, and attaches

most sensitive and

are of intermediate
intermediate-to-high
The presence of a
on T2WI indicates a

fibrous core, which suggests the diagnosis of an endometrial polyp.

MR images can help to distinguish most polyps from endometrial carcinomas on the basis of morphologic features. Accuracy does not appear to be sufficient to obviate biopsy, partly because carcinomas and polyps frequently co-exist. A central fibrous core and intratumoural cysts were seen more frequently in endometrial polyps than in carcinomas; myometrial invasion and necrosis showed high predictive value for carcinomas.

IV. Endometrial hyperplasia

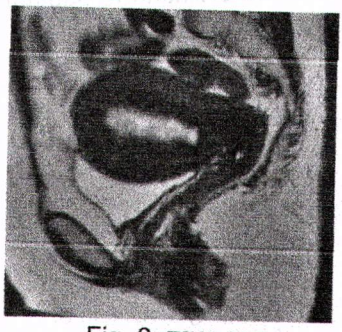


Fig. 8: T2WI SAG

T2WI SAG image shows bulky uterus with thickened endometrium (Fig.8) with few rounded high signal areas, suggestive of cystic changes. Features could represent endometrial hyperplasia.

Discussion

At transvaginal sonography (TVS) endometrial hyperplasia should be suspected whenever *endometrium is more than 4 mm in thickness in* postmenopausal patient, who is not on Hormone Replacement Therapy (HRT). On patients with HRT, the *cut off limit is 8mm. However ultrasound cannot reliably differentiate endometrial hyperplasia from carcinoma.* MR imaging shows thickened endometrium with multiple cystic changes. Surface irregularity and myometrial invasion are better depicted on T2W sequence. Tamoxifen induced cystoglandular endometrial hyperplasia exhibits multiple cysts and lattice - like enhancement on post contrast images. However MR findings are not sufficiently specific to obviate biopsy.

V. Endometrial carcinoma

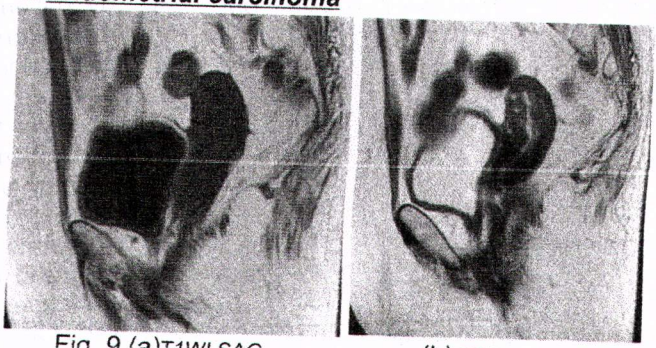


Fig. 9 (a)T1WI SAG (b) T2WI SAG

T2W Sequence demonstrates (Fig. 9) the thickened endometrium in fundus and upper uterine body, with loss of differentiation and indistinct junctional zone.

Discussion

MRI is the most accurate imaging modality as pre-treatment assessment and for the staging of known endometrial carcinoma. It can differentiate between superficial and deep-muscle-invasive-tumours, and the presence of cervical invasion which can significantly alter surgical management. MRI has been shown to be superior to both CT and ultrasound in assessing myometrial invasion, cervical extension, and nodal involvement.

Endometrial carcinomas appear iso-intense on T1W images (Fig. 9a) and commonly hyperintense on T2W images (Fig. 9b). It usually enhances less than the myometrium does, with the difference less marked on delayed images. Myometrial invasion is best visualized on T2W images, where it appears as a disruption or an irregularity of the junctional zone by a mass. Transmyometrial extension of tumour is identifed by interruption of the normal low signal intensity of the serosal surface. Vaginal, parametrial and lymph node involvement and best depicted on T1W images. MRI can also detect tumour extension outside the true pelvis, as well as bladder and rectal invasion.

Role of multi-phasic dynamic contrast: The maximal contrast between tumour and myometrium is observed at about 90 to 120 seconds after contrast injection, and hence multiphasic dynamic contrast study shows early enhancement and rapid wash out of contrast by tumour, but slow enhancement of myometrium.

VI. Cervical carcinoma

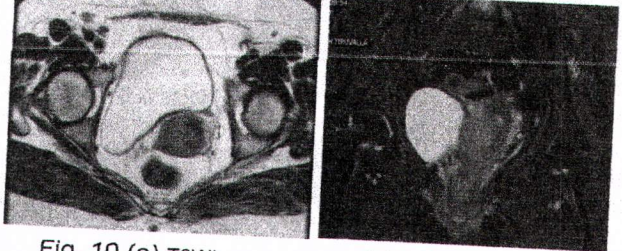
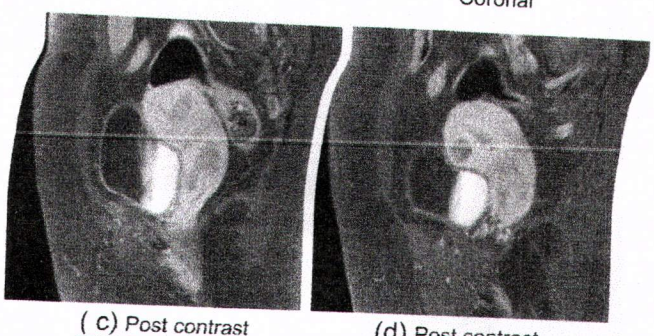


Fig. 10 (a) T2WI Axial (b) T2WI FAT SAT Coronal



(c) Post contrast T1W Fat Sat SAG (d) Post contrast T1W Fat Sat SAG

Images (Fig.10) show mass in right lip which exhibits high signal on T2W and T2W images, and was intermediate on T1W ima dynamic contrast study the lesion showed enhancement in early arterial phase, with wa venous phase, suggestive of arterio-venous sh There was stromal invasion but no parametrial in (Stage II A).

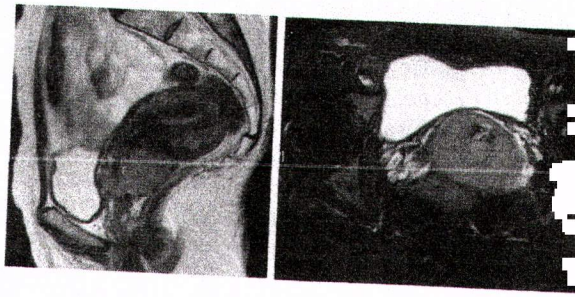
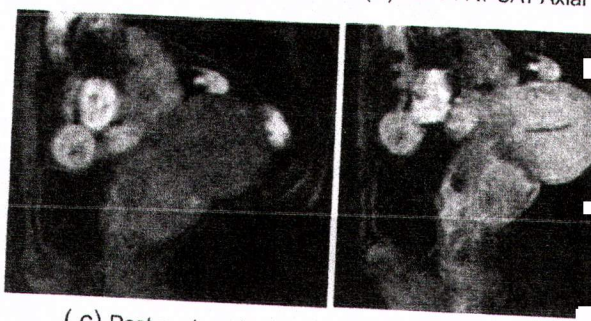


Fig. 11 (a) T2WI SAG (b) T2W FAT SAT Axial



(c) Post contrast LAVA SAG(Early phase) (d) Post contrast LAVA SAG (Venous pha

Posterior lip of cervix is bulky and shows signal on T2W and T2W Fat Sat images. On dyna contrast study the lesion showed early art enhancement more than myometrium, and rapid out of contrast in venous phase. Stromal parametrial invasion was noted (Stage II B).

Discussion

MRI is used to stage cervical carcinoma women who have had a diagnosis established by a P smear or biopsy. T2-weighted images obtained in sagittal plane and in a plane along the short axis of cervix are the most useful for local staging. On T2 images cervical cancer appears hyperintense than adjacent fibrous cervical stroma (Fig. 10 and Fig. 11 but hypointense than the endometrium. If the low sign intensity of the inner cervical stroma is preserved, stage IIB or higher disease is excluded, which indicates that the patient is likely a surgical candidate.

MRI has an accuracy range of 75% to 95% in assessing parametrial invasion, pelvic side wall invasion and obstruction of the distal ureter. Localizing the tumour and determining the presence or absence of ureteral obstruction can provide a road map for radiation therapy.

VII - Invasive mole

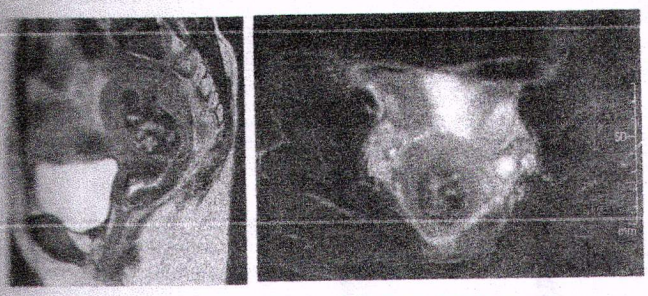
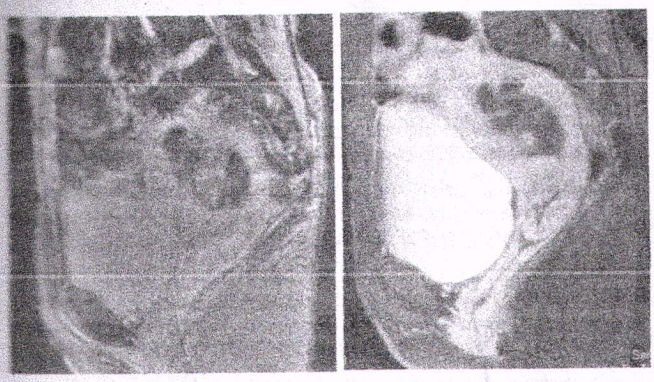


Fig. 12 (a) T2WI SAG (b) T2WI FAT SAT Axial



(c) T2 GRE SAG (d) Post contrastT1W Fat Sat SAG

A 33 year old female patient presented with history of bleeding per vaginum after dilatation and curettage. MRI showed (Fig.12) a heterogeneous collection in endometrial cavity which exhibits low signal intensity on T2WI with high signal areas within and blooming on gradient, suggestive of haemorrhage. Post contrast image showed enhancement of anterior septae. The endometrial-myometrial junction appeared indistinct in a few areas (invasive mole).

Discussion

The gestational trophoblastic disease encompasses a broad spectrum of conditions, including hydatidiform mole, invasive mole, choriocarcinoma, and placental site trophoblastic tumour. Although sonography is the examination of choice for the initial diagnosis, MR imaging has a role in the detection of gestational trophoblastic disease and the evaluation of the extent of its complications.

On T2WI a complete mole appears as a heterogeneous mass of high signal intensity that distends the endometrial cavity. Numerous cystic spaces may be present in the mass. An invasive mole appears as a poorly defined mass displaying mixed signal intensity on T2WI and deeply invades the myometrium. Complete or partial disruption of the junctional zone may also be seen. On T1WI, the mass is iso-intense to the myometrium with scattered foci of high signal intensity due to the presence of haemorrhage. Molar like structures appear as tiny cystic lesions within the well-enhanced zone of trophoblastic proliferation in a mass of the invasive mole. With the penetration of the tumour into the myometrium, the invasive mole appears as a more aggressive entity than does choriocarcinoma.

Choriocarcinoma is usually seen as an intrauterine mass with heterogeneous high signal intensity on T2W and marked enhancement on post-contrast images, findings that reflect the high vascularity of the tumour. Tumour vascularity can also be reflected by focal signal voids on T1- and T2W. Myometrial invasion is visible as high-signal-intensity foci within the myometrium, which demonstrate enhancement on post-contrast images. Enhancing parametrial soft tissue is characteristic of local spread. MR imaging can also help to detect metastatic disease, particularly within the pelvic organs and lymph nodes.

VIII. Uterine arteriovenous malformation (AVM)

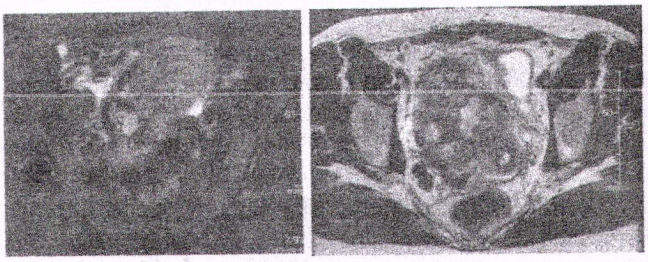
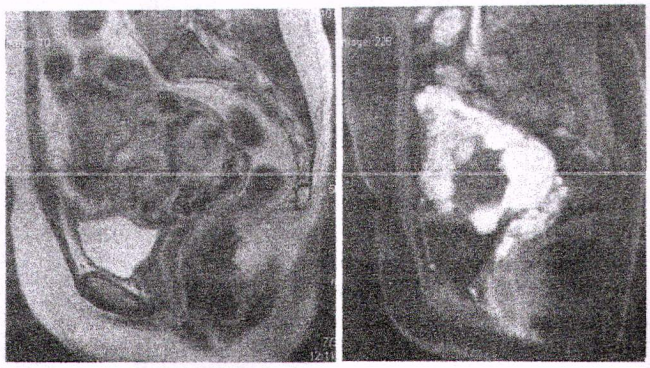


Fig. 13 (a) T2W FAT SAT Axial (b) T2WI Axial



(c) T2WI SAG (d) Post contrast T1W Fat Sat SAG.

Bulky uterus with heterogenous signal intensity and multiple flow voids in right lateral wall, posterior myometrium and parametrium on T2W/ T2W Fat Sat images, related to arterio-venous malformation. On post-contrast study the lesion showed intense enhancement

Discussion

Although conventional angiography was considered the modality of choice for diagnosing vascular abnormalities, MR imaging and MR angiography are emerging as effective modalities for non-invasive evaluation of such conditions. An AVM is a distinct disease entity composed of a tangle of vessels that possess the histologic characteristics of both arteries and veins with lack of an intervening capillary network.

MR imaging allows non-invasive diagnosis of AVMs on identification of a cluster of serpentine flow-related signal voids within a thick myometrium. Contrast-enhanced dynamic MR angiography can be useful for both planning therapeutic embolization and monitoring the effects of treatment.

Conclusion

Ultrasound remains the first line of imaging for the female pelvis, with high diagnostic accuracy for uterine abnormalities. At the same time MRI has an established role as a problem solving tool in the pre- and post-procedural assessment for uterine artery embolization in leiomyoma and vascular malformations, diagnosis of adenomyosis, and staging of known endometrial and cervical carcinomas and gestational trophoblastic disease.

Acknowledgement

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✪ ORIGINAL ARTICLE

A morphological and microscopic study of human placentae in uncomplicated pregnancies

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Abstract

Background: The placenta can sometimes provide exceedingly useful information relating to the perinatal morbidity and mortality, and the prognosis of subsequent pregnancies. Examination of the placenta in cases of poor pregnancy outcome could provide information useful to the Obstetrician and Neonatologist. **Objectives:** To study the normal variations in macroscopic and microscopic features of normal human placenta. **Materials and methods:** Two hundred and twenty four placentae were collected from the labour room of Pushpagiri Medical College Hospital over a period of one year. Of these 96 were from clinically uncomplicated, full term, singleton deliveries, and were subjected to morphological and histopathological examination. **Results:** In normal pregnancies there was significant correlation between the baby birth weight and the placental weight. Also female babies were found to have lower birth weight and placental weight as compared to male babies. A number of variations in the macroscopic and microscopic structure could be observed in many of the specimens, even though the pregnancy outcome appeared clinically within normal limits. **Conclusions:** A morphological and microscopic study of the placenta in uncomplicated pregnancies showed a wide range of variations, compatible with a normal maternal and foetal outcome.

Key words: Placenta, Umbilical cord, Discoid placenta, Chorionic villi, Syncytiotrophoblast, Cytotrophoblast, Syncytial knots, Fibrinoid deposits.

Introduction

Placental tissue is arranged as a chorionic plate on the foetal side and a basal plate on the maternal side, and between the two, the chorionic villi and the intervillous spaces. Each villus has a core of connective tissue containing foetal capillaries, covered by the cytotrophoblast cells and a layer of syncytiotrophoblast. The inter-villous space contains maternal blood. The placental barrier is made up of the endothelium of the foetal blood capillaries resting on its basement membrane, the surrounding extra-embryonic mesoderm (EEM), the cytotrophoblast and its basement membrane, and the syncytio-trophoblast. The total area of this membrane varies from 4 to 14 sqm. The effective absorptive area is greatly increased by microvilli on the surface of the syncytiotrophoblast. Later during pregnancy, the efficiency of this membrane is increased by the disappearance of cytotrophoblast and considerable thinning of the EEM, and its thickness gets reduced from 0.025 mm to 0.0002 mm. Towards the end of the pregnancy, fibrinoid deposits appear on the membrane, reducing its efficiency.

The placenta and the foetal membranes (aminion and chorion) are usually not subjected to systematic examination, and the concerned medical practitioner is generally considered responsible for examining the placental morphology, which may get overlooked due to more pressing reasons. The objectives of the present work were to study the morphology and variations in placentae obtained from clinically uncomplicated pregnancies and to study the microscopic features and normal variations of placental structure. We conducted a detailed evaluation of 96 such placentae.

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Materials and methods

Whole placentae and umbilical cords, numbering 224, were collected from the delivery room of Pushpagiri Medical College hospital, over a period of one year, after obtaining approval from the Institutional Ethics Committee (No. PIMS & RC/Eth/809/2007). Placentae from both vaginal deliveries and caesarean sections were included in the study.

The relevant antenatal history was noted, with maternal age, gravidity, gestational period (in days), and sex and weight of the foetuses. The type of placenta, its weight, shape, number of cotyledons, infarction/ retroplacental haematoma, subchorionic fibrinoid and haematoma, if any, were studied in a total of ninety six specimens, obtained from clinically uncomplicated pregnancies. These placentae were subjected to macroscopic and microscopic examination in the Department of Anatomy, and the observations were analyzed.

The percentages of placental types, infarctions, subchorionic fibrinoid and haematoma, and amnion nodosum were noted. The placenta number in relation to the gravidity and the shape of the placentae were plotted graphically. The descriptive statistics of various parameters (maternal age, gestational age, baby birth weight, placental weight and number of cotyledons) were analyzed. Correlation of baby birth weight with the gender, and the weight of the placenta were done.

Observations and results

Of the total 224 placentae collected, 218 were singleton pregnancies, four were twin pregnancies, one had triplets and one had quadruplets. Among the 218 singletons, 96 were considered normal from the antenatal and perinatal history. The remaining 122 were clinically complicated pregnancies. The gestational age of all the normal pregnancies were between 230 and 283 days.

Of the total 96 uncomplicated singleton pregnancies, the maximum cases were primigravida (Fig. 1), and the number got reduced sequentially as the gravidity increased.

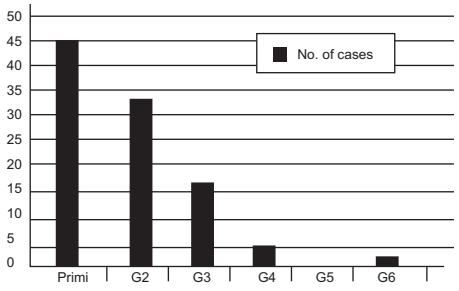

Fig. 1: No. of placentae in relation to gravidity

The descriptive statistics of some of the important parameters *(maternal age, period of gestation, baby birth weight, placental weight and the number of maternal cotyledons)* is shown in Table 1.

Table 1. Descriptive statistics of 96 placentae

Parameter	Min	Max	Mean	Std. deviation
Maternal age (Years)	19	37	27.54	4.04
Gestational age(days)	230	283	270.65	8.13
Baby birth weight (kg)	1.53	4.00	2.87	0.40
Placental weight (gm)	100	780	492.14	138.53
No. of cotyledons	6	28	17.43	3.98

The mean birth weight of the female newborns (51 in number), was found to be lower, 2.82 kg (std. deviation = 11.57) than that of the male babies (45 in number), 2.92 kg (std. deviation = 11.64), by 108.30 gm. The mean placental weight also was lower in the female babies, a mean 473.63 gm (std. deviation = 138.24) than the male babies, with a mean 513.11 gm (std. deviation = 137.36).

An effort was made to correlate the placental weight with the baby birth weight. Fig. 2 proves that there is a significant correlation between the two parameters (R^2= 0.18).

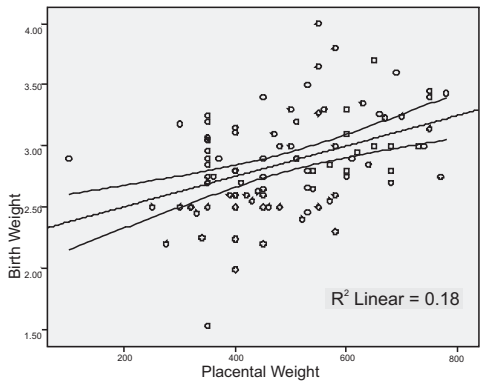

Fig. 2: Correlation of placental weight with baby birth weight

➢ Morphological features

Among the 96 specimens with normal uncomplicated clinical history, 24 (25%) were circum-marginate placentae (Fig. 4a) showing the foetal membranes attached away from the placental rim.

The shapes of the placentae were observed closely. Discoid placentae were most frequent (Fig. 3). There were two cases of multilobed placentae (Fig. 5) and bilobed placentae each.

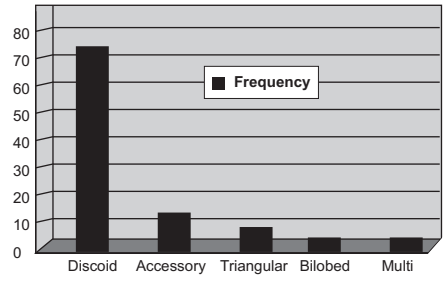

Fig. 3: Frequency of different placental shapes

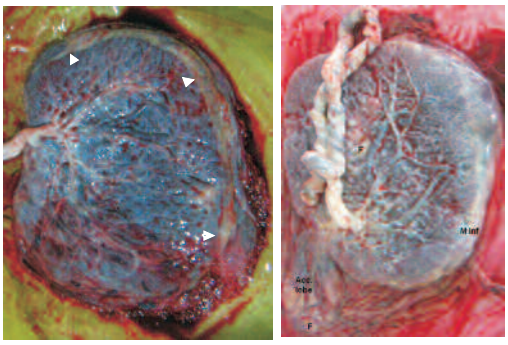

Fig. 4a: Circum-marginate placenta, membrane attachment (arrows).
4b: Accessory lobe, Fibrinoid (F), Marginal infarct

Subchorionic fibrinoid deposits (Fig. 4b) were observed in 22 cases (22.92%). Subchorionic haematoma was observed in two cases (2.08%). Placental infarction (Fig. 4b) was observed in 67 cases (69.79%) and retroplacental haematoma in ten cases (10.42%). An accessory lobe was present in 12 cases (12.5%) as seen in (Figs. 4b,5).

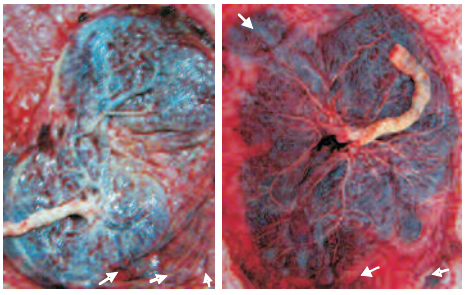

Fig. 5: Multilobate placentae with accessory lobes (arrows)

Amnion nodosum was observed in eight cases (8.33%). Chorangioma and gross anaemia could not be noted in any of the specimens. Foul odour was not reported by the attending Obstetrician in any of the above samples.

➢ **Microscopic structure with normal variations**

All the 96 normal placentae collected from uncomplicated, full term, singleton deliveries were subjected to histopathological examination with Haematoxylin and Eosin stains. Though the antenatal and perinatal clinical features in all these pregnancies were within normal limits, a good number of histological variations were observed in many of these. These observations are grouped under following heads:

A.Chorionic villi : The various parts of the chorionic villi, and a good number of normal variations could easily be distinguished under the microscope (Fig. 6) in many of the sections. *Cytotrophoblast* cells were seen scattered within the trophoblast basement membrane. In some areas cytotrophoblastic islands were seen. Most of the syncytiotrophoblast variants could be observed in the normal placentae in our study. *Syncytial sprouts* connected to the parent villus by a narrow stalk, were seen projecting into the intervillous space. *Syncitial knots* appeared as multilayerd nuclear clumps extending only slightly above the villous contour. A *few exaggerated syncytial knots* projecting well beyond the villous surface (Tenney Parker sign) were also seen. *Syncytial bridges* were found to bridge across adjacent syncytial knots.

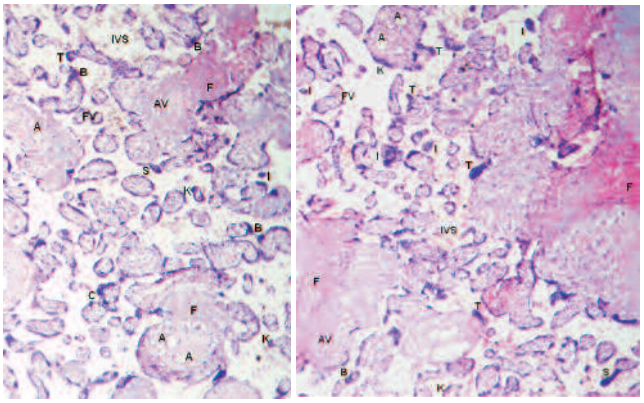

Fig. 6: Microscopic structure of chorionic villi (H and E x 100X)

AV. Anchoring villi FV. Floating villi IVS. Intervillous space
A. Foetal capillaries B. Syncytial bridge
F. Fibrinoid deposit C. Cytotrophoblast island
T. Tenney Parker sign I. Trophoblast island
K. Syncytial knot S. Syncytial sprout

Villous stroma was seen to contain plenty of fibroblasts and a good number of Hofbauer cells, in addition to the foetal blood vessels. Smooth muscle was not found in the blood vessels in the stroma.

B. Placental interlobular septae: could be seen only in pieces.

C. Decidua: could not be made out as a continuous layer; it contained large stromal cells.

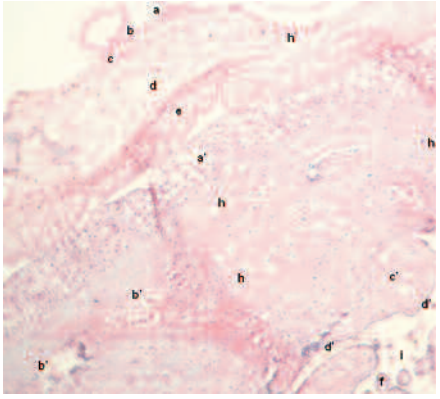

Fig. 7: Microscopic structure of Amnion and Chorion (H and E x 100X)

a - e: Layers of amnion
a. Epithelium. b. Basement membrane c. Compact reticular layer
d. Thick fibroblast layer e. Spongy layer of EEC
a' - d': Layers of chorion
a'. Cellular layer of fibroblasts b. Reticular layer
c'. Pseudobasement membrane d. Trophoblast
h. Hofbauer cells f. Floating villi I. Intervillous space

D. Amnion: All five layers of the amnion could be made out (Fig. 7); the epithelium was flat/ cuboidal (a), resting on a basement membrane (b), inner to which lay a compact layer of reticulum (c), devoid of cells. The fourth layer of fibroblasts (d) is thick (contains Hofbauer cells), inner to which lay a spongy layer (e), the tissue of extraembryonic coelom.

E. Chorion: Hofbauer cells were present throughout the thickness of the chorion. The layers (Fig. 7) seen are the cellular layer of fibroblasts(a') closest to the amnion, the reticular layer (b') made of parallel reticulin fibres and containing foetal vessels, a pseudo-basement membrane (c') formed by dense connective tissue and (d') trophoblast in contact with intervillous space.

Discussion

The placentae chosen for the present study were from uncomplicated, full term, singleton deliveries. The maternal age, gravidity, gestational age, baby gender and baby birth weight were noted in all cases, in addition to the placental studies. The mean maternal age was 27.54 (std. deviation = 4.04), and the mean gestational age was 270.65 days (std. deviation = 8.134). The mean male baby weight was 108.30 gm more than mean female baby weight at term. This is lower when compared to the study of Nahum GG, *et al.* who noted a difference of 136 gm (5 oz)[1]. Many previous studies have shown that female foetuses are systematically smaller than males when appropriately matched for gestational age and other factors, although the precise cause for this difference is unknown[2-5].

Our series of placenta were all considered 'normal' because the babies which were supported in-utero by them had satisfactory clinical outcome, even though the placentae were morphologically and microscopically in a very wide range of definition of normality.

The mean baby birth weight in our series was 2.87 kg, and mean placental weight was 492.14 gm. The mean foetal to placental weight ratio was hence 5.84. In the present study, it was observed that the baby birth weight has a significant correlation with the placental weight. Placenta weight has a nonlinear relation to birth weight, and is an important predictor of birth weight, observes Sanin *et al*.[6]. The placental weight could be modified by many factors as observed by Benirschke K *et al.*[7]; hence as assessment of placental growth and function is better made by calculating the foetal:placental weight, observes Gruenwald P *et al.* [8].

A full term placenta weighing more than 750 gm is considered large and may be associated with increased foetal surface dimensions; it can reflect the added mass of a retroplacental haematoma, effect of maternal fluid administration, large thrombi or foetomaternal haemorrhage[9,10]. It is noted that the large placenta in our study (780 gm) was not associated with any maternal or foetal complications, and the baby birth weight in this case was also high (4.0 kg). Small placental weight may reflect underperfusion of placental bed as in PIH, pre-eclampsia, and diabetic vasculopathy[9] chronic villitis and confined placental mosaicism[11-13]. In our study, the lowest placental weight noted was 100 gm, and the birth weight was 1.53 kg; still the baby was delivered at term normally.

Normally the transition from villous to membraneous chorion occurs at the edge of the placenta; in circum-marginate placenta the chorionic plate is smaller than basal plate, hence foetal membranes arise inner to the placental circumference. Fox H[14] noted that 18-30% of placentae exhibit this condition. In the present study, 24 (25%) of circum-marginate placentae were observed.

A bilobate/ bipartite placenta is composed of two almost equally sized lobes with cord inserted between the two lobes, usually velamentous, but may be into a bridge of chorionic tissue. Fox[14] put forward an incidence of 0.3%. In our study it was found in 2 cases (2.08%). Multilobate placentae are very rare (Faye-Petersen), but we found two multilobated specimens (2.08%).

Accessory lobes are reportedly present in three percent of specimens[9], but in our study it was found in 12 study cases (12.5%). An accessory or succenturiate lobe represents a mild expression of abnormal villous regression or asymmetric placental development. It has no clinical significance, except in instances of retention of accessory lobe, or disruption of its intramembranous vascular supply and foetal haemorrhage[7,14]. The condition is suspected when there is tear in the membranes, and intramembranous vascular branches extend to the limits of the tear, observe Cunningham *et al.*[15].

Retroplacental haematoma is reportedly seen in 4.5% of all placenta specimens[14] with a higher incidence in pre-eclampsia, HT and thrombophilias. In contrast to this, the incidence in our study of clinically uncomplicated cases was quite higher (10.42%).

Massive floor infarction or massive diffuse perivillous fibrinoid deposition was not observed in our study. This conforms to the earlier reports of low incidence, 0.028% (Bane *et al.*[16]) to 0.09% (Andres *et al.*[17]). Small areas of fibrinoid deposition were noted in many cases of our study.

Normally, primary chorionic villi appear by the end of the first gestational week, secondary villi with a mesenchymal core (from EEM), in the second week, tertiary villi by the end of the third week describes Popek[18]. Further villus development includes the formation of anchoring, mesenchymal, stem, immature intermediate, mature intermediate and terminal villi that represent various levels of branching of the mature vascularized villous system[19,20]. The terminal villi are the

functional units of placenta, forming from 21-24 weeks of gestation, becoming the predominant villi by 33-36 weeks gestation as observed by Vicovac [21].

The various types of cell aggregates in the villi were found to be extremely variable in the normal placentae subjected to the present study. Cytotrophoblast (Langhan's) cells were always seen as a discontinuous layer, comparable to other studies which observe that they cover only 20% of villi at term[19]. Cytotrophoblastic islands were seen at the tips of some of the chorionic villi. Syncytial sprouts representing the development of new villi; and exaggerated knots (Tenney Parker sign[22]), (seen in post-mature placenta, pre-eclampsia and margins of infarcts) were seen; so also syncytial bridges, acting as an internal strut system to protect villous capillaries[18]. Extravillous intermediate trophoblast cells (X cells) could be seen as a part of placental septae, and in areas of perivillous fibrinoid[19].

Villous stroma contains fibroblasts and Hofbauer cells, in addition to the foetal blood vessels. Smooth muscle is not found in the blood vessels in the stroma; only reticulin and collagen fibres were seen around the blood vessels[19].

All the five layers of amnion could be made out in the study, (0.02 to 0.5 mm thick according to Bourne [23]. The observation that all four layers of chorion contain Hofbauer cells[23] was confirmed by the present study. The trophoblast layer is in many places replaced by subchorionic (Langhan's) fibrinoid.

Conclusion

A detailed study on the morphological and microscopic features of placenta obtained from clinically uncomplicated deliveries proves that their structure at term varies considerably in different specimens. A wide range of normal variations could be observed in the shape, number of cotyledons, foetal/ placental weight ratio, accessory lobes, the chorionic villi structure and foetal membranes. This would imply that the placenta is capable of extending its physiological potential to a great extent, so as to enable the foetus reach term and be delivered normally, as in the present study. Further studies in this regard would be necessary to enable us to delineate the placental changes that might lead to an unfavourable foetal/ maternal outcome.

Acknowledgement

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PUSHPAGIRI MEDICAL JOURNAL

✪ ORIGINAL ARTICLE

Making Multiple Choice Questions useful for application of Medical student knowledge

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Abstract

Background: There have been several attempts at finding out the most valid way of assessing the outcome of teaching. The long essays gave way to multiple choice questions (MCQ) which later were scrapped in favor of short structured questions. Multiple choice questions had many problems like cueing and very straight forward way of framing questions. Use of clinical vignettes and application of knowledge made MCQs a powerful tool to assess associative learning. Clinical competence could thus be evaluated using scenario based questions. **Objectives:** To determine whether a vignette or scenario based problem solving approach in MCQs will lower or improve the scores of students. **Design:** A double trial of MCQs with old and new pattern questions. **Setting:** A medical school in the middle-east. **Subjects:** Non-English speaking population of students. **Methods:** Two tests were conducted for 85 students one with straight forward questions and answers and a second one with vignette based and scenario based questions. Double negatives or other confusing ways of asking questions were avoided. Item analysis was conducted for both exams. Item facility index, modified caution index, point biserial index and discrimination index were worked out for each question and averaged for each examination. **Results:** While seventeen students did better on the vignette dominant examination, majority could not handle this examination very well. The overall score was significantly lower with vignette dominant examination. MCQs were found to differentiate the good and bad students in terms of discrimination index. Our study pointed out the weakness of students in applying the knowledge. We had the problem of a non-English speaking population of students faced with Americanized questions. At the same time it was evident that writing skills of such students needed to be improved. This aspect was never tested with the use of MCQs. **Conclusions:** MCQs are more efficient, reliable and valid provided problem-solving type of questions which work at a cognitive level without perusing too much of vignettes for a non-English speaking population are used.

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Introduction

The teaching process must logically involve evaluation before the trainee is certified, promoted or licensed. However, it is difficult to create near-to-life simulations of actual day-to-day problems in an examination scenario. There are various ways of testing the assimilated knowledge and acquired skills of a medical student or other trainee. Each method can be criticized for the extraneous influences which modify the extent to which the test results resemble the real-life responses. For example, the traditional essay and short answer questions are deemed as lacking objectivity; each student being given credit for knowing different aspects of the same problem with some 'value-additions'. Different examiners can potentially attribute different weightage to these quirks and twists which may or may not bear importance in the actual practice of medicine.

Multiple choice questions (MCQs) were introduced as a solution to this lack of objectivity in the 1920s in the USA. This method gained approval for several reasons; examinees were found to score the same way regardless of the time limit of examinations (an issue which used to plague any traditional written examination) and, needless to say, the bias of examiners never could affect the results.[1] However, it is also obvious that life never presents with structured multiple options and very often

the usual type MCQs, especially in the East, is simple and straight-forward. Professional competence of a physician, even if he is just reading and assimilating a scientific article, never follows a 'by-rote' system. Problems are presented to a doctor in a mixed, vague and confusing fashion, and the physician needs to decode the problems to be able to approach the solution. This differs considerably from straight-away being given a simple scenario which needs be matched word-by-word to the standard medical text book. The present MCQs test isolated facts without reference to possible related information.

Epidemiology is a subject which is becoming more and more important in the daily workings of physicians in that they are being deluged by conflicting information. Popular press and even vested interests are toying with epidemiological information with levity and an average physician is caught up with cracking the codes of wisdom after going through an epidemiology course lasting a few hours and involving a few simple and straight-forward MCQs of the run-of-the-mill kind. Needless to say, this is simply inadequate. For example, questions of the following nature abound in qualifying examinations across middle and south-east Asia: “Which of the following is one of the best sources of pooled study results in medical literature?”

- International Red cross
- United Nations
- Cochrane collaboration
- Doctors without borders
- CONSORT organization

The question itself is point-blank and does not require any intelligent assessment of the situation. It depends only on recall or even 'hearsay' learning. While it is important to know the fact implied in the answer, it does not equip a medical student to become an analyst. It must be said that it may be easier for students to score well in examinations containing simple recall MCQs and, consequently, students may prefer such questions, provided the curriculum is tightly constrained within the covers of a single textbook. However, high scores need not mean better competency and may not encourage the students to achieve higher levels of competition. The criticisms against simple MCQs are many, such as students often can find the correct answers by elimination and guessing, MCQs encourage cueing, and students often focus on amassing collections of old questions and trying to learn from those without acquiring fundamental knowledge of the content related to the questions.

Several ways of overcoming these limitations have been tried. To avoid the simple deviant of cueing in MCQs, bigger list of options have been suggested in the UnQ method. However, the criticism still holds when questions test only student recall, such as “Which one of the following organs of the body pumps blood?”. To put the issue in context, a recall-based MCQ in epidemiology dealing with blinding in trials could simply be: “Which one of the following is said to be done when similar-looking packaging and colour of tablets are used for both treatment and placebo arms in a randomized trial?” In contrast, a problem-solving MCQ would not give occasion to generate a simple straight-forward answer as in the above question. For illustration, a student would need to link two concepts before cracking the question, “Which bias can be avoided by hiding the treatment information from the physician in a trial?”, connecting the concepts of 'blinding process' with 'assessment bias'.

The addition of clinical vignettes has been shown to have enriched the problem-solving skills of students. For example, the straight-forward question given above can be remodeled with the same distracters as: “Patients with cirrhosis and ascites were randomly assigned to receive either trimethoprim-sulfamethoxazole or norfloxacin for the prevention of infection. The treatment information was hidden from the treating physician by the use of similar-looking packaging and color of tablets. This procedure would be useful in reducing which one of the following?”

- Placebo effect
- Assessment bias
- Restriction bias
- Chance effect
- Hawthorne effect

Clinical competence and problem-solving ability are involved in analyzing the body of the question, and recall ability to some extent is used in picking the right option from the choices given. The glitch here is that, depending on the clinical vignette, the question may appear to be somewhat ill-constructed to students who are not language-competent, which could trigger strange anchor points in such students.

To test the change in student scores when vignettes are introduced into problem-solving MCQs in a language-constrained group of students, we tested the two variants of questions in sequential assessment tests of a medical school course in Epidemiology.

Methods

Two tests were conducted for a class of 85 students in their second preclinical science year of medical school. The test items were audited by an expert for removing errors and grammatical nuances. One test comprised of 30 questions of straight problem-solving type. E.g. “A treatment outcome prediction score was made from the data of a randomized controlled trial which comprised the treatment along with some prognostic variables. The dependant variable was occurrence of a complication (dichotomous). Which is the regression model used in this assessment?”

- Linear
- Logistic
- Residual
- Poison
- Ordinal

The second examination had eighteen vignette-based problem-solving questions without any direct reference to the key issue. E.g. "A transcription of a chimeric gene was detected at primary diagnosis in 21 of 648 children suffering from acute lymphoblastic leukemia (ALL), selected for a multi-centre childhood ALL randomized controlled trial. The prevalence estimate of presence of this gene from this data could be suffering from which one of the following?"

- Lack of sensitivity
- High specificity
- Assessment bias
- Sampling error
- Restriction

All efforts were taken to avoid questions containing double negatives and also the EXCEPT type of question. The mean values of the actual scores and percentages of both examinations were calculated and *paired-t test* was used to find the significance of the difference between the two tests. The examinations were conducted via computer using SOLE (Secure Online Learning Environment), a propriety software program of West Virginia University (Morgantown, West Virginia, USA). Item analysis was carried out by SOLE using the indices which are mentioned below[2]. These indices were compared using paired t-tests. A *p-value* of 0.05 was considered to be statistically significant.

Item facility index was calculated as the percentage of students answering the item correctly. The item facility index, also called difficulty index, can range from 0 to 100%. Higher values indicate easy items while lower values are associated with difficult items. The percentages of upper and lower 27% of students answering items correctly also were calculated.

Modified caution index (MCI) for items are cautionary items displaying atypical response patterns with easier items incorrectly answered by higher ranking students and harder items correctly answered by lower ranking students. Items with an MCI exceeding 30 are considered to display an atypical response pattern.

The point biserial indicated how well an item differentiated between the most- and least-able students. In other words, the point biserial is a correlational score that indicates how well an item differentiates between the most- and least-able students based on comparison of all students in the group. The higher the positive value of the point biserial, the better the test item discriminates between high- and low-scoring students. A point biserial of zero shows the item does not discriminate, while a negative value shows the item was correctly answered more often by the low-scoring students than by the high-scoring students.

Discrimination index was also calculated which compared the top (most able) and bottom (least able) 27% of the students (whereas, the point biserial was based on all students). Discrimination is an index that compares how the most able students performed on an item to how the least able students performed. The higher the positive value of discrimination index, the better was the test item in discriminating between high-scoring and low-scoring students. A discrimination index of zero showed that the item does not discriminate, while a negative value shows the item was correctly answered more often by the low-scoring students than by the high-scoring students.

Results

The results of the two examinations for 85 students are shown in Table 1. Only 17 students did better on the vignette-based questions in comparison with the straight problem-solving questions. The overall score was poorer for the whole class on the vignette-dominated test (paired t-test p value = 0.000). Of the students who improved with vignette-based examinations, seven were repeaters, i.e., students who had failed a year previously and, presumably, are weaker academically than regular students. This showed that the vignette-dominated examination affected both regulars and repeaters equally with no special deleterious effect on repeaters.

Table 1: The performance of the students (n=85) in the two tests

Statistics	Straight MCQs (n=30 questions)		Vignette-based MCQs (n=18 questions)	
	Score	Percent	Score	Percent
Mean	23.84	79.46%	12.44	69.12%
St. deviation	4.03	-	2.72	-
Median	24	80%	13	72.22%
High score	29	96.67%	18	100%
Low core	12	40%	7	38.89%

The effect of the vignette on the item analysis of the questions in both examinations is presented in Table 2. None of the test items had an item facility (difficulty) index of less than 35. In other words, none of the questions were judged to be overly difficult.

Table 2: Item analysis of the two tests

Statistics	Straight problem-solving MCQs (n=85 students)	95%CI	Vignette-based problem-solving MCQs (n=85 students)	95%CI	*p* value
Difficulty	90.05%	82.34% 97.77%	69%	60.72%-77.27%	0.034
Top 27%	99.75%	92.76% 100.0%	87.63%	81.31%-93.94%	0.062
Bottom 27%	74.75%	66.18% 83.32%	49.24%	37.62%-60.87%	0.091
Point Biserial	35.3	30.11-40.55	34.9	29.72-40.05	0.596
Modified caution index	28.89	24.97 32.80	26.72	23.56-29.88	0.579
Discrimination	25	18.15%-31.85%	38.4	29.84%-47.04%	0.350

Modified caution index was higher than 30 for 33.3% for straight problem-solving MCQs and 44.4% for the vignette-based MCQs. Point biserial and discrimination indices were never negative.

The tests displayed equal discrimination between the most-and the least-able students. The discrimination and point biserial values did not differ statistically between the two tests. Likewise, the modified caution indices was similar for both tests.

There was a significant decrease in the item facility index with the vignette model of questions thereby implying less percentage of students answering the items correctly. However, the worsening of performance when taken separately in upper and lower 27% sections of the student population was not statistically significant. In other words, the most-able students performed equally well on both tests and the least-able students performed equally poorly on both tests. Overall, the data suggest that the midclass student (i.e, the middle 46% of the student population) performed poorer on the vignette-based test as compared to the straight problem-solving test.

Discussion

MCQs are very useful as an assessment tool, with a simple design, easy implementation (with appropriate staff development), and clarity of focus. There are many types of these questions: single best answer (A-types); matching questions (M-types); and multiple true/ false questions (X-types) or in another methodological way: the five choice completion, multiple completion, and assertion-reason types. Nonetheless, many authorities such as Wilson and Case (1993) have proposed that MCQs be replaced with better methods of asking questions[3]. Wood (2003) pointed out that (i) MCQs assessed "remembering isolated pieces of information" rather than "the ability to use knowledge" and (ii) they could be answered by eliminating the incorrect options (distracters)[4]. However, if staff are trained to design proper distracters, the problem of 'answering the question by a process of elimination' can totally be avoided[5].

If the purpose of education is to make students know the general terms and concepts of a subject, then the good old MCQs can be designed to test the construct knowledge of students. Whereas, the individual scores may be better with recall questions, our study pointed out the weakness of students in applying their knowledge. The modified caution index probably pointed to unpredictable performance of the middle 46% of students who got distracted by too much information in the body of question. Examples of MCQs testing all of the six competence levels of Bloom's (1972) competencies have been discussed previously[6,7]. As an argument against the use of long stems (i.e., the lead-in part of questions), extended matching questions could be used to reduce the body of individual sub-questions.

Even this latter approach failed to stimulate the thought processes in our cluster of students in another test situation which is not presented here. The specific student context of our study is a non-English speaking population which struggled to adjust to an American curriculum. It is said that assessment drives learning[8]. However, it is equally important that the assessment approach matches the teaching approach. When the teaching approach concentrates on providing material in a straight-forward recall fashion, then assessment questions of the problem-based vignette model can tend to drive a non-English speaking student off on a wild goose chase. The language skills, recall-based learning, and pattern-matching strategy of the students fail to get to the bottom of a problem such as "Patients with cirrhosis, admitted because of variceal bleeding, were allocated to receive either nadolol and isosorbide-5-mononitrate alone, or combined with endoscopic band ligation surgery. The allocation to the groups is best done using which one of the following methods?"

- Patient characteristics
- Choice by the relatives
- Random assignment
- Systematic sampling
- Arbitration

It can be argued that students are not provided a chance to defend their answers in a typical MCQ scenario. Item analysis seems the only way to assess the inferiority of a MCQ. This often irritates the teachers because they feel a student must know certain facts, irrespective of the superiority or inferiority of a question. The way out of this catch-22 situation is by having an amalgamation of methods. Another issue worth pointing out is the need for a non-English population of students to write answer paragraphs such that their language skills improve side-by-side with their course knowledge. Modified Essay Questions (MEQs) were claimed to be a compromise between MCQ and essay. An example:

a. A 46-year-old woman presented to the emergency department with a three-month history of early satiety and anorexia. Over the last two weeks, she had been vomiting most days and has been unable to eat or drink much. Describe what other information you would seek from the history that would help you establish a diagnosis and justify your answers.

b. From the history you think that the patient has gastric outlet obstruction. Describe the physical findings you would look for on examination and explain why they might occur.

c. Assuming that a <… > was to be performed as part of the work-up, what are the features suggesting <…> that would be sought?

Even these authors, ultimately, pointed out that it is possible to produce an MCQ paper that tests a broad spectrum of a curriculum, measures a range of cognitive skills and does so, on the basis of structurally-sound questions[9]. Results have also indicated that

MCQs are more efficient, reliable and valid than patient management problem items[10]. Considering that extended MCQs have their own set of disadvantages, one would still persist with the problem-solving type of questions which work at a cognitive level without perusing too much of vignettes for a non-English speaking population of students.

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✪ ORIGINAL ARTICLE

Profile of Retinopathy of prematurity in newborns

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Abstract

Background: Retinopathy of prematurity (ROP) is a major cause of blindness and visual morbidity. **Objective:** To study the incidence and contributing factors of retinopathy of prematurity in newborns. **Methods:** This prospective study was conducted in the neonatology unit. Seventy five newborns with gestational age between 27 weeks and 40 weeks, who had one or more of the known risk factors, were studied during a one year period. They were followed up by an ophthalmologist until both retinae matured or they developed ROP. Cases (those requiring laser treatment and those with spontaneous resolution) were further followed up. **Results:** The incidence of ROP was found to be 32%. Lower gestational age (p=0.00009), lower birth weight (p= 0.00006) and a higher concentration of oxygen therapy (p= 0.00005) were found to be the significant contributing factors in the development of ROP, while factors like sex, duration of oxygen therapy, phototherapy, apnoea, thrombocytopenia, sepsis and blood transfusions were found to be insignificant. **Conclusions:** Low gestational age, low birth weight and high concentrations of oxygen therapy are the important risk factors in the development of ROP.

Key words: Retinopathy of prematurity, Prematurity, Oxygen therapy

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Introduction

Retinopathy of prematurity (ROP), previously known as retrolental fibroplasia, is a vaso-proliferative condition of retina and is a major cause of blindness and visual morbidity in many of the surviving premature infants[1]. Prematurity is the single most important risk factor responsible for retinopathy of prematurity. Incidence of ROP increases with decreasing gestation and birth weight. However, not all preterm neonates develop ROP.

Important risk factors which increase the probability of developing ROP are oxygen therapy, anaemia needing blood transfusion, sepsis and apnea[2-5]. Many advances in neonatal care have considerably improved the survival of premature children. This has, in turn, led to an increase in the incidence of ROP. Being a preventable cause of blindness, it is advisable to screen all premature babies to detect ROP, follow up relevant cases, and treat as and when required.

Material and methods

This was a prospective study conducted over a period of one year (January 1st to December 31st 2009) in the Unit of Neonatology, Department of Child Health, Pushpagiri Institute of Medical Sciences and Research Centre, Tiruvalla, Kerala.

Newborns of gestational age 27 to 40 weeks who were admitted in the Neonatology ICU, and had one or more of the risk factors known to cause or contribute to the development of ROP were included. An indirect ophthalmic examination was done at 31 weeks of post-conceptional age or four weeks of chronological age, whichever was later. Further follow up depended on the intra-ocular findings.

All the data were entered in a pretested proforma. Analysis were done and the results were presented as frequencies, percentages and relative risk. *Chi-square test* was used to assess the statistical significance of association of the factors involved.

Observations and results

1. Incidence

Out of the 75 children studied here, 24 had ROP. This places the incidence of ROP as 32% in the current study.

2. Sex distribution

Comparing the two sexes, 34.15% of males and 29.41% of females developed ROP. This difference was not significant (p=0.66).

3. Gestational Age

Table 1. Distribution of study group according to gestational age

Age (weeks)	Total	ROP Cases - No (%)	RR
= 32	18	13 (72.22)	18.78
32^{+1}-34	31	10 (32.26)	8.39
= 34	26	1 (3.85)	1.00

p=0.00009 RR: Relative risk

Table. 1 indicates that the incidence of ROP is higher in children with lower gestational ages at birth, and its association with the gestational age is highly significant.

4. Birth weight

Table 2. Distribution of study group according to birth weight

BW (grams)	Total	ROP Cases - No (%)	RR
<1000	6	5 (83.33)	13.33
1001-1500	16	9 (56.25)	9.00
1501-2000	37	9 (24.32)	3.89

p=0.00006; BW: Birth weight, RR: Relative risk

Table. 2 indicates that the incidence of ROP is higher in children with lower birth weight and its association with birth weight too is highly significant.

5. Oxygen therapy

Table 3.1: Distribution of study group according to the pattern of oxygen therapy

FiO2 (%)	Total	ROP Cases - No (%)	RR
60	12	9 (75.00)	5.13
50	22	9 (40.91)	2.8
40	44	6 (14.63)	1

p=0.00005; RR: Relative risk.
FiO2: Fraction of inspired air in a gas mixture

Table. 3.1 indicates that the incidence of ROP is higher in children who received a higher concentration of oxygen therapy and the association is highly significant.

Table 3.2: Distribution of study group according to the duration of oxygen therapy

Duration	Cases	Total	%
= 7 days	7	28	25
> 7 days	17	47	36.17

p=0.31

Table. 3.2 indicates that the duration of oxygen therapy is not significant in the development of ROP.

6.Treatment

Out of the 24 (79.17%) children diagnosed with ROP, 19 underwent laser therapy, and five cases (20.83%) showed complete resolution without any treatment.

Discussion

The incidence of ROP in various western studies were reported to vary from 21 to 65.8%[6-9]. Indian studies place the incidence at 38% to 51.89%[10-12]. In our study, the incidence was found to be 32%.

The incidence of ROP was found to be highest in children born at or before 32 weeks of gestational age and the least in those above 36 weeks. The only child of gestational age below 28 weeks and all five children between 28-30 weeks developed ROP. There were no cases in children above 36 weeks. The risk of developing ROP among the newborns decreased as the gestational age at birth increased, as reflected in the relative risk shown in table1. This inverse relationship between the incidence of ROP and gestational age agrees with the data from Western studies[13].

The incidence of ROP was found to be the highest in children with extremely low birth weight. Five out of six children (83.33%) with birth weight below or equal to one kilogram had ROP. There were no cases in children with birth weight above 2.5 kg. The relative risk was as high as 13.33 for birth weight below 1000 grams as compared to the above two kilograms group. Similar observations were made by Giannantonio *et al.* [13].

Newborns were categorised according to the oxygen therapy as those who received a maximum FiO2 of 60% or more, 50% and 40%. The relative risk was determined after taking children who received a maximum FiO2 of 40% as the baseline group. The relative risk was 2.8 fold for 50% and 5.13 fold for 60%. The duration of oxygen administration was, however, found to be insignificant. Various observational studies have reported that incidence and severity of ROP is lowered if oxygen saturation targets are kept in a desirable range[14,15].

Other factors like sex (p=0.66), duration of oxygen therapy (p=0.31), phototherapy (p=0.74), apnoea (p=0.2), thrombocytopenia (p=0.24), sepsis (p=1.00) and blood transfusions (p=0.24) were found to be statistically insignificant.

Conclusions and Recommendations

The incidence of ROP in our study was 32%. A lower gestational age and a lower birth weight are the significant contributing factors. The higher concentration of oxygen therapy is also significant, though the duration of the same is yet to be studied to have a contributing role.

Based on these conclusions, we recommend that the upper limit of gestational age for screening be raised from the current suggestion of 32 weeks to 34 weeks, the birth weight cut-off for screening be raised from the current suggestion of 1500 grams to 2000 grams, and the upper limit of oxygen given be reduced from the current recommendation of FiO2 of equal to or above 60% to below 50%.

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✪ ORIGINAL ARTICLE

Factitious Hyperkalemia

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Abstract

Background: Potassium is one of the most frequently tested analytes in the clinical biochemistry laboratory. Owing to the important role of potassium in homeostasis, erroneous potassium values can significantly affect treatment and patient care. As hyperkalemia can result in life-threatening arrhythmias and cardiac arrest, elevations of the level have to be taken up seriously. Therefore, it is absolutely necessary to differentiate between real and false hyperkalemia. **Materials and methods:** Fifty healthy subjects, with their informed consent, were studied with three readings of their potassium levels by collecting blood as a free flowing sample, after tourniquet application, and with fist clenching. **Results:** it was found that the mean difference between the initial sample (k_1) and the sample taken after tourniquet application (k_2) was not significant. The difference between k_2 and the sample taken following tourniquet application and fist clenching (k_3) was highly significant. Difference between k_1 and k_3 was also significant. **Conclusion:** The observed pseudohyperkalemia could be due to the transcellular shift of K^+ ions, mediated by aldosterone.

Introduction

Potassium is one of the most frequently tested analytes in the clinical biochemistry laboratory. Hyperkalemia is a rare occurrence in normal subjects, because the cellular and urinary adaptations prevent any significant potassium accumulation in the extracellular fluid. It can be seen in normal healthy individuals during blood collection and is often referred to as pseudohyperkalemia. It is defined as a spurious elevation of the serum concentration of potassium occurring when potassium is released *in vitro* from cells in a blood sample collected for a potassium measurement, usually as a result of improper collection technique with *in vitro* haemolysis[1]. It is a laboratory artifact rather than a biological abnormality and can be misleading to the caregivers[2]. Overzealous correction is unwarranted and could be potentially dangerous[3]. Thus it becomes very important for the practising physician to differentiate between the true and pseudo-hyperkalemia cases. Although the diagnosis and treatment of pseudo-hyperkalemia remains paramount[4], recognizing factitious hyperkalemia is important to preclude unnecessary investigations and potentially hazardous interv-ention[5,6]. It poses a particular problem in the context of out-of-hour services, when not all patient information is necessarily available to on-call doctors, and is a source of serious concern to the patients.

The phenomenon of pseudo-hyperkalemia was first reported by Hartmann and Mellinkoff[7] in 1955 as a marked elevation of serum potassium levels in the absence of clinical evidence of electrolyte imbalance. Hartmann and his colleagues[7,8] concluded that the high potassium in serum is due to leakage from platelets *in vitro* during the clotting process, and was confirmed in many studies thereafter[9,13]. Nilsson *et al*[14], in order to explain some of the observed cases, suggested that potassium could be released from some other cellular components and assumed that the red cells might be the source. Furthermore, in 1966, Bronson *et al*[15] described three cases of pseudohyperkalemia in chronic myelogenous leukemia in transformation, and concluded that white blood cell breakdown could cause the release of potassium during

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coagulation as well.

Therefore a study was planned to examine the possibility of pseudohyperkalemia in three different occasions: without tourniquet application, after tourniquet application, and following tourniquet application and fist clenching, in fifty healthy medical students.

Aims and objectives

To find out the varying levels of serum potassium in a series of three readings:

- Free flowing sample
- After tourniquet application
- Tourniquet application and fist clenching

This study compared the varying K^+ levels in various clinical settings, and helped to interpret the condition accordingly, so that we can have a better outcome, beneficial to the patients as well as the physician.

Materials and methods

Setting : The study was done in Pushpagiri Institute of Medical Sciences and Research Centre.
Duration of study : Two months
Type of study : Quasi-experimental

Fifty healthy medical students, after obtaining their written consent, were subjected to three readings of serum potassium values, by collecting blood as a free flowing sample, after tourniquet application, and with fist clenching. The mean difference was noted on obtaining the results.

Inclusion criteria:

Only normal healthy human volunteers

Exclusion criteria:

1. Patients who were undergoing any kind of drug therapy at that time.
2. Patients with any systemic disease.

Sample collection*:* Blood was drawn from a vein in the cubital region by venipuncture. It was collected in a vial and was sent to the laboratory.

Procedure: The serum potassium values were estimated in the laboratory by the, *"the ion selective electrolyte method"*. In this method, there were two electrodes; one to detect serum potassium levels and the other for serum sodium. Each electrode would selectively detect the respective ions. The values obtained on the machine were printed out.

Statistical analysis

Mean and Standard Deviations (SD) of serum potassium levels of all the subjects were calculated for the three samples taken. The mean differences between the samples were examined. The mean differences were also evaluated in relation to age, sex, and personal habits such as diet, alcoholism, smoking and exercise.

Student's t-test and One-way *ANOVA* were done to compare the mean differences. A *p*-value of less than 0.05 was considered as statistically significant.

Results

The data collected from the subjects were analyzed using Microsoft Excel and EPI INFO Version 3.3.2. The observations are presented in this section.

I. Age and sex distribution:

Age of the subjects ranged from 19 to 23 years, with a mean age of 21years. Twenty girls and thirty boys were included in the group. The age-sex distributions of these subjects are given in Table 1.

Table 1: Age-sex distribution of the study subjects

Age (years)	Male	Female	Total (%)
19	4	0	4 (8)
20	1	4	5 (10)
21	13	11	24 (48)
22	10	3	13 (26)
23	2	2	4 (8)
TOTAL	30 (60%)	20 (40%)	50 (100)

II. Distribution of personal habits:

The habits noted under the study included dietary habits, alcoholism, smoking and exercise, all observed in relation to their gender, and are given in Table 2. The study subjects were 96% non-vegetarians, 28% occasional alcoholics, 06% smokers and 78% took some form of exercise regularly.

Table 2: Personal habits of the study subjects by gender

Habits		Gender		Total	
		Male	Female	Number	%
Dietary	Non-vegetarians	30	18	48	96
	Vegetarians	0	2	2	4
Alcoholism	Alcoholics	14	0	14	28
	Non-alcholics	16	20	36	72
Smoking	Smokers	3	0	3	6
	Non-smokers	27	20	47	94
Exercise	Yes	24	15	39	78
	No	6	5	11	22

III. Serum potassium levels:

Three samples taken from each of the subjects were analyzed and it was found that the serum potassium levels ranged from 3.5 to 5.5 mEq/L, which is the normal range. The mean serum potassium values of these 50 subjects are shown in Table 3.

Table 3: Mean serum potassium levels of the study subjects

Sample number	Mean	SD
k_1 k_1	4.33	0.38
k_2 k_2	4.31	0.29
k_3 k_3	4.48	0.34

IV. Potassium values in the three settings:

The mean difference between the initial sample (k_1) and the sample taken after tourniquet application (k_2) was not significant. The difference between k_2 and the sample taken following tourniquet application and fist clenching (k_3) was highly significant. Difference between k_1 and k_3 was also significant. These mean differences are presented in Table 4.

Table 4: Mean difference in the serum potassium levels

Difference between	Mean	SD	t-test	'*p*' value
k_1 k_1 and k_2 k_2	0.02	0.35	0.411	0.68
k_3 k_3 and k_2 k_2	0.17	0.30	4.02	0.0002
k_3 k_3 and k_1 k_1	0.15	0.45	2.38	0.0211

V. Comparison with Age and Sex

The mean differences of k_1 and k_2 for different age groups and for males and females are given in Table 5. The mean differences were not statistically significant for age and sex.

Table 5: Mean difference between k_1 and k_2 in relation to Age and Sex

Characteristics		No	Mean difference	SD	F	Significance (*p*)
Age (in years)	19	4	- 0.1	0.18	2.513	0.055
	20	5	0.64	0.22		
	21	24	0.1	0.21		
	22	13	- 0.112	0.21		
	23	4	0.495	1.04		
Sex	Male	30	- 0.049	0.22	2.95	0.093
	Female	20	0.125	0.49		

The mean differences for k_2 and k_3 for various age and sex are given in Table 6. The differences were not significant for age and sex.

Table 6: Mean difference between k_2 and k_3 in relation to Age and Sex

Characteristics		No.	Mean Difference	SD	F	Significance (*p*)
Age (in years)	19	4	0.32	0.36	0.396	0.81
	20	5	0.226	0.13		
	21	24	0.173	0.29		
	22	13	0.136	0.4		
	23	4	0.073	0.15		
Sex	Male	30	0.2	0.28	0.843	0.363
	Female	20	0.12	0.34		

Table 7 presents the mean differences of k_1 and k_3 in relation to age and sex. The difference is statistically significant for sex.

Table 7: Mean difference between k_1 and k_3 in relation to Age and Sex

Characteristics		No.	Mean difference	SD	F	Significance (*p*)
Age	19	4	0.33	0.43	2.109	0.095
	20	5	0.16	0.18		
	21	24	0.16	0.29		
	22	13	0.25	0.41		
	23	4	0.42	1.11		
Sex	Male	30	0.25	0.33	4.072	0.049
	Female	20	0.001	0.56		

VI. Comparison with personal habits

The mean differences of k_1 and k_2, k_2 and k_3, and k_1 and k_3 were calculated in relation to personal habits and are shown in Table 8, Table 9 and Table 10 respectively. None of the mean differences were statistically significant.

Table 8: Mean differences of k_1 and k_2 in relation to personal habits

Parsonal Habits		No.	Mean difference	SD	F	Significance (*p*)
Alcholism	Yes	14	0.22	0.28	0.48	0.49
	No	36	0.15	0.31		
Smoking	Yes	3	0.33	0.41	0.903	0.347
	No	47	0.16	0.29		
Exercise	Yes	39	0.17	0.32	0.001	0.977
	No	11	0.17	0.21		

Table 9: Mean differences of k_2 and k_3 in relation to personal habits

Personal habits		No.	Mean difference	SD	F	Significance (*p*)
Alcholism	Yes	14	0.001	0.16	0.06	0.807
	No	36	0.029	0.41		
Smoking	Yes	3	0.03	0.13	0.002	0.964
	No	47	0.02	0.37		
Exercise	Yes	39	0.016	0.39	0.033	0.857
	No	11	0.038	0.14		

Table 10: Mean differences of k_3 and k_1 in relation to personal habits

Personal habits		No.	Mean difference	SD	F	Significance (*p*)
Alcholism	Yes	14	0.22	0.32	0.438	0.511
	No	36	0.12	0.49		
Smoking	Yes	3	0.30	0.46	0.360	0.551
	No	47	0.14	0.45		
Exercise	Yes	39	0.16	0.49	0.015	0.902
	No	11	0.14	0.24		

Discussion

In the present study, pseudohyperkalemia was compared in three different situations, i.e., without any tourniquet application, after tourniquet application, and following tourniquet application and fist clenching. The mean difference between the initial sample (k_1) and the sample taken after tourniquet application (k_2) was not significant. The difference between k_2 and the sample taken following tourniquet application and fist clenching (k_3) was highly significant. Difference between k_1 and k_3 was also significant. It was clearly revealed from the study that the serum potassium levels of the study subjects were not due to the variation in their personal habits such as alcoholism, smoking and exercise, irrespective of gender.

In all these three settings, death or lyses of cells in the test tube release potassium into the serum, increasing the measured value. Collection artifact does not increase serum potassium levels to abnormal levels unless the platelet count becomes greater than 1,000,000/cmm[16].

It was also reported that repeated fist clenching with a tourniquet tightly in place can increase K^+ release from muscle cells, factitiously increasing the serum K^+levels[17,18]. Muscle clenching and failure to release the tourniquet before sampling may lead to anaerobic glycolysis, leading to limited adenosine triphosphate (ATP) production. A delay in centrifugation (prolonged serum-cell contact leading to glucose depletion) and temperature changes (chilling inhibits glycolysis) lead to inhibition of glycolysis with decreased availability of ATP. This leads to inhibition of the sodium-potassium-ATP-ase pump, which results in potassium leakage from cells[19]. The present study also supported this fact. Since this study was carried out in healthy subjects, the results were also in agreement with the above mentioned reports.

Several reports had indicated that ischaemia due to tight and prolonged tourniquet application and fist clenching increases K^+ levels by about 1-1.6 mEq/L[20]. Repeated clenching and unclenching of the fist may artifactually increase K^+ by 01 to 02 mmol/L[21]. It might also be caused due to the prolonged use of a tourniquet or excessive tight application of the tourniquet, by inducing release of K^+ ions from the skeletal muscle into the venous system.

Is haemolysis a cause of Pseudohyperkalemia?

Application of tourniquet for an extended time leads to an increase in venous pressure and extravasation of fluid into the intracellular space. If the tourniquet is left in place too long, a haematoma can develop as well. Owing to the decrease of the liquid phase of blood, there is haemoconcentration and altered water balance in the cells, which causes lysis of RBC's and platelets and release of intracellular potassium into the blood, resulting in pseudohyperkalemia[22]. It has been reported that there are three components to the net potassium flux across the red cell membrane: the Na^+, K^+-ATPase pump, the $Na^+K^+2Cl^-$ co-transport system, and the passive diffusion of potassium across the membrane[23]. The present study also supported these facts.

It was reported that aldosterone stimulates sodium re-absorption by increasing the number of open sodium channels in the luminal membrane; this loss of cationic sodium makes the lumen more electronegative, thereby enhancing the electric gradient, favouring the secretion of cellular potassium into the tubular fluid through the potassium channels in the luminal membrane[24]. Since the current study was based on normal healthy subjects, the results also supported this hypothesis.

In order to prevent misdiagnosis by the clinician and potentially hazardous outcomes, certain corrective measures may be undertaken. These include:

- Disengagement of the tourniquet as soon as the blood flow is established; this should be done no longer than one minute after tourniquet application[25].
- Avoid fist clenching; dangle the arm for one to two minutes or massage the arm from wrist to elbow; tap sharply at the venipuncture site with the index and second finger
- Apply a warm damp cloth (about 40°C) to the site for five minutes before withdrawal[25].

Conclusion

In the present study, pseudohyperkalemia was compared in three different clinical settings. The study subjects were fifty healthy medical students of varying personal habits from both genders, and it was found that there was significant variation in the samples taken after tourniquet application (k_2), and the samples taken following tourniquet application and fist clenching (k_3), and also between the initial sample (k_1) and the sample taken following tourniquet application and fist clenching (k_3). It was clearly revealed from the study that the serum potassium levels of the study subjects were not related to the variation in their personal habits such as alcoholism, smoking and exercise, and were observed irrespective of their gender. Several studies also have reported that prevalence of pseudohyperkalemia might be due to one of the following mechanisms like transcellular shift of K^+ from the skeletal muscle, effect of aldosterone on Na^+/K^+ pump in the luminal membrane, and K^+ efflux from red cell membrane.

Further studies are needed to find out the real mechanism for K^+ efflux from the intracellular region to the extracellular region and also the duration of the prevalence of pseudohyperkalemia following disengagement of the tourniquet.

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PUSHPAGIRI MEDICAL JOURNAL

✪ ORIGINAL ARTICLE

Profile of Hand, foot and mouth disease outbreak in Central Kerala, 2009

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Abstract

Objective: To study the clinical profile of the relatively new viral exanthematous fever, Hand foot and mouth disease. **Method:** By retrospectively analyzing the medical records of patients who attended Paediatric department of Pushpagiri Medical College. **Period:** A six month period from June to November 2009. **Results:** The disease caused mild to moderate physical discomfort for 2-3 days on an average, the main complication in very young children being febrile seizures, which occurred in 20% cases. **Conclusion:** The disease has been a benign illness so far, but virological studies are essential to find the prevalent strains, so as to identify emerging new strains and epidemics.

Key words: Hand foot and mouth disease, Enterovirus.

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Introduction

Hand, foot and mouth disease is a distinctive rash syndrome caused by Enteroviruses, especially Coxsackie A16. It could also be caused by Enterovirus 71, Coxsackie A 5, 7, 9 and 10 and by Coxsackie B 2 and 5[1]. Though generally a benign disease, there are reports of fatalities during outbreaks. It is not commonly seen in India; only a few reports are available in the literature. Many deaths have been reported due to severe outbreaks of HFMD from many Asian countries[2-4].

Methods

The study was conducted in the outpatient and inpatient sections of the Department of Paediatrics in Pushpagiri Medical College, Tiruvalla. The department attends to around 80-100 out patients daily and has an inpatient capacity of 60 patients in Paediatrics. The study period was six months from June 2009 to November 2009. The diagnosis of hand foot and mouth syndrome was made clinically by the presence of the typical skin rash and enanthem. Around 250 children with hand foot and mouth syndrome attended the OP during this period, out of which 20 required to be admitted. The major clinical presentations were noted and were compared with the presentations previously reported.

Virological studies were not performed because of lack availability of the required tests.

Observations and results

Though the majority of children with this syndrome attended the OP were in the age range of one to five years, infants predominated among those requiring hospitalization. The most common presentation was with skin lesions, but some presented with other complaints like drooling, sore throat, fever and irritability one or two days prior to the onset of the typical skin rash. In some children the illness was mistaken as chicken pox or pyoderma by the parents. The average duration of illness was less than a week. Though more than half of children, especially infants had ulcers in soft palate, feeding was seriously affected only in three babies, who required IV fluids for less than 24 hours. Due to the incessant cry, one was investigated for intussusception by USG abdomen and another for meningitis (including lumbar puncture) on the day of admission. Unlike the usual description of lesions on the anterior aspect of buccal mucosa and tongue in this syndrome, all children examined by us had lesions in soft palate (Fig. 1) without involvement of anterior part of mouth. Skin lesions were typical with small vesicles distributed on the soles

of feet (Fig. 2), extensor aspect of knees (Fig. 3), elbows and hands (Fig. 4). Some had lesions on buttocks (Fig. 5) and perianal region (Fig. 6).

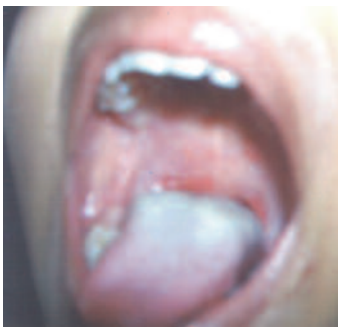

Fig 1: Erythematous lesions on soft palate

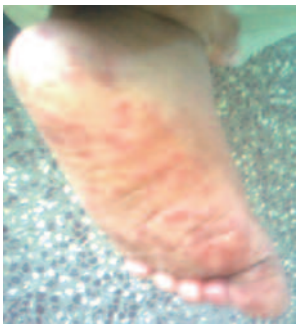

Fig 2: Erythematous papulovesicular lesions on sole

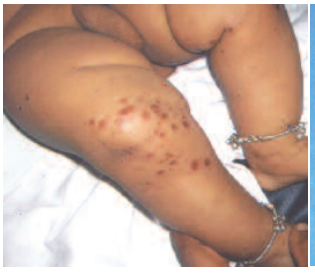

Fig 3: Lesions on extensor aspects of knee

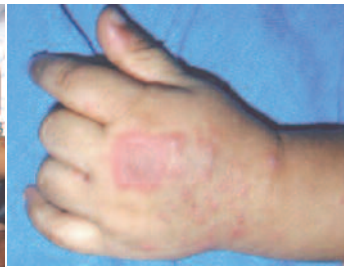

Fig 4: Lesions on extensor aspect of hand

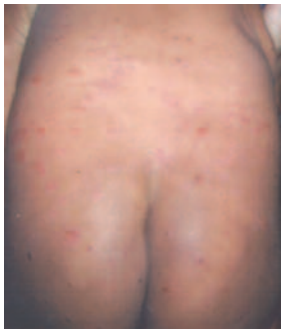

Fig 5: Lesions on buttocks

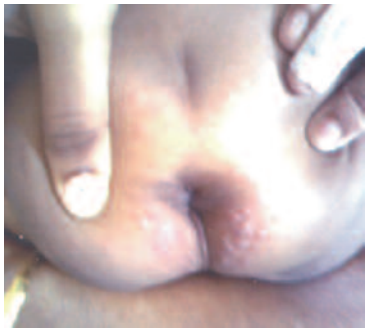

Fig 6: Perianal lesions

The total no. of children with hand foot and mouth disease who required hospitalization was twenty; the indications for admission are shown in Table 1.

Table 1: Inpatients, with the indication for admission

No.	Indication for admission	No. of patients	%
1	Incessant cry	7	35%
2	Febrile seizure	4	20%
3	Poor feeding	3	15%
4	Vomiting	2	10%
5	High fever	2	10%
6	Severe sore throat	1	5%
7	Dysuria	1	5%
Total		**20**	**100%**

Four patients showed exfoliation of nails during convalescence. A recurrence of exactly similar skin lesions after a gap of one to two months was seen in four patients. One child developed varicella one month after HFMS. No case of life threatening illness was noticed in children with this syndrome. The only neurological problem encountered was simple febrile seizures.

Discussion

Hand, foot and mouth syndrome is a common example of enteroviral exanthematous illnesses. The most frequent aetiological agent is Coxsackie A16, but it has also been attributed to Coxsackie A5, A9, A10, B1 and B3 and enterovirus type 71[5]. It is characterized by vesicular lesions in the anterior aspect of mouth and on the hands and feet in association with fever[6].

In the WHO review of enteroviral infections for the four year period from 1967 through 1970, Coxsackie A16 was associated with almost half of all skin and mucous membrane diseases included as hand foot and mouth syndrome[7]. HFMS due to Enterovirus 71 may be associated with neurological complications. Of historical importance is the fact that HFMS was apparently a new clinical entity in 1956[8]. It was noted in sporadic outbreaks till 1963[9] and since then it has been a regularly recurring disease throughout the world. Serological data suggests that Coxsackie A16 was not in wide circulation until 1963. Chronic and recurring skin lesions are described in HFMS due to Coxsackie A16[10]. Evans and Waddlings described an 84 year old woman with chronic, recurring skin lesions of more than two years duration. Nankerns and associates noted both subacute and recurring skin lesions in children[11]. Kaposi's varicelliform eruption has been described in a one year old child with eczema[12]. We also observed recurrence of the lesions in three children with age eight months, one year and one and a half years.

HFMD caused by Coxsackie virus A16 (CV-A16) is usually a mild disease and the patient recovers in five to seven days time without any complication[2]. Rarely is HFMD severe, leading to meningitis, encephalitis, a poliomyelitis-like paralysis and even death[2].

Several deaths occurred due to a severe outbreak of HFMD due to Enterovirus 71 (Ev71) in Malaysia[2], Taiwan[3] and Singapore[4]. Although major outbreaks have been reported from Asian countries, not many cases are reported from India. Sasidharan *et al.* reported 81 cases of HFMD from Calicut, seen between October 2003 and February 2004[13]. Although this outbreak was caused by EV 71, it was a mild illness without any complication or mortality. Coxackie virus A16 was isolated from one of the four children reported with HFMD from Nagpur[14], Central India, seen between September 2005 and April 2006 which indicates that the outbreak in Nagpur is not related to the outbreak reported from Kerala (due to EV71), and there may be different serotypes prevalent in the country.

There are various subtypes of EV 71 and only some of the subtypes such as B4 and C2 are associated with severe disease, whereas subtype B3 is associated with mild disease[2]. Genetic recombination is known to occur between various subtypes producing new subtypes with differing pathogenic potentials[2].

Conclusion

According to the present study, hand foot and mouth disease remains a benign disease so far in our state. The only major complication was febrile seizures. This is in keeping with other reports from the state and our country[13,14]. The trend may change in future as happens in many viral illnesses. Usually only one type of enterovirus multiplies within the intestine of an individual at any particular time. Polio vaccination eliminates polio viruses from the gut, thereby increasing the chances of Coxsackie viral and Echoviral infections[15]. A benign illness can become a deadly disease because of genetic recombination of viruses. This makes it all the more important to take up virological studies more widely in our country and medical professionals be aware of the emerging and re-emerging viral illnesses.

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✪ REVIEW ARTICLE

Tissue engineering: Basic concepts and Opportunities in burn and wound management

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Abstract

Burn injuries constitute a major health problem in the developing world resulting in high mortality and morbidity, when compared to its incidence in the western world. In the developed countries, increased life expectancy and high affluence have increased the incidence of chronic wounds and ulcers associated with aging and diabetes. Tissue engineered skin and artificial skin substitutes have attracted ample attention from researchers and clinicians alike, in the management of burns and chronic wounds. This article reviews the basic concepts of tissue engineering, specially focusing on its applications in burn and wound management.

Introduction to Tissue Engineering

Man, in the course of history, has utilized many types of materials to aid in the recovery of diseases and to improve the quality of life in various disabilities. Initially, he relied mainly on many external aids, but with the advancement of science he became more confident in using materials inside the body. This was made possible with a better understanding of human physiology and the immune system, helping him to design medical devices that elicited minimal immune reaction in the body. Thus, presently we see among our midst, the use of the most humble walking stick to the highly advanced intraocular implants and high-strength titanium-made knee and hip joint replacements. Undoubtedly, scientific research and the use of many biomaterials have significantly improved the quality of human life.

One of the major conceptual advancements in the field of biomaterials and bioengineering is the development of 'Tissue Engineering'[1]. Tissue engineering essentially involves the **repair**, **replacement** and **regeneration** of the damaged tissues to make a normally functional one. It involves **three major components**; the **cells**, the **scaffolds** and **signaling systems for tissue formation**[2]. It is the creation of new tissue for the therapeutic reconstruction of the human body, by the deliberate and controlled stimulation of the selected target cells, through a systematic combination of the molecular and mechanical signals[3]. The long term ambition of tissue engineers is to develop tissue constructs that can help patients with diseases like organ failure, to regain true functionality, and significantly improve the quality of life. ***Research in tissue engineering*** is justified by the fact that there is a shortage of donor tissues and organs worldwide, which is worsened by the increase in the ageing population[4].

Summing up, the pioneering work of scientists like Robert Langer and Mina Bissell have given birth to the truly interdisciplinary field of 'Tissue Engineering' where the expectations and challenges are very high[5,6]. On the brighter side, it has bought together the best minds from varied fields like biomaterials, cell biology, bioprocess engineering and even computer simulation to work for the common goal of healing the body in grave diseases like organ failure, where presently we have few treatment modalities to offer.

Role of scaffolds in Tissue engineering

The three major components of tissue engineering as mentioned earlier are the cells, the scaffold which act as an artificial extra cellular matrix (ECM) to support cell growth, and

specific signaling pathways like hormones and growth factors to maintain proper differentiation of cells (Fig. 1).

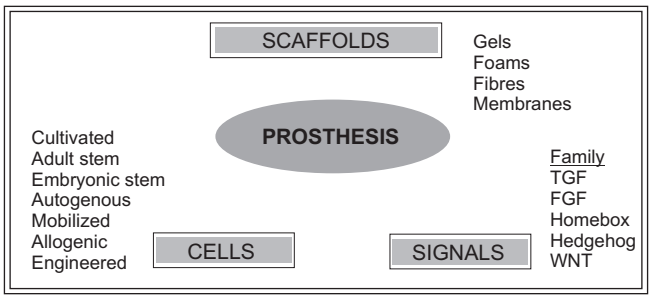

Fig 1: Tissue Engineering Triad
(Metcalfe AD and Ferguson MW, 2005)

Initially, the natural ECM of the body was thought to function mainly as a passive scaffold, but research revealed that it is made of dynamic substances which help defining cellular behaviour and tissue function[7].

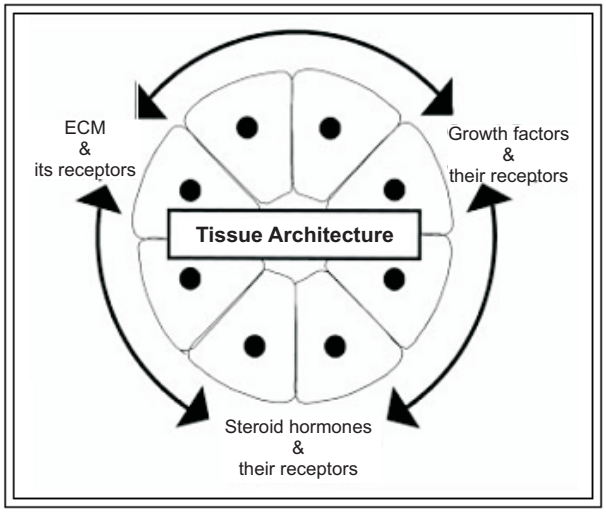

Fig 2: ECM-Cell interactions (Bissell MJ, 1982)

The extracellular matrix provides mechanical and biochemical cues to the cells in the tissue microenvironment that determines the pattern of gene expression of the cells (Fig. 2). Tissue specific differentiation is a dynamic process involving both the cell and its environment[8,9]. ECM is a major component of the tissue environment and is composed of *collagen, glycoprotein, proteoglycans and glycosaminoglycans*, that are secreted and assembled locally into an organized network to which cells adhere[10].

In tissue engineering, the scaffold plays the role of natural extracellular matrix. The tissue engineer's goal is to mimic the close relationship between the cells and the scaffold in a controlled environment, so as to induce *three dimensional tissue growth*. Central to this approach is the design of appropriate scaffolds with natural or synthetic biomaterials, that can support three dimensional growth of cells[11]. Scaffold has multiple functions analogous to that provided by ECM of the target tissue in the native state. It provides structural support for cell growth, rigidity and stiffness to the engineered tissue and facilitates interactions between the cells for proliferation and differentiation. Apart from this, scaffolds serve as delivery vehicles for growth factors and provide void space for new tissue formation during remodeling.

Bioengineers have tried formulating scaffolds for cell growth from a wide variety of materials. ***Natural materials like collagen*** have been widely used to formulate scaffolds, because the cells have the inherent tendency to attach and proliferate in collagen. But, it has disadvantages like lack of strength and lack of mouldability into structures of desired shape and size. This has led to the use of synthetic materials to design scaffolds[12]. The ***Synthetic biomaterials*** are easily processable into three dimensional structures and have suitable properties like the desired rate of biodegradability. These materials are also more amenable to surface modification and surface mobilization of various factors which are important in tissue engineering applications.

Usually, the scaffolds are made from biodegradable and biocompatible polymers, and after providing an initial support system for cell growth, they undergo slow degradation to give way to organized tissue growth[13]. The most widely evaluated biodegradable polymers for formulating scaffolds for tissue engineering applications are **poly DL-lactic acid (PLA), poly glycolic acid (PGA)** and **poly lactide-co-glycolide (PLGA) polymers**[14]. These polymers are approved for human use and are in clinical use as sutures[15,16]. They can be easily processed into three dimensional matrices and has been shown to support cell growth[17]. Many processing techniques have been developed to design scaffolds using biodegradable polymers. Commonly used techniques are *fibre bonding[18], solvent casting and particulate leaching[19], gas foaming[20], emulsion/ freeze drying[21] and phase separation[22]*. Modern engineering techniques like *rapid prototyping* and *photolithography* are increasingly being used to fabricate tissue engineering scaffolds with well defined shape and precise structural features[23,24].

Tissue engineering scaffolds are being made which not only provide structural support for cell growth, but also release drugs and growth factors in a controlled way to the tissue micro environment[25]. The ideal scaffold fabrication method must be easily available, providing structural strength and desired topology, should have the ability to incorporate biomolecules, and release them in a controlled manner (Fig. 3). Scaffolds which mimic the extracellular matrix in terms of the microenvironment, cellular adhesions and signals to promote cell growth and differentiation are preferred to build tissue constructs[26]. Using biomaterial based scaffolds, various tissue engineered products for skin, bone, cartilage and for many other organs are at different stages of clinical evaluation[27].

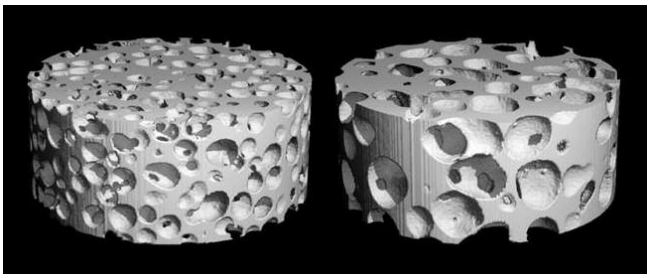

Fig 3: Typical porous polymer scaffolds (Freed *et al*. 1994)

Most commonly used biodegradable polymer, as mentioned earlier, are poly lactic acid and poly lactic-co-glycolic acid (PLA and PLGA)[28]. Other polymers accepted for use as medical devices include poly (dioxanone), poly (trimethylene carbonate) copolymers, and polycaprolactone[29]. In addition to these approved polymers, work on new polymers for medical and implantable devices is continuing[30,31]. It has been shown that scaffolds made from simple biomaterials with optimized mechanical and structural features and seeded with appropriate cellular components can support a high level of tissue organization[32,33]. The ability to mould the scaffolds according to the required application is also sometimes required. For example, bone tissue engineering typically requires a *cube or disc shaped scaffold*[34], while nerve, vascular and trachea tissue engineering usually require *tube-shaped scaffolds*[35]. Skin, intestines and liver tissue engineering generally requires scaffolds in the form of a *flat matrix*[36]. Scaffolds are also available in the form of *injectable gels*, which can also be used to fill irregularly shaped defects[37].

PLA and PLGA polymers continue to be most popular in fulfilling these functions of a scaffold, due to their excellent biocompatibility with a safe history of use in the clinics, and can be processed to scaffolds of desired shape[38,39]. Morgan et al used *hollow fibers* made from PLGA for the expansion of human bone marrow stromal cells for use in *skeletal tissue engineering*[40]. In certain cases PLGA scaffolds were made bioactive by *incorporation of microspheres* in the scaffold that can release factors for bone tissue engineering[41]. Another example of a PLA/ PLGA based bioactive scaffold for tissue engineering was the use of PLA porous scaffold with surface immobilized collagen and basic fibroblast growth factor for *cartilage tissue engineering*[42]. Composites of PLA have also been used to fabricate scaffolds to improve the structural and biological properties of the scaffold. Guarino et al used PLA fiber reinforced polycaprolactone scaffolds for *bone tissue engineering*[43] and films prepared by solvent casting blends of poly (L-lactide-co-D,L-lactide) (70/30) and poly(hydroxybutyric acid-co-3-hydroxyvaleric acid) has been seeded with human keratocytes or retinal pigment epithelial cells to create a *corneal equivalent*[44].

Many of these specifically designed scaffolds are under evaluation for growing specific cell types. Examples include *cartilage models* made from chondrocytes and PLA scaffold,[45] *intestinal tubes* made from enterocytes and PLGA scaffold,[46] *vascular grafts* made from endothelial cells expanded on polytetrafluoroethylene[47] and *liver tissue constructs* from hepatocytes and polyvinyl alcohol scaffolds[48]. Few of the tissue engineered products which are already available in the market include '*Dermagraft'* (cryopreserved human fibroblasts on a polyglactin 910 mesh) for treatment of diabetic foot ulcers, *INFUSE Bone graft, Medtronic* (Bovine type 1 collagen sponges soaked in rhBMP-2) for use in cases of spinal fusion, and *CaReS, Arthro Kinetics* (rat tail type 1 collagen matrix seeded with chondrocytes) for repair of articular cartilage injury[49].

Tissue engineered Skin for Burn and Wound management

Human skin is a highly specialized organ which carries out many important functions necessary for maintaining the homeostasis of the body. Skin is comprised of several cell types, of which *keratinocytes* are the most common cell type in the epidermis and form the surface barrier layer. *Melanocytes* are found in the lower layers of epidermis and provide skin colour. The fibroblast cells in the dermis provide strength and resilience to the skin. Burn injuries resulting in damage to large areas of skin can lead to severe disability and death. The burden of burn cases and injuries is huge in India and other developing countries[50]. The changing socio-economic scenario has led to increased incidence of burn related injuries in industrial units and homes, and is fast reaching epidemic proportions.

Tissue engineered skin has emerged as a potential treatment for burns and chronic wounds supplementing the existing current therapies[51]. Impaired healing due to infection and inflammation and excessive scarring are grave problems faced by burn patients. The major goals of burn wound management are preventing wound infections, promoting rapid wound closure and minimal scarring[52]. In burn wound management, early tangential excision and skin graft is still considered the gold standard[53]. **Autologous skin grafts,** however, have limited availability, and the feasibility depends on the available area of normal skin the patient has. Also, skin grafting creates additional donor site wounds equivalent to second degree burns, thus increasing the total body surface area affected[54].

As an alternative and to augment existing approaches of burn management, **artificial skin substitutes and tissue engineered skin** have been widely explored. Available skin substitutes can act as temporary wound cover or permanent skin replacements depending upon their design. Naturally available wound covers which are commonly used are **amnion, cadaveric skin** and **xenografts**. The skin substitutes can be epidermal replacements, dermal replacements or composite replacements.

In case of epidermal reconstruction, use of **cultured epithelial autografts** (CEA) can be life saving in cases with massive full thickness burns[55,56]. The advantage of CEA is the large surface area obtained from a relative small biopsy of healthy skin of the patient; however disadvantages like fragility and high costs exist[57]. *'Laserskin'* is a commercially available CEA, where keratinocytes are cultured on thin hyaluronic membranes with pores and can be directly used for grafting.

Alternatively, many groups are working on the development of alternative systems for the delivery of cultured autologous keratinocytes which can reduce costs and improve the take of the resulting epidermis. These systems include *fibrin glue suspension* (Bioseed-S) and *cultured keratinocytes in suspension* (Cellspray).

In case of dermal reconstruction, **dermal regeneration templates** aim at reconstructing the dermal component of skin. The templates for dermal regeneration can either be **acellular or cellular**. *'Integra'* (Fig. 4) is one of the earliest introduced acellular dermal regeneration templates; it has a bilaminar structure, consisting of cross-linked bovine collagen and glycosaminoglycan, coated on one side with a silicone membrane that provides epidermal function. The collagen layer gradually gets integrated with the wound to form a vascular *'neodermis'* and once this stage has been reached, the silastic layer can be removed and a *thin split skin graft* can be applied[58].

Other similar products include *'Alloderm'* which is basically a cadaveric graft, chemically treated to remove epidermal cellular components and *'Biobrane'*, which consists of a synthetic membrane bound to one surface of a nylon mesh and coated with porcine collagen.

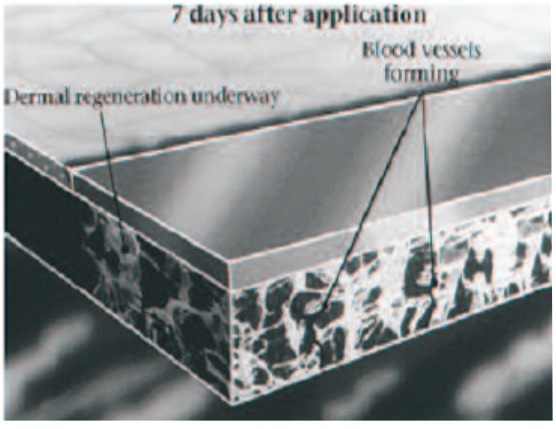

Fig. 4: 'Integra' artificial skin substitute

Collagen is the most widely used biomaterial for bioengineering of skin substitutes[59]. Novel skin substitutes based on different biomaterials other than collagen are being developed; examples include **keratin based sponge, PLGA/ chitosan hybrid membrane** and **alginate based materials**[60,61].

Another example of a polymer based **acellular template** used for faster wound closure is *Suprathel,* which is a PLA based membrane for burn treatment. Clinical evaluation showed that *Suprathel* reduced pain, was easy to handle and adhered rapidly to the wound thus protecting against infections and promoting wound healing[62].

In case of **cultured dermal constructs,** the template contains autologous cultured fibroblasts which have been shown to enhance the re-epithelialization of wounds when compared to acellular templates[63]. Examples include *'Dermagraft'* which is manufactured by cultivating neonatal allogenic fibroblasts on a polymer scaffold and *'Transcyte'* which consists of neonatal fibroblasts grown in a nylon matrix.

Composite constructs have both epidermal and dermal components and living bi-layered skin construct consisting of human neonatal keratinocytes and fibroblasts in a collagen matrix and have been tested in a wide variety of wounds[64-66]. A commercially available product is *'Epicell'* which consists of autologous keratinocytes and fibroblasts cultured separately and then combined on a collagen-glycosaminoglycan matrix[67].

Artificial skin substitutes need to comply with three major requirements before they can enter clinics, namely they should be (a) safe for the patient, (b) clinically effective and (c) convenient in handling and application[68]. Polymer based acellular skin substitutes are suited to be used widely since they are *cost effective, user friendly and possesses a long shelf life*.

The membrane should have certain properties like being non-toxic when absorbed, and cause minimal immunological reaction. It should prevent fluid loss from wound surface and protect the wound from infection[69]. 'Integra', one of the first acellular regeneration templates to be introduced in the wound market has now been widely adopted for the treatment of full thickness burns[70]. The matrix of the graft becomes populated with fibroblasts from the wound, and contributes towards neo-dermis formation; at the same time the scaffold degrades in a controlled way. The silicone layer protects the wound from fluid loss and bacterial infection.

Conclusion

Burn injuries continue to be associated with high mortality rate and most of these patients are in the rural and semi-urban areas having little access to proper burn care. Autologous skin graft is still the treatment of choice for these patients but many a times this is not sufficient to manage cases with large burn areas. In these patients, **artificial skin substitutes** consisting of skin regeneration templates or human skin equivalents can tip the scale in favour of the patients.

Unfortunately, they are yet to be widely available mainly due to the high cost. Cadaveric skin banks are being set up at many centres in our country, and a few specialized burn centers do offer skin substitutes. But this is hardly sufficient, given the gravity of problem of burns in India and other developing countries. In such a situation, it is imperative that effective and affordable artificial skin substitutes are developed for the management of burn and other severe wounds. In this regard, **acellular artificial skin substitutes** are more suited for wider use for burn and wound cover due to their relatively lesser cost compared to their cellular counterparts, ease of handling and storage, and the benefits for wound healing offered by the skin regeneration template. *'Integra'* was one of the first acellular artificial skin substitutes to be developed and widely used in US, with very good results in burn patients. To successfully develop such a product in our country, a thorough understanding of the basic principles of tissue engineering, especially regarding the nature of interaction between the cells and the scaffold is essential.

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✪ REVIEW ARTICLE

Exposure to Formaldehyde in the Medical field and a review of its toxic effects

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Abstract

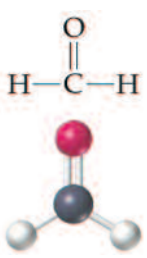
Several European countries have restricted the use of formaldehyde, including the import of formaldehyde-treated products and embalming. In spite of its regular widespread use in the medical and industrial fields and the awareness of its toxic effects, like atopic dermatitis, respiratory problems, neurotoxic, genotoxic and carcinogenic activity, no genuine effort has yet been made in India for conducting a systematic study on the matter and to bring them to light. Further studies are necessary to develop useful methods of assessment of personal exposure, outdoor and indoor formalin concentrations, mechanism of toxic effects and to put forward preventive and corrective measures.

Introduction

Formaldehyde is a recognized pollutant in Anatomy and Pathology laboratories[1]. Significant exposure is present, and irritant and toxic effects have been reported from the department of Forensic Medicine, the surgical theatres, and the museums attached to almost all academic departments in the Medical Colleges. Teaching faculty, medical students, laboratory technicians and attendants are exposed to significantly higher levels of formaldehyde, many a time amounting to toxic levels. Toxicity of formaldehyde is a significant consideration for human health in view of its widespread use, toxicity and volatility[2]. Since September 2007, the European Union has banned the use of formaldehyde due to its carcinogenic properties (under Biocidal Products Directive (98/8/EC)[3,4]. An effort has been made in this review article to focus on this problem in the medical field.

Chemistry of formaldehyde

Formaldehyde is an organic compound with the formula CH_2O. It is the simplest of all aldehyde, with the systematic name ***"methanal"***.



A colourless gas at normal room temperature, it has a characteristic pungent odour. It is an important precursor to many other chemical compounds, especially polymers. It combines with water to form methanediol or methylene glycol $H_2C(OH)_2$, and the aqueous solution containing about 40% formaldehyde by volume or 37% by mass, is called *'100% formalin'*. Commercial grade formalin contains 10% to 12% of methanol (added as a stabilizer to limit oxidation and polymerization) in addition to the various metallic impurities. Formaldehyde does not accumulate at all normally in the environment, as it breaks down within a few hours by the action of sunlight or bacteria (in soil or water). Humans metabolize formaldehyde quickly; so it does not accumulate, but gets converted to formic acid.

Uses of Formaldehyde

I. Medical applications

- *Disinfectant and biocide*

An aqueous solution of formaldehyde is useful as a disinfectant as it kills most bacteria and fungi, (including most fungal spores). Formaldehyde solutions are applied topically to dry the skin, as in the treatment of warts. It is used to inactivate unwanted bacterial products

in toxoid vaccines, and to kill unwanted viruses and bacteria that might contaminate the live vaccines[5].

Urinary infections could be treated using methenamine, a derivative of formaldehyde. This method is often chosen because it prevents overuse of antibiotics and the development of bacterial resistance. Some topical creams, cosmetics and personal hygiene products also contain derivatives of formaldehyde as their active ingredient. This is intended to prevent the growth of potentially harmful bacteria within these products, and their person-to-person transmission by sharing of these products. It is regularly used as a fumigant[6] in surgical theatres and intensive care units. For decades, formaldehyde has been applied in consumer goods[7] with the primary function of ceasing spoilage by microbial contamination.

- *Tissue fixative, denaturing and embalming agent*

In the Department of Anatomy formaldehyde based solutions are used in embalming to disinfect and temporarily preserve human bodies. The ability of formaldehyde to fix the tissue produces firmness of flesh in the embalmed body. Pathology department uses formalin as a fixative for immune-histochemistry and histopathology. The specimens collected during surgery for macroscopic and microscopic study and tissue organ samples removed during post-mortem examination in the department of Forensic Medicine are routinely fixed in formaldehyde. The percentage of formaldehyde used may vary based on the method of analysis. So also preservation of specimens in the museum requires formalin.

- *Applications in molecular studies and research*

Formaldehyde preserves or fixes tissues or cells by reversibly cross-linking primary amino groups in proteins with other nearby nitrogen atoms in protein or DNA through a - CH_2 - linkage. This is exploited in Chip-on-chip transcriptomics experiments. Formaldehyde is also used as the denaturing agent in RNA gel electrophoresis, preventing RNA from joining together to form secondary structures.

II. Industrial and miscellaneous applications

In food industry, formaldehyde is used as an antibacterial agent and preservative in processing of foodstuffs[8] including seafoods. It is widely used in food processing for its bleaching effect and also to prevent spoilage by microbial contamination.

Formaldehyde is used in the synthesis of resins, urea-formaldehyde[9], phenolic-formaldehyde, penta-erythritol and other resins[10,11]. Its use is related also to fertilizer production, in many fields of industry like wood fixatives, dry cleaning solutions, solvents, boilers, chemical productions, oil, gas and petroleum production, paper and pulp production, cosmetics[12], and food and textile industries[8,13].

Studies on formaldehyde

The studies and research on the health aspects of formaldehyde have been discussed in this review under the following sub-sections:

A. Safety levels of formaldehyde

Formaldehyde concentration in humans prior to any exposure to external source has been found to be approximately 2 μg g^{-1} of venous blood[14]. It is produced during the normal metabolism of amino acids serine, glycine, methionine and choline. It enters the dehydrogenase metabolic pathway and is eliminated as formate in urine, or as CO_2 in expired air[15].

The Reference Dose (RfD) for formaldehyde is 0.2 mg/kg/day. It is an estimate of a daily oral exposure, likely to be without appreciable risk of deleterious non-cancer effects. It is rather a reference point to gauge the potential toxic effects. The Agency for Toxic Substances and Disease Registry (ATSDR) has established a chronic inhalation minimal risk level (MRL) of 0.003 ppm (0.004 mg/m^3) based on respiratory effects. It is an estimate of the daily exposure likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure[16].

Several regulatory agencies recommend an occupational exposure limit (OEL) for formaldehyde. In USA, an Industrial Health Foundation panel concluded that generally, eye irritation occurs only if levels reach at least 1.0 ppm. Severe eye, nose, and throat irritation occurs only if airborne concentration exceeds 2.0-3.0 ppm. The data indicated that below 1.0 ppm, any irritation that occurs would rapidly subside by getting accustomed. It was noted that at a concentration 0.5 ppm [eight-hour time-weighted average (TWA)] eye irritation was not observed in 80% of industrial workers. Consequently, the panel recommended an OEL of 0.3 ppm as an 8-h TWA with a ceiling value (CV) of 1.0 ppm[17].

The Formaldehyde Standards for Composite Wood Products Act[18] was signed in to law by President Obama on July 7th, 2010. This bill set US nationwide emission standards, to limit formaldehyde release.

B. Environmental and Industrial pollution studies

- ***Acute toxic effects***

The most frequent immediate toxic effects of acute exposure include irritation and watering of the eyes, and inhalation producing nose and throat irritation. In individuals prone to developing toxicity, exposure to high levels of formaldehyde cause laryngitis, asthmatic attacks, chest pain, and bronchitis[19,20]. Ingestion exposure may cause inflammation and ulceration of oral mucosa, oesophagus, and stomach[19,20].

- ***Carcinogenic effects***

In 1991, the U.S. Environmental Protection Agency (EPA) classified formaldehyde as a B1 "probable" carcinogen[19]. This means that epidemiologic studies provide sufficient evidence of animal carcinogenicity, but limited evidence of human carcinogenicity. Occupational studies have noted statistically significant associations with incidence of lung and nasopharyngeal cancer. The evidence is considered "limited," rather than "sufficient," due to possible exposure to other agents that might have contributed to the higher incidence[20,21]. However, formaldehyde was reclassified as a human carcinogen (Group 1) by the International Agency for Research on Cancer (IARC) in June 2004 based on 'sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans[22,23].

The final Report[24] on Carcinogens Background Document for Formaldehyde, as submitted by the National Toxicology Program, 2010, stated that among cohort studies, a statistically significant increase in mortality from nasopharyngeal cancer was observed in the large NCI cohort (SMR = 2.10, 95% CI = 1.05 to 4.21, 8 deaths) (Hauptmann *et al*. 2004)[25], and statistically non-significant elevated risks were observed among white embalmers from the United States (PMR = 1.89, 95% CI = 0.39 to 5.48, 3 deaths) (Hayes *et al.* 1990)[26].

Some authors have questioned the biological plausibility of its association to leukemia, because it is rapidly metabolized, and is not expected to enter the systemic circulation (Cole and Axten 2004,[27] Golden *et al.* 2006,[28] Heck and Casanova 2004,[29] Pyatt *et al*. 2008[30]). They stated that formaldehyde does not cause bone marrow toxicity or pancytopenia, which are common features of known leukemogens, and that the genotoxic and carcinogenic effects in animals and humans are limited to local effects.

Formaldehyde is reportedly genotoxic[31] in vitro, as seen in cultured mammalian cells. The biological mechanisms associated with formaldehyde-induced cancer are not completely understood, but chemicals are known to act through varied mechanisms to induce cancers (Guyton et al. 2009)[32]. Reports of adducts in leukocytes of smokers (Wang *et al*. 2009)[33], albumin adducts in medical research workers (Pala *et al*. 2008)[34], DNA-protein crosslinks measured in peripheral blood cells of hospital workers (Shaham *et al*. 2003)[35], and the hematologic changes measured by Zhang *et al.* 2010[36] suggest that it might enter systemic circulation. Epidemiological studies of occupational exposure of FA are associated with elevated risks for cancers at various sites, including the brain (Coggon *et al*. 2003[37]; Hayes *et al.* 1990[27], nasal cavities (Blair et al. 1990[38]; Coggon *et al.* 2003[37]), lung (Coggon et al. 2003[37]; Gardner et al. 1993[39]), pancreas (Stone *et al*. 2001[40]), and lymphohematopoietic system (Hauptmann et al. 2003[26]; Pinkerton *et al*. 2004[41]).

Hauptmann M *et al.*[26] studied the mortality from lymphohematopoietic malignancies and brain cancer among embalmers. Duration of embalming and formaldehyde exposures in the funeral industry were associated with statistically significantly increased risk for mortality from myeloid leukemia.

Bosetti *et al*.[22] in a comprehensive review of cancer in industry workers and professionals observe no appreciable excess risk for oral, pharyngeal, sinonasal or lung cancers. For brain cancer and lymphohaematopoietic neoplasms they report modestly elevated risks. Duhayon *et al*.[23] observe that human studies fail to raise a convincing conclusion concerning the carcinogenicity, and don't delineate a possible dose-response relationship.

In genotoxicity studies, formaldehyde is considered to be a weak genetic toxicant[42]. Studies of genetic effects in buccal/nasal mucosal cells[43,44] and peripheral lymphocytes[45] have proven positive, but in some studies such effects were not observed[42]. An increased incidence of micronucleated buccal or nasal mucosal cells has been reported in some surveys[43,44]. Evidence of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes has been reported[46,47]. Formaldehyde is genotoxic *in vitro* in cultured mammalian cells. When it reaches nuclear DNA, it forms DNA-protein cross-links (DPX); incomplete repair of this DPX can lead to the formation of mutations, in particular chromosome mutations and micronuclei (MN) in proliferating cells. Speit *et al*. suggested that it leads primarily to local genotoxic effects at the site of contact due to its high reactivity[48]. A study by KunLu, 2010[49] provides strong evidence supporting genotoxic/ cytotoxic mode of action for the carcinogenesis in nasal epithelium but does not favour the suggestion that it causes leukemia.

Klein-Szanto *et al.*[50] studied formaldehyde-induced lesions of xenotransplanted human nasal respiratory epithelium. Histological examination along with autoradiographies revealed that it causes involutional changes like erosion and atrophic epithelium, and proliferative reactions like hyperplastic-metaplastic lesions. These epithelial changes had higher labeling index in some focal areas, and reached values 10 to 20 times higher than normal, proving it to be an effective carcinogen.

- ***Respiratory toxicity, Asthma and Allergy***

Chronic exposure to formaldehyde by inhalation in humans has been associated with chronic respiratory symptoms and asthmatic bronchitis[12,13,19,20]. Akbar-Khanzadeh F *et al.*[51] studied the changes in the respiratory function following exposure to formaldehyde. The increase in respiratory function of the exposed subjects was significantly less than that of the control subjects. There was no significant correlation between concentration of formaldehyde in the breathing zone and changes in the respiratory function of exposed subjects.

The exposure was correlated to asthma among young children in a population-based control study by Rumchev KB, *et al.*[52], which suggested that domestic exposure to formaldehyde levels of > or = 60 μg/m^3 are at increased risk of having bronchial asthma. Ezratty V *et al.*[53] conducted a study to investigate whether exposure to a low level of formaldehyde enhances inhaled allergen responses. They found that exposure to 500 μg/m^3 formaldehyde had no significant deleterious effect on airway allergen responsiveness of patients with intermittent asthma; they found a trend towards a protective effect.

McGwin *et al*[54] in 2009 reported the results of a systematic review of published literature in order to provide a more comprehensive picture of this relationship. They found that a significant positive association exists between formaldehyde exposure and childhood asthma. However, given the largely cross-sectional nature of the studies underlying the meta-analysis, they suggested that further well-designed prospective epidemiologic studies are needed.

- ***Neurotoxicity***

According to Maria C Mirabelli *et al*.[58] prolonged exposure has been associated with mild neurological symptoms, including headaches and dizziness, and genetic damage. Songur A *et al*. (2010)[59] studied the toxic effects of formaldehyde on the nervous system and have indicated that formaldehyde has neurotoxic and systemic toxic effects. It is also suggested that inhalation during early postnatal period is linked to some neurological diseases that occur in adults. In a study on its neurotoxicity, formalin was observed by Bas O *et al.*[60] to affect the cerebral oxidant/ antioxidant systems and cause oxidative damage.

Although reactive oxygen species (ROS*)* are essential for many biological processes, their excessive production and accumulation could become hazardous to cells and tissues (Bas *et al.* 2007[60]; Gurel *et al*. 2005[61]; Sarsilmaz *et al*. 2003[62]; Tian *et al.* 2005[63]). Kilburl KH *et al*. in 1994[64] studied the neurobehavioral impairment and seizures resulting from formaldehyde. Its extensive use at work, or repeated airborne exposure appears to lead to impaired central nervous system function, reports the study.

- ***Exposure during pregnancy, and effect on menstruation***

Dueva LA, *et al.*[65] in 2004 evaluated the immunologic criteria for health changes caused by chemicals that cause pollution of environment leading to problems in infants and pregnant women. The authors revealed relationship between pregnancy disorders and changed humoral immunity parameters, including the production of anti-hapten antibodies to chemical pollutants (formaldehyde, nickel and lead).

Collins JJ, *et al.* in 2001[66] made a review of adverse pregnancy outcomes and formaldehyde exposure. They found evidence of reporting biases and publication biases, ignoring which they found no evidence of increased risk of spontaneous abortion (meta-relative RISK=0.7, 95% CI 0.5–1.0). The small number of studies on birth defects, low birth weight, and infertility among formaldehyde workers seemed to increase the risk of spontaneous abortion among workers exposed to formaldehyde (meta-relative RISK=0.7, 95% CI 0.5-1.0).

Dorairajan G in 2010[67] reported the incidence of a case from the Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India, of a pregnant woman exposed to high doses of formaldehyde through inhalational route in the second trimester. Later she was found to have severe oligohydramnios with dysplastic foetal kidneys and ascites. The author concludes that this can be due to transplacental nephrotoxic effect of formaldehyde.

An increased incidence of menstrual disorders was observed in female workers using urea-formaldehyde resins. However, possible confounding factors were not evaluated in this study[19,20]. A study of hospital equipment sterilizing workers did not report an association between formaldehyde exposure and increased spontaneous abortions[19,20].

C. Studies conducted in the Medical field

Tanaka K *et al*.[68] observed that the evaporation of formaldehyde from cadavers can produce high exposures among students and instructors. Japan Ministry of Education, Culture, Sports, Science and Technology (MEXT) set a guideline to reduce formaldehyde in dissection laboratories and a guide to medical students about its toxicity and protective measures. They measured gaseous formaldehyde concentrations and analyzed the related symptoms, and use of protective measures. Immediately after exposing the cadaver, formaldehyde concentrations in the dissection room increased sharply to reach a peak point of 0.62 ppm after 10 minutes of starting class (0.5 ppm set by Japan Society for Occupational Health). After 30 minutes, level started decreasing gradually to 0.11 ppm. Toxic symptoms were observed in 59% of students. Although guidelines about the toxicity of formaldehyde and its protective measures were informed, only 52% used them without fail.

In another study, Maria C Mirabelli *et al.*[58] observed that the risk of inhalation exposure is particularly high due to the close proximity of embalmed tissue to the students/ instructors. They found that despite the known toxicity of formaldehyde and its potential health effects, Anatomists and others have shown little enthusiasm for reducing or replacing the cadaver dissection experience; measures have to be taken to increase the use of personal protective equipment (PPE), improve laboratory ventilation and exhaust air circulation.

Airborne concentrations of this chemical were measured by L Vimercati *et al.*[1] using High Performance Liquid Chromatography (HPLC). The data obtained exceeded the National Institute for Occupational Safety and Health Threshold Limit Value-Time Weighted Average (NIOSH TLV-TWA:0.02 mg/m^3) and, in a few cases, even the American Conference of Industrial Hygienists Threshold Limit Value-Ceiling level (ACGIH TLV-C: 0.37 mg/m^3).

A group of 34 workers in a gross anatomy were evaluated by Akbar-Khanzadeh F *et al.*[69] who noted that the TWA exposure to formaldehyde ranged from 0.07-2.94 ppm. More than 94% were exposed to formaldehyde in excess of the ceiling value of 0.3 ppm. The eight-hour TWA exposure of 31.7% of the subjects exceeded the action level of 0.5 ppm set by the Occupational Safety and Health Administration (OSHA). The results strongly support the necessity for designing and testing special local exhaust-ventilated worktables.

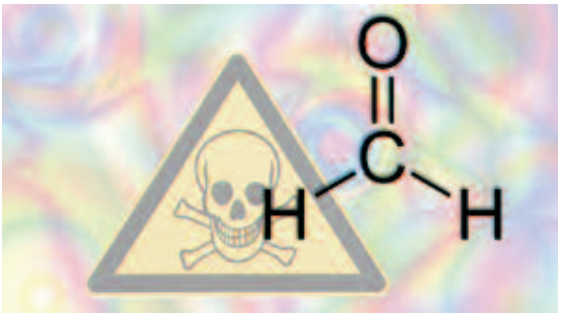
In a study by Chia SE, *et al*. in 1992[70], the students' exposure to formaldehyde in a gross anatomy laboratory was 0.50 ppm and the personal sample was 0.74 ppm. The concentration of formaldehyde was determined in three different places of the department in the Dalian Medical University, China, for nearly one hundred times[71]. The result showed that highest concentration was 1703 mg/m^3 in laboratory, and exceed ten times the permissible levels.

A review artcle by Songur A *et al*.[59] felt that all anatomists must know and understand the effects of this toxic agent and take precautions to avoid unnecessary exposure. Although complete prevention is impossible precautions should be taken to decrease the toxic effects.

Ohmichi K *et al.*[72] correlated the personal exposure levels and indoor concentrations. Samples were collected from instructors and students and analysis was carried out using HPLC; the levels were higher than the guideline limits. The indoor concentrations varied depending on the contents of laboratory sessions and seemed to increase when body cavity or deep structures were being dissected. Formaldehyde levels at the center of the room were higher than those in the corners, probably due to the doors and windows. The personal exposure levels were 2 to 3-fold higher than mean indoor concentrations.

Conclusion

Most of the information with regard to the toxic side effects of formaldehyde in the available literature has been gathered from the various studies in the fields of environmental and industrial pollution. Much to the disgrace of the medical fraternity, there have been only very few studies on formalin toxicity in the broad scenario of Medical and Surgical practice, and Medical Education. A systematic approach to the current exposure status and toxic symptoms would pave way for further studies and analyses in this field. The authors regret that there are no reports of human studies in the available Indian medical literature, pertaining to this problem.



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PUSHPAGIRI MEDICAL JOURNAL

✪ CASE SERIES ARTICLE

Unusual presentations of Non-Hodgkin lymphoma

Part III: Precursor B lymphoblastic leukaemia/ lymphoma: An unusual presentation

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Abstract

Precursor B lymphoblastic leukaemia/ lymphoma is a neoplasm of lymphoblasts committed to B cell lineage, and may present as leukaemia and/ or lymphoma. Clinically a case is defined as lymphoma if there is a mass lesion and less than 25% blast cells in the bone marrow, and as leukaemia if there are more than 25% blast cells in the marrow with or without a mass lesion. Most cases involve blood and bone marrow (B acute lymphoblastic leukaemia: B-ALL) and a few present with primary nodal/ extranodal tissue deposits (B lymphoblastic lymphoma: B-LBL). There is significant biological and clinical overlap between neoplasms diagnosed as B-ALL and B-LBL. Although some patients present with predominantly lymphomatous involvement, most have or later develop marrow involvement. Similarly patients who present with leukaemia may have or develop extramedullary tumours. Since B-LBL and B-ALL share considerable clinico-pathological and biological properties, they are considered the same disease.

The present report discusses the case of a ten year old boy who presented with pathological fractures at multiple sites. His absolute neutrophil count and platelet count were normal, and no blast cells were seen in the peripheral blood at the time of presentation. Biopsy from the fracture site, followed by further investigations proved him to have precursor B lymphoblastic leukaemia.

Key Words: Precursor cells, B Lymphoblasts, Leukaemia, Lymphoma, Bone marrow, Multiple fractures.

Introduction

Lymphoblastic neoplasms include leukaemias and lymphomas arising from precursor lymphoid cells. Since they share considerable clinico-pathological and biological properties they are considered the same disease by WHO classification system of Non Hodgkin lymphoma. Lymphoblastic lymphomas usually present with mass lesions involving skin, soft tissues, bone and lymph nodes. Generally acute leukaemias present with signs and symptoms of pancytopenia (i.e., anaemia, neutropaenia and thrombocytopenia), like weakness, fatigue, infections, and haemorrhagic manifestations. Occasionally the primary presenting feature is persistent and often multifocal musculoskeletal pain. Skeletal morbidity is increasingly being recognized in ALL. Upto 25% of children have radiographic evidence of osteopaenia, and multiple fractures are observed in 10% of them[1]. Here we describe an unusual presentation of acute lymphoblastic leukaemia in a boy who presented with multiple bone fractures.

Clinical presentation

A ten year old boy who was admitted in the Orthopaedics department of Pushpagiri Medical College Hospital on 28-09-2010 had severe pain on both lower limbs and shoulder region. He gave a history of fall eight months back, following which he had pain both hips and difficulty in walking. The pain was increasing in severity, and he was bed-ridden for two months prior to admission, being unable even to lift his head from the bed. He never had any bleeding manifestations or any history of infections during this period.

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Clinical examination revealed an emaciated bed ridden boy, with pallor and mild hepatomegaly. He had no significant lymphadenopathy or splenomegaly. Both clinical and radiological evaluation revealed pathological fracture neck of right femur, proximal metaphyses of femur and humerus bilaterally, and neck of left humerus (Fig. 1A and 1B). Some ill-defined areas of destruction were noted along the shaft of humerus bilaterally. Radiological study also revealed extensive *moth-eaten* destruction of both pelvic bones (Fig. 2), fractures of bilateral superior pubic rami, fracture neck of right femur and protrusion of acetabular rim.

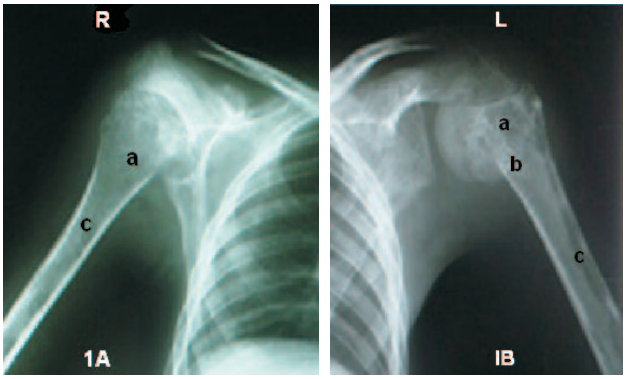

Fig. 1A and 1B: Plain X-ray of shoulder region (Rt and Lt)
a. Moth-eaten destruction of humeral metaphyses
b. Fracture neck of left humerus
c. Ill defined areas of destruction along humeral shaft

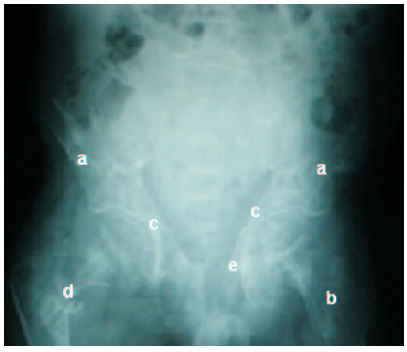

Fig. 2: Plain x-ray of pelvis with extensive moth eaten destruction in
a. Bilateral pelvic bones b. Femoral metaphyses
c. Protrusion of acetabuli d. Right femoral neck (with fracture)
e. Superior pubic rami (with fracture)

Haematological investigations showed a haemoglobin level of 8.3 gm/dl, total WBC count of 6000 cells/cmm, DC: P71, L26, E3 and platelet count 1.8 lakhs/cmm. His ESR was 135 mm in the first hour.

A biopsy was taken from the fracture site of right femur neck. Microscopy of the bony fragments (Fig. 3) showed a neoplasm composed of sheets of small round cells. Individual cells had scanty cytoplasm and nuclei with minimal pleomorphism (Fig. 4) and condensed or slightly dispersed nuclear chromatin with indistinct nucleoli. Occasional mitoses were seen. Correlating with the clinical and radiological findings the possibility of infiltration by a small round cell neoplasm, possibly lymphoma/ leukaemia was considered.

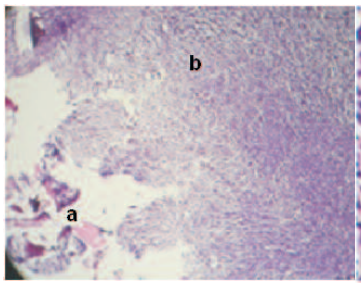

Fig. 3: Microscopy - bone fragment (H and E, 40X).
a. Fragmented bone tissue
b. Sheets of small round cells

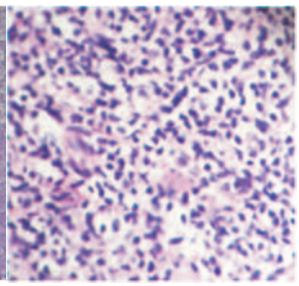

Fig. 4: Round cells have scanty cytoplasm, mildly pleomorphic nuclei (H and E, 400X)

The patient was referred to Regional Cancer Centre, Trivandrum for further evaluation and management, where he was diagnosed to have Precursor B lymphoblastic leukaemia. Immuno-phenotypically the cells were positive for CD19, CD22, CD10, CD34 and HLA DR. With specific treatment he attained bone marrow remission and had started walking with support.

Discussion

According to the WHO classification system for haematological malignancies, the lymphoblastic neoplasms are divided into two general categories based upon their lineage, Precursor B lymphoblastic leukaemia/ lymphoma and Precursor T lymphoblastic leukaemia/ lymphoma. B lymphoblastic leukaemia/ lymphoma is a neoplasm of precursor cells (lymphoblasts) committed to the B cell lineage. They are typically composed of small to medium sized blast cells with scanty cytoplasm, moderately condensed to dispersed chromatin and inconspicuous nucleoli involving the blood and bone marrow and occasionally presenting with primary involvement of nodal or extra nodal sites.

By convention the term B lymphoblastic lymphoma (LBL) is used when the process is confined to a mass lesion with absent or minimal evidence of peripheral blood and bone marrow involvement. With extensive BM and peripheral blood involvement, lymphoblastic leukaemia (B acute lymphoblastic leukaemia/ ALL) is the appropriate term. If a patient presents with a mass lesion and lymphoblasts in the BM, distinction between leukaemia and lymphoma is arbitrary. For many treatment protocols, 25% BM blasts is used as the threshold for defining leukaemia.

Acute lymphoblastic leukaemia is a disease of children; about 75% of cases occur in children under six years of age. The world-wide incidence is estimated to vary between 01 to 4.75 in one lakh persons per year. B-LBL constitutes approximately 10% of all lymphoblastic lymphomas, and the remainder would be of T cell lineage. Approximately 64% of 98 cases reported in a literature review were in children below 18 years age[1,2].

By definition the BM is involved in all cases B-ALL, and peripheral blood is usually involved.

Extramedullary involvement is frequent with particular predilection for the central nervous system, lymph nodes, spleen, liver, and testes . The most frequent sites of involvement of B-LBL are the skin, soft tissue, bone and lymph nodes. Mediastinal masses are infrequent.

Most patients with B-ALL present with evidence and consequences of BM failure: thrombocytopenia and/ or anaemia and/ or neutropenia. The leukocyte count may be decreased, normal or markedly elevated. Lymphadenopathy, hepatomegaly and splenomegaly are frequent. Bone pain and arthralgias may be prominent. Patients with B-LBL without leukaemia are usually asymptomatic and most have limited stage disease. Head and neck presentations are particularly common, especially in children. Marrow and peripheral blood involvement may be present but the percentage of lymphoblasts in the marrow is less than 25%.

Lymphoblastic leukaemias are also reported to have other rare presentations. Anelia *et al.* has reported a case of precursor B lymphoblastic leukaemia presenting as bilateral nephromegaly and non oliguric acute renal failure in a 21 month old child[3].

Farhat *et al.* has reported a case of B lymphoblastic leukaemia/ lymphoma in a 31 year old male who presented with severe eosinophilia (absolute eosinophil count 34,560/cmm), without blast cells in peripheral blood. Clinically he presented with aches and pains all over the body, especially over the temporomandibular joint[4].

According to Neth O *et al.* in a series of 27 cases of precursor B-LBL, 21 had nodal disease, six had subcutaneous manifestations, and eight cases had *BM disease*(< 25% blast cells). The median age of 27 patients with precursor B-LBL was 6.2 years with a range 0.7-15[5].

Few rare sites of primary involvement of precursor B-LBL are also reported. Ren-Ching Wang *et al.* has reported the case of an eleven year old boy with primary appendiceal precursor B-LBL[6]. Abla, Oussama *et al.* report leptomeningeal precursor B-LBL in a six year old boy who presented with head ache, and papilloedema as the only initial manifestation. Diagnosis was confirmed by presence of precursor B lymphoblasts in CSF[7]. Precursor B-LBL presenting as orbital mass was reported by Mark Alford *et al*[8].

In recent years more reports of precursor B lymphoblastic leukaemia/ lymphoma presenting as lytic bone lesions have appeared. Approximately one third of patients present with bone pain and half of them have bone involvements, which include osteopenia, osteolytic lesions and pathological fractures. These patients are misdiagnosed especially when blast cells are absent in peripheral blood smear and even in BM aspirates[9].

The mechanisms underlying the skeletal manifestations are varied. Leukaemic disease process is associated with a low bone turnover state. Acquired growth hormone insensitivity, impaired bone metabolism by factors secreted by leukaemic cells such as osteoblast inhibiting factor, parathyroid hormone related peptide and direct infiltration of leukaemic cells into bone, and expansion of marrow spaces may result in destruction of the spongiosa[10].

In our patient, it was not definite whether the leukaemic process was the primary event or it is a leukaemic transformation of a lymphomatous process. In either case, *normal absolute neutrophil and platelet counts and absence of blast cells in the peripheral blood with such extensive bone involvement are rather unusual.*

Conclusion

Patients with acute lymphoblastic leukaemia usually present with acute illness. Features of bone marrow failure like pallor, bleeding manifestations and infections are the common presenting symptoms, with lymphadenopathy, hepatosplenomegaly and presence of lymphoblasts in peripheral blood and bone marrow. Skeletal morbidity is increasingly being recognized in acute lymphoblastic leukaemia. This is an important problem which may result in fractures, pain, and loss of mobility and may be the presenting feature as in our case. These patients may be misdiagnosed especially when blast cells are absent in the peripheral blood. Biopsy from the fracture site along with bone marrow examination will confirm the final diagnosis.

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✪ CASE SERIES ARTICLE

Anomalous arteries in the upper limbs of a cadaver

Part II: Bilateral double profunda brachii and unusual anastomosis related to biceps brachii tendon

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Abstract

We observed a number of very unusual variations in the upper limb arteries, differing on the right and left sides, in a male cadaver in the dissection hall. The variations observed were many and are hence presented as a series, in four parts. The first part reported the variations in the axillary and brachial arteries, with superficial brachioradial arteries seen bilaterally. This second part of the article describes the branches of the brachial arteries on the two sides specially focusing on the double profunda brachii, and an extremely unusual cubital anastomosis. The third part would deal with variations in the arteries of the left forearm and hand, with a prominent arteria nervi mediana taking part in the formation of the superficial palmar arch. The clinical significance of all these anomalies will be considered at length in the last part of this series article.

Arteria profunda brachii on either side was seen to be double. On the right side both profunda brachii arteries arose as a common trunk along with posterior circumflex humeral artery, from the brachial artery. On the left side the first profunda brachii arose along with posterior circumflex as a common trunk, and the second arose as an independent branch from the brachial artery.

Arterial anastomoses around the elbow joint also showed marked variations bilaterally. The anterior and posterior ulnar recurrent arteries arose as a common trunk from the ulnar artery on both sides. On the left side there was a very peculiar transverse anastomosis between the ulnar and superficial brachioradial arteries, lying superficial to the tendon of biceps brachii. In the right cubital fossa no such communication was observed between the brachioradial and ulnar arteries. The radial recurrent artery also seemed to be absent and the recurrent branch ascending anterior to the lateral condyle was seen to arise from the right artery. The right radial artery failed to make any contribution to the cubital anastomosis.

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Key Words: Brachial artery, Superficial brachioradial artery, Double profunda brachii, Cubital anastomosis, Transverse anastomosis superficial to tendon of biceps brachii.

Introduction

The brachial artery is the continuation of the axillary artery beyond the inferior border of the teres major muscle. It usually gives off an arteria profunda brachii[13], superior and inferior ulnar collateral arteries, nutrient artery to humerus and muscular branches. A single profunda brachii artery normally traverses the radial groove along with the radial nerve. The present study describes a rare anatomical variant, i.e., double profunda brachii arteries, traversing the radial groove, one on either side of the radial nerve.

An anastomosis normally exists between the descending branches of brachial artery, and the recurrent ascending branches of radial and ulnar arteries, around the elbow joint[14]. The anterior and posterior descending branches of profunda brachii anastomose with the radial

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recurrent artery anteriorly, and the interosseous recurrent artery posteriorly, in relation to the lateral epicondyle (Fig. 4). On the medial side, the superior and inferior ulnar collateral arteries from the brachial artery anastomose with the posterior and anterior ulnar recurrent branches ascending up from the ulnar artery. This cubital anastomosis showed marked variations in the present study.

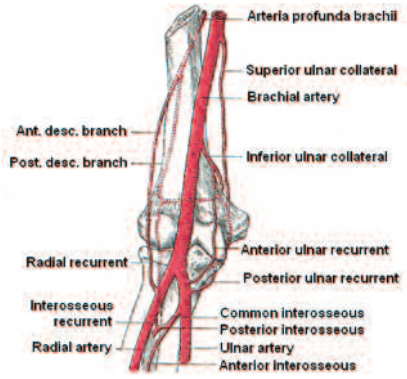


Fig. 4: Normal arterial anastomosis around the elbow joint

Materials and methods

The arterial variations were observed during the routine student dissection of a male cadaver in the Department of Anatomy, Pushpagiri Institute of Medical sciences and Research Centre, Tiruvalla, Kerala. The branches of the arteries of upper limb were traced carefully up to their termination, the arteries were coloured, and photographs were taken. A specific correlation of the observed variations with embryonic development of the arteries of the upper limb has also been made.

Observations

In the present study, out of the 80 upper limb specimens that had been dissected in the past few years, only one case of such wide variations in the branching pattern of upper limb arteries was observed, which, in peculiar, differed on the two sides.

A. i. Double arteria profunda brachii: right side

As discussed in the first part of this series article, the third part of right axillary artery was seen to give off brachioradial artery three centimetres above the lower border of teres major muscle. About six centimetres further distally, the posterior circumflex humeral artery and two separate arteries accompanying the radial nerve in the radial groove (one on either side of the nerve), ***double profunda brachii arteries***, were seen to be given off as a common trunk from the right brachial artery (Fig. 5). Both profunda brachii entered the spiral groove through the lower triangular intermuscular space. The first profunda branch was seen to descend down in place of the anterior descending branch, and the second profunda, after traversing the groove descended down as the usual posterior descending branch.

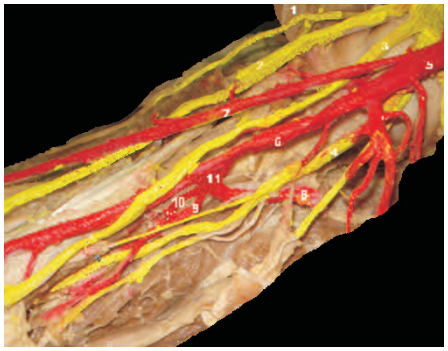


Fig. 5: Double profunda brachii on right side

1. Teres major 2. Median nerve 3. Ulnar nerve
4. Radial nerve 5. Axillary artery 6. Brachial artery
7. Brachioradial artery 8. Posterior circumflex humeral artery
9. First profunda brachii 10. Second profunda brachii
11. Common trunk of 8,9 and 10

ii. Double arteria profunda brachii: left side

The left brachioradial artery was found to be given off from the brachial artery at a lower level compared to the right. The pattern of origin of the double profunda brachii was also different. The first branch given off from the brachial artery (Fig. 6) was a common trunk dividing into posterior circumflex humeral and the first arteria profunda brachii. After traversing the radial groove, this profunda branch was seen to end supplying the lateral head of triceps muscle. In contrast to the right side, the second profunda brachii artery on the left side, originated independently, one centimetre below the first, and gave off the usual anterior and posterior descending branches.

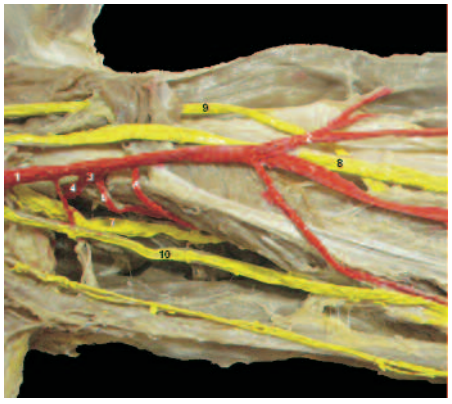


Fig. 6: Double profunda brachii on left side

1. Axillary artery continuing as brachial artery
2. Superficial brachioradial artery 3. Common trunk of 4 and 5
4. Posterior circumflex humeral artery
5. First arteria profunda brachii 6. Second arteria profunda brachii
7. Radial nerve 8. Median nerve
9. Musculocutaneous nerve 10. Ulnar nerve

B. Anastomosis around the elbow: right side

The right radial artery failed to make any contribution to the cubital anastomosis; it was formed entirely by the ascending branches of ulnar artery. The

recurrent branch ascending anterior to the lateral condyle was also seen to arise from the ulnar artery. There was no communication at all between the brachioradial and ulnar arteries. The anterior and posterior ulnar recurrent arteries were seen to originate as a common stem from the ulnar artery.

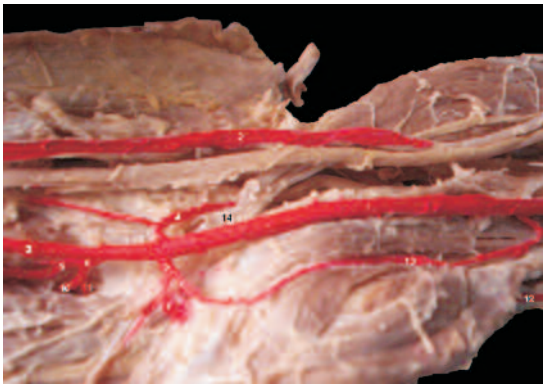


Fig. 7: Anastomosis in the right cubital fossa

1. Brachial artery 2. Superficial brachioradial artery
3. Ulnar artery
4. Lateral recurrent branch from ulnar artery
5. Common stem of 6 & 7 6. Anterior ulnar recurrent
7. Posterior ulnar recurrent 8. Common interosseous
9. Anterior interosseous 10. Posterior interosseous
11. Interosseous recurrent 12. Superior ulnar collateral
13. Inferior ulnar collateral 14. Tendon of biceps brachii

The first profunda brachii descended down as the anterior descending branch, and the second profunda as the usual posterior descending branch, to anastomose in relation to the lateral epicondyle, with the recurrent branch from the ulnar artery and the interosseous recurrent artery (arising from the posterior branch of the common interosseous branch of ulnar artery). The inferior ulnar collateral artery anastomosed with anterior ulnar recurrent, and the superior ulnar collateral with the posterior ulnar recurrent; the anastomosis posterior to the medial epicondyle appeared feeble.

Hence, the cubital anastomosis is formed entirely by branches of brachial artery, and the ulnar artery, which seems to be the direct continuation of the brachial artery. The right brachioradial artery did not take part at all in the right cubital anastomosis.

ii. Anastomosis around the elbow joint: left side

Cubital arterial anastomosis (Fig. 7) showed very peculiar variations on the left side also. A very rare *transverse anastomosis was seen between the ulnar and superficial brachioradial arteries, lying superficial to the tendon of biceps brachii,* in front of the lateral epicondyle.

The *radial recurrent artery seemed to ascend up from this transverse anastomosis.* Two muscular branches, both ending on the extensor carpi radialis longus, were also seen to arise from this anastomosis. The *anterior and posterior ulnar recurrent arteries were seen to arise as a common trunk* from the ulnar artery and ascend up to take part in the cubital anastomosis with the anterior and posterior descending branches of the second profunda brachii.

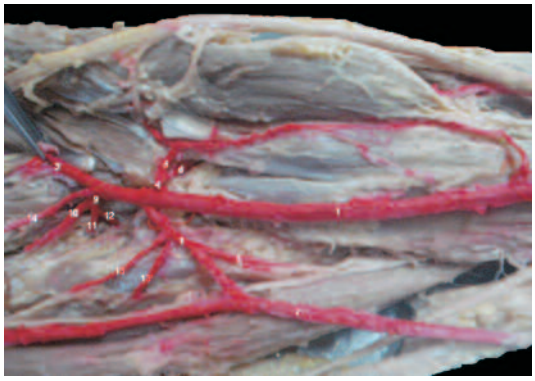


Fig. 8: Anastomosis in the left cubital fossa

1. Brachial artery 2. Superficial brachioradial artery
3. Ulnar artery 4. Common stem of 5 and 6
5. Anterior ulnar recurrent 6. Posterior ulnar recurrent
7. Transverse anastomosis between ulnar & brachioradial arteries
8. Radial recurrent 9. Common interosseous
10. Anterior interosseous 11. Posterior interosseous
12. Interosseous recurrent 13. Muscular branches to ECRB

The superior and inferior ulnar collateral arteries anastomosed with each other five centimetres above the line of the elbow. Inferior ulnar collateral artery (supratrochlear) anastomosed with anterior ulnar recurrent artery in front of, and the superior ulnar collateral artery anastomosed with posterior ulnar recurrent branch behind, the medial epicondyle. The posterior anastomosis appeared quite feeble.

A transverse anastomosis, posterior to elbow, in ***relation to olecranon fossa*** was present bilaterally

Discussion

A. Double profunda brachii

Origin of arteria profunda brachii has been reported to be quite variable in many studies. In a similar case report, along with a high bifurcation of brachial artery, Srijit Das and team noted double profunda brachii arteries in a single limb[15], one of which supplied lateral head of triceps muscle, and the other anastomosed with a recurrent branch of ulnar artery. Such unilateral occurrence of double profunda brachii arteries, along with a higher bifurcation of brachial artery and a communication between the radial and ulnar arteries overlapping the tendon of biceps is reportedly very rare.

Double profunda brachii arteries, both arising from brachial artery in common with superior ulnar collateral artery has been reported by Patnaik[16] in 2007.

Charles *et al.*[17] specified seven types of origins of profunda brachii:

Table 2: Types of origin of profunda brachii

Type	Origin of profunda brachii	%
I	Single branch of brachial	55
Ia	2 separate origins	0.7
Ib	3 separate origins	0.3
II	Common trunk with superior ulnar collateral	2.2
III	At lower border of teres major (axillary/brachial)	8
IV	Branch of 3rd part of axillary	8.7
V	Common truck with posterior circumflex humeral	4
VI	Common with subscapular and both circumflex humeral	0.7
VII	Absent profunda brachii	0.7

In our study there were two profunda brachii arteries each, on both limbs, which accompanied the radial nerve in the radial groove, one on its either side. On the right side both of them arose as a single trunk along with posterior circumflex humeral artery (type V) from the axillary artery; on the left side the upper one arose as a common trunk with posterior circumflex and the lower as a separate branch from brachial artery. Such a variation, differing on the two sides, has not been observed in the available literature.

The double profunda brachii could well be correlated with the peculiarity in the anastomosis around the elbow. The arterial anastomosis behind the medial epicondyle appeared to be feeble on both sides. The arterial supply to the lower part of the posterior aspect of the arm could have been deficient due to this feeble posterior anastomosis. The compromised blood flow might be getting compensated for by the additional profunda brachii artery, which supplied the triceps muscle, on both sides.

B. Anastomosis around the elbow joint

In our specimen the anastomosis in front of the medial and lateral epicondyles is very prominent bilaterally; but behind the epicondyles the anastomosis was thinner, especially on the medial aspect.

The anastomosis in front of the lateral epicondyle of the left elbow was prominent and very peculiar. The communication between the ulnar and the brachioradial arteries at this site, lying on the tendon of biceps brachii, is a very rare occurrence. The variations in cubital anastomosis has been reported to have a frequency varying between one and six percent by various authors[17-19]. Based on their form, the anastomoses are classified into *sling-like loop* or *rectilinear*; based on the calibre of the anastomotic vessels they are grouped into *large or slender*; and based on their length into *long and short vessels*. About 50% to 80% are reportedly rectilinear vessels, varying in their length and calibre[17,20] and the remaining 20% to 50% form sling like loop anastomoses, with thick and short vessels.

Many authors observe that the superficial brachial artery may increase in calibre after receiving the anastomosis, in which case the proximal segment has been variably termed as *vas aberrans*[21], a *collateral trunk*[22], or a *slender superficial brachial artery*[23]. In such case the segment distal to the anastomosis could be an unusual origin of radial artery[18] as per Choueki-Guttenbrunner *et al*.

Rodriguez-Niedenfuhr M and associates[24] observed that at the cubital fossa the brachioradial artery anastomosed with the brachial artery in 14 cases (26.4%). This anastomosis adopted a rectilinear form in five cases (two in front of and three behind the bicipital tendon) and a sling-like loop morphology in ten cases (six in front of and four behind the bicipital tendon). When a brachioradial artery was present, the radial recurrent artery originated from it in 23 cases (46%), from the deep brachial artery in 17 cases (34%), and from the anastomosis between those vessels in ten cases (20%). A second radial recurrent artery was present in twelve cases (22.6%), passing behind the bicipital tendon.

A similar pattern of anastomosis between a recurrent branch of the brachial artery proper and the superficial brachial artery has been reported by Ljubomudroff[21]. In a similar study, a second recurrent radial artery arising from the deep brachial artery, passing behind the biceps tendon has been reported in 2.6% of cases[23] by Adachi.

The transverse anastomosis between the superficial brachioradial and ulnar arteries was present only on the left side. The radial recurrent artery was seen to originate from this transverse anastomosis. The anastomosis in front of the lateral epicondyle appeared to be taking place between this radial recurrent branch and the radial collateral branch. This variation also can be explained on the basis of the embryological development. Usually the anterior and posterior ulnar recurrent arteries arise as two separate branches from the ulnar artery; but here they were seen to arise as a single stem, which soon divided.

The right cubital fossa had no such transverse anastomosis; there was no communication at all between the two arteries. The anterior recurrent branches on the lateral and medial aspects arose directly from the ulnar artery; the posterior ulnar recurrent and the interosseous recurrent branches also ultimately turned out to be branches of ulnar artery. The brachioradial artery had only muscular branches. This peculiar anastomosis with the radial artery not making any contribution is a very rare occurrence.

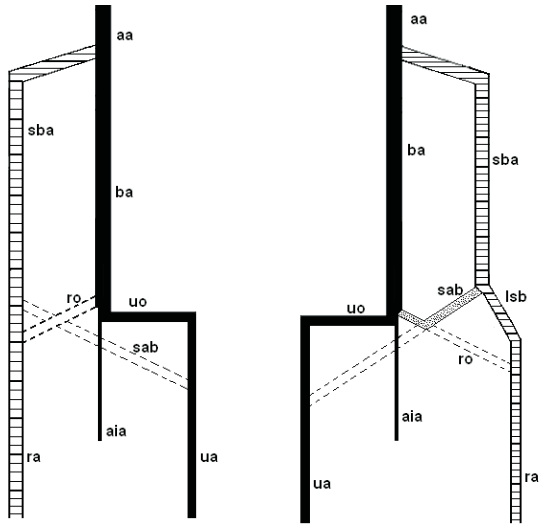
Developmental correlation

Baeza *et al.* (1995) postulated that superficial brachial artery is a consistent vessel in the normal arterial morphogenesis of upper limbs[20]. It has two branches, a lateral branch which forms a part of the

definitive radial artery, and a medial branch, known as superficial antebrachial artery. This medial branch further gives off two terminal branches, which on their own establish connections with the primitive axis artery, to give rise to the ulnar artery medially, and the median artery lateral to it. The same theory applies to the observations in the present study as well.

Anastomosis between the superficial and deep brachial arteries at the elbow has been described during embryonic development[17,25]. In such cases studied extensively, the retained primitive anastomosis could be forming a more significant blood pathway for the distal parts of the limb, than the proximal segment originating from the axillary artery or brachial artery.

Many authors describe the anastomotic vessels as lying superficial to biceps tendon, and some lying deep to it[17,25]. Some others[19,20,24] suggest that during embryonic life there had been an arterial network around biceps tendon, part of which is retained in rare situations, as observed in the present study.



A: Right side B: Left side

Fig. 9: Developmental correlation of the major arteries in the cubital fossa, right and left side

aa. Axillary artery ba. Brachial artery
sba. Superficial brachioradial artery
lsb. Lateral branch of superficial brachioradial
sab. Superficial antebrachial artery
ro. Deep origin of radial artery ra. Radial artery
uo. Deep origin of ulnar artery ua. Ulnar artery
aia. anterior interosseous artery

The transverse arterial anastomosis lying on the tendon of left biceps brachii can be explained with the help of Fig. 9B. The lateral branch of superficial brachioradial artery (lsb) could normally continue as the radial artery (ra) after being joined by a deep sprout from the brachial artery (ro). Persistence of the medial branch of superficial brachioradial artery, known as the superficial antebrachial artery (sab) could account for this unusual communication between the brachioradial and ulnar arteries. This branch along with the normal sprout (ro) of radial artery could have led to the apparently transverse anastomosis between the two major arteries. The communication could have been followed by the disappearance of the post-anastomotic parts of both 'ro' and 'sab' parts. The anastomosis appeared to be a loop like one, lying superficial to the tendon of biceps brachii. A recurrent branch arising from this transverse anastomosis could be ascending up, to anastomose with the anterior descending branch of arteria profunda brachii, thus completing the anastomosis in front of the lateral epicondyle.

Contrary to this, on the right side, probably the deep origin of the radial artery failed to gain predominance (Fig. 9A); so also the superficial antebrachial artery here failed to develop/ persist. As a result, the brachioradial artery showed no communication to any of the other arteries in the cubital fossa.

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PUSHPAGIRI MEDICAL JOURNAL

✪ CASE REPORT

Management of difficult airway in a child with impacted toothbrush

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Abstract

Proper airway management is an essential skill for an Anaesthesiologist. We report a case of difficult airway management performed in a four year old child, with a tooth brush impacted in the retromolar region on the left side. The child was intubated and the foreign body was removed surgically, without any intra-operative or post-operative complications. This case report discusses the complications, diagnosis and management of oropharyngeal injuries by stick-like foreign bodies such as a toothbrush or a chopstick, which though appear trivial, may prove fatal. The article also focuses on basic airway management, and on some oxygenation and tracheal intubation techniques that may be performed to solve a difficult airway.

Keywords: Impacted tooth brush, Difficult airway management, Retromolar region, Laryngeal mask airway, Combitube, Oropharynx.

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Introduction

The practice of airway management has become more advanced in recent years, as testified by the introduction of newer airway devices. Majority of them have been included in *American society of Anaesthesiologists' difficult airway management algorithm.* Management of the difficult airway remains one of the most relevant and challenging tasks for an Anaesthesiologist. For a successful manoeuvre it is essential to have an understanding of anatomy of upper airway passages, have the necessary equipments and technical expertise, and awareness of the complications of laryngoscopy, intubation and extubation. Patient safety depends on the practical management, keeping in mind each of these aspects. In the present case the toothbrush got impacted in the *retromolar trigone,* which is at the crossroads of the oropharynx, nasopharynx, buccinator space, floor of the mouth and the parapharyngeal space.

Case report

A four year old male child was presented to our emergency department with the tooth brush impacted into the region of the retromolar trigone on the left side. He had been running around with the tooth brush in the mouth, accidently hit the wall, and the brush got impacted.

On examination his vital signs were stable. Blood pressure was 90/50 mm of Hg. His respiratory system and cardiac examination were normal. The toothbrush did not appear to be pulsating. The child was shifted immediately to the operation theatre and a quick airway assessment was done. Mask ventilation was nearly impossible with the tooth brush in the oral cavity. Mouth opening and neck mobility were restricted due to pain; the thyro-mental distance was normal. IV cannulation was done with 22 gauge cannula. Inj atropine 0.1mg was given followed by induction dose of ketamine. As soon as the child fell asleep, intubation was done quickly using endotracheal tube (ETT), without giving any paralyzing agent. The toothbrush was removed from the left retromolar trigone. There was minimal bleeding which was secured with sutures. Intra-operative and post-operative periods were normal.

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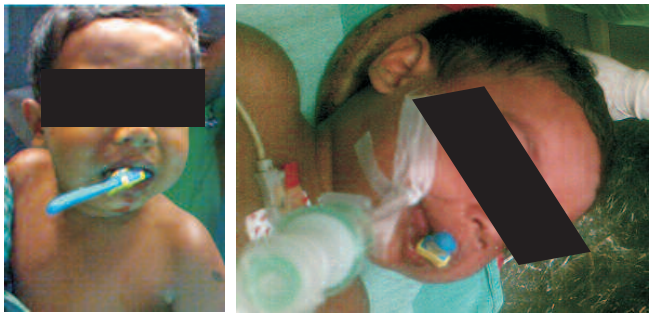

Fig. 1: Impacted tooth brush, and the difficult airway managed with ETT

Discussion

Airway management remains a vital skill in the practice of anaesthesia and intensive care. One third of airway related catastrophes leading to brain damage or death occur as a result of inability in maintaining *a patent airway on time.* The maxilla-facial trauma patients often present with the problem of difficult mask ventilation and difficult intubation. The trauma usually disrupts the normal anatomy and causes bleeding and oedema in the walls of oral cavity and oropharynx. Awake or lightly anaesthetized patients may cough or even develop laryngeal spasm during airway insertion, if laryngeal reflexes are intact. Artificial airway inserted through the nose or mouth is the only way to create an air passage in such cases. Placement of an oral airway is sometimes facilitated by depressing the tongue.

In the present case mask ventilation was impossible. The child was conscious, and sedation and analgesia had to be administered cautiously, since the airway could be lost following any injudicious use of drugs. The tooth brush was pushed to the left side, laryngoscopy was done and endotracheal tube was introduced, though with difficulty, and secured. After confirming ventilation, Inj. Atracurium was given.

A case of a ten year old boy with oropharyngeal injury caused by a toothbrush which penetrated the parapharyngeal space was reported from AIIMS, New Delhi by Sagar S *et al*[1]. It was surgically removed without any intraoperative or postoperative complications. Similar cases of impacted foreign bodies in the walls of oral cavity and pharynx have been reported[2,3]. Sasaki T *et al*. reported the case of a ten year-old girl with pharyngeal injury caused by a toothbrush[4], the snapped head of which lodged in her upper oropharyngeal wall pulsating in synchrony with internal carotid artery pulsations.

Oropharyngeal impalement is a potentially life-threatening injury, though attention to airway obstruction and active haemorrhage take initial priority[5]. Thrombosis of the internal carotid artery is a potential risk, especially in injuries of the peritonsillar region, as in our case. Such patients typically have a delayed onset of symptoms, sometimes more than 24 hours; so close observation is warranted.

Innocent-looking injuries of the oropharynx may result in intravascular thrombosis of the internal carotid artery (ICA). Bar T *et al.*[6] presented a case from Israel, in which an apparently minor injury of the oropharynx developed into a life-threatening thrombus stretching from the ICA in the peritonsillar region to the brain. In a continuous series article the cases of a child and an adolescent in whom ICA thrombosis followed non-penetrating trauma to the paratonsillar area were discussed by Pitner SE[7], together with 10 similar cases collected from the literature.

Complications arising from similar cases of intubation and other airway management procedures can have significant morbidity and mortality risks, observe Loh KS and Irish JC[8]. Awareness of potential "difficult" airway and employing appropriate techniques to maximize airway visualization can minimize the risk of these complications.

Difficult intubation is said to occur when multiple laryngoscopies, manoeuvres, and/ or blades are used by an experienced airway practitioner[9]. Failed intubation occurs when the trachea cannot be intubated after multiple attempts. When intubation attempts are repeated beyond three or four times, the incidence of airway trauma and oedema can increase and may ultimately create a critical airway event[9,10] such as *"cannot mask ventilate - cannot intubate" (CMVCI).* If CMVCI occurs, rapid intervention using a supraglottic ventilation device is usually effective in restoring ventilation and oxygenation[9,10].

Wilson W observed that a comprehensive airway examination incorporates both quantitative and qualitative tests that together may increase the probability of predicting difficult intubation[11]. One such system, the *"6-D" method*, was expanded by Mallampati S from a previously described method of airway assessment[12]. It examined the airway for six separate signs that can be associated with difficult intubation: (a) disproportion, (b) distortion, (c) decreased thyro-mental distance, (d) decreased inter-incisor gap, (e) decreased range of motion, and (f) dental overbite. The 6-D assessment method helps in remembering the six signs because like the word *difficult*, each sign begins with the letter D.

The challenge in performing an endotracheal intubation arises mainly from difficulty in visualising the vocal cords. Numerous *airway devices* and equipments have been developed to overcome these obstacles, such as the *fibre optic bronchoscope*, which enable indirect visualisation of the vocal cords. Supraglottic devices such as the *laryngeal mask airway* or *combitube* (oesophageal-tracheal twin lumen airway device) can be inserted blindly even without visualizing the vocal cord by any means.

Laryngeal mask airway (LMA) is being increasingly used in the place of a face mask or endotracheal tube for various purposes:

a. During administration of an anaesthetic to facilitate ventilation

b. To facilitate the passage of an endotracheal tube in a patient with difficult airway

c. To aid in ventilation during fibre optic bronchoscopy/ placement of bronchoscope

LMA consists of a wide bore tube whose proximal end is connected to a breathing circuit; the distal end bears a cuff which can be inflated through a pilot tube (Fig. 2). The deflated cuff is lubricated and inserted blindly into the hypopharynx; once inflated the cuff forms a low pressure seal around the entrance into the larynx. The LMA partially protects the larynx from pharyngeal secretions, and should remain in place until the patient regains airway reflexes. The reusable LMA is autoclavable.

Fig.2: Laryngeal mask airway

Another supraglottic ventilator device is the *oesophageal-tracheal twin lumen airway device, 'combitube'* (Fig. 3), which consists of two fused tubes and two inflatable cuffs. The longer tube has an occluded distal tip; gas exits from it through a series of side perforations. The shorter clear tube would enter the oesophagus. The smaller distal cuff would lie in the oesophagus (95% cases), and the larger proximal cuff would occlude the oropharynx and nasopharynx. The combitube is inserted blindly through mouth and advanced until the two black rings on the shaft lie between the incisors. Ventilation will force oxygen out through the side perforations into the larynx, and the inflated proximal and distal cuffs prevents air from escaping through the oesophagus, or back out of the oropharynx and nasopharynx. Alternatively, if the tube has entered the trachea, ventilation is achieved through the distal lumen through the shorter clear tube.

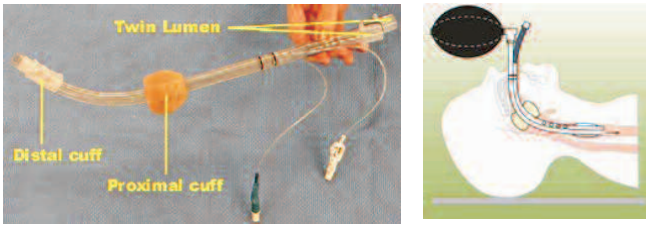

Fig. 3: Oesophageal-tracheal combitube

The combitube offers better seal and better protection against gastric aspiration. But it is available in only one disposable adult size.

If ventilation cannot be established using a supraglottic airway device, transtracheal jet ventilation[13] is the standard method to provide oxygenation and avoid disability or death[14]. The final option is creating a *surgical airway* via. cricothyrotomy or tracheostomy, thus bypassing the larynx and establishing direct access to the trachea. *Percutaneous dilatational tracheostomy* is the most commonly performed tracheostomy technique. *Translaryngeal tracheostomy* is considered to be safe and cost effective, and can be performed at the bed side. *Surgical tracheostomy* is more invasive and can be performed only in an elective manner in a sterile environment.

Conclusion

Most airway problems can be solved with relative simple devices and techniques. But clinical judgement born of experience is crucial to their application. Specific airway management techniques are greatly influenced by the specific problems of individual cases and anatomical variations. Successful management requires combinations of devices and technical skills.

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✪ CASE STUDY

A microscopic study of human skin from various anatomical sites of a cadaver

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Abstract

Background: The structure of the various layers of skin varies according to the anatomical site in the body from which the skin is taken. It is difficult to obtain samples of human skin from different anatomical regions, even from a dead body. Hence such studies from various hairy and non-hairy, and exposed and covered, areas of skin from the same individual are not frequent. **Objectives:** To understand the basic microscopic skin structure in various anatomical regions of the body. **Materials and methods:** The skin structure was studied under the light microscope using haematoxylin and eosin staining. All the samples were obtained from the same dissection hall cadaver of a middle aged Indian male, one month after it was embalmed. **Observations and results:** The thickness of the entire epidermis, the cellular and corneocyte layers, the suprapapillary epidermal plates, and the ratio of these values showed considerable variations in the various anatomical sites in the same body. So also the distribution and microanatomy of the skin appendages also showed wide variations. **Conclusions:** The structure of the skin is intricate and varies in different body sites. Regional variations in cutaneous topography and structure, for the most part, are adaptations for particular functions.

Introduction

The skin is multi-layered, made of epidermis and dermis. The epidermis is an external, stratified epithelium devoid of blood or nerve supplies, of ~ 5-100 µm thickness (can reach 600 µm on palms and soles)[1]. It is composed of several distinct cell populations; the keratinocytes and melanocytes being main constituents. Keratinocytes comprise ~ 95% of the epidermis and are arranged in four layers (Fig.1). The *stratum basale (germinativum)* is a single layer of cells attached to a non-cellular basement membrane. It consists mostly of basal keratinocytes, which have stem cell-like properties, and at least two different types of neural crest-derived cells, Merkel cells and melanocytes. *Stratum spinosum* has irregular polyhedral keratinocytes with a limited capacity for cell division. Also found here are the bone marrow-derived sentinel cells of the immune system, Langerhans' cells. *Stratum granulosum* contains flattened, poly-hedral non-dividing keratinocytes producing keratohyaline granules. The granules increase in size and number as the nuclei gradually degenerate and the cells die. *Stratum corneum* contains nonviable, but biochemically active cells, corneocytes. The keratinocytes continue to differentiate as they move from the basal layer to the stratum corneum, forming cornified cells that contain abundant keratin, and lack cytoplasmic organelles. This epidermal barrier functions to reduce the transepidermal water loss from within and to prevent invasion by infectious agents and noxious substances from without[2]. *Stratum lucidum* is a homogenous layer with traces of small flattened nuclei, deep to corneocytes, appreciable only in the thick skin of palm and sole.

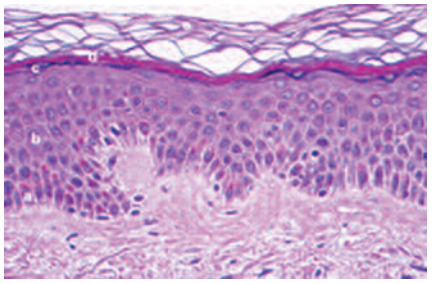

Fig. 1: Layers of epidermis

a. Stratum basale b. Stratum spinosum
c. Stratum granulosum d. Stratum lucidum
e. Stratum corneum

Materials and methods

Samples of skin were collected from different anatomical regions of a single embalmed cadaver in the Anatomy dissection hall of PIMS & RC, Tiruvalla. This was resorted to, as there was no means of obtaining samples of human skin of many anatomical regions from any other source. Samples were collected from the scalp, eyebrows, eyelids, lobule of the ear, abdominal wall, pubic region, palm of hand and sole of foot, and also from the ciliary body and iris of the eyeball. They were subjected to routine tissue processing and staining by haematoxylin and eosin and subjected to microscopic study.

The thickness of the entire epidermis, suprapapillary epidermal plates and stratum corneum (in microns) in all the regions were measured using oculomicrometer. In the hairy regions, the number of hair follicles per low power field was counted, and the depth of the bulb of the hair follicles below the epithelial surface was noted. The density of the sweat and sebaceous glands, and the presence of the arrector pili were also noted. The number of rete pegs (epidermal papillae) per millimeter of the dermo-epidermal junction and the number of basal keratinocytes along a millimeter of the suprapapillary epidermal plates were also noted. Comparison of all these measurements, in the exposed and covered areas of skin, and in the hairy and non-hairy areas, was made.

Observations and Results

The non-hairy areas of skin selected for study were the palm of hand and the sole of foot, and the hairy areas selected were the scalp, eyebrows, eyelids, lobule of the ear, anterior abdominal wall and pubic region. Also samples were taken from the ciliary body and iris, for comparison with the skin.

The thickness of the entire epidermis of skin and the suprapapillary epidermal plates in the various regions was measured in microns (Fig. 2).

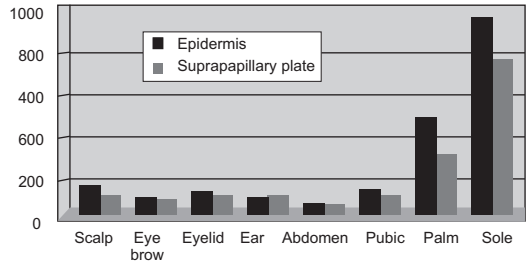

Fig. 2: Thickness of entire epidermis and suprapapillary epidermal plates (μm)

Stratum corneum forms the nonviable layer, and the rest of the thickness of the epidermis is constituted by the viable cellular layers. The thickness of entire epidermis, cellular layers, and the stratum corneum, distributed unevenly in different areas, was compared (Fig. 3). The thickness of stratum corneum was the least in the region of the scalp and the highest in the sole of foot.

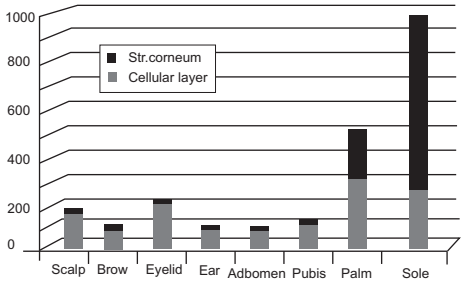

Fig. 3: Thickness of stratum corneum and cellular epidermal layers (μm)

The skin appendages were looked for in all the samples, and the relative abundance was noted, (Table 1.)

Table 1: Appendages of skin: relative abundance in different areas

No.	Anatomical site	Hair follicle	Sebaceous gland	Sweat gland	Arrector pili
1	Scalp	+++	+++	+++	+++
2	Eye brow	+++	+++	+	+
3	Eye lid	+++	+	+	+
4	Ear lobule	++	+	+	+
5	Adbomen	+	+	++	+
6	Pubic region	+++	+	+	+
7	Palm of hand	-	-	+++	-
8	Sole of foot	-	-	++	-

The depths of the deepest hair follicles from the epithelial surface were measured in the various hairy regions. They were found to be deepest in the scalp (Fig. 5), extending upto 2000 μm (2 mm) depth. In the other hairy areas they were shallower (200 μm in ear lobule skin, 115 μm in the pubic region, 75 μm in the abdominal wall and 60 μm in the eye brows: Figures 7,8,9,10). The pilosebaceous units in the eyebrows (Fig. 7) appeared very peculiar in that they showed a definite branching pattern at the root of the follicle. The root sheath cells of the follicle were seen to split into many rami. The sebaceous glands, however, appeared similar to other sites. The follicles of the eyelids (Fig. 6) were comparatively smaller and rounded, and were seen distributed in many rows at various depths.

The number of epidermal papillae (rete pegs) per millimetre of the dermo-epidermal junction (Fig. 4) were counted in different regions, which was found to be the highest in the palm (100) and the least in the ear lobule (30). The number of basal keratinocytes per millimetre of the epidermal basement membrane *in the intervals between the rete pegs* was counted in all regions, and was found to be the maximum in the scalp (560), and the least in the eyelid (320).

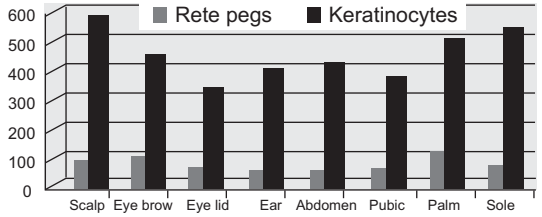

Fig. 4: No. of rete pegs and keratinocytes per mm of dermo-epidermal junction

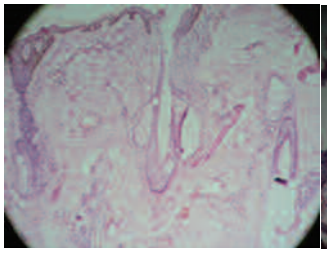

Fig. 5: Thin hairy skin of the scalp (H and E, 100X)

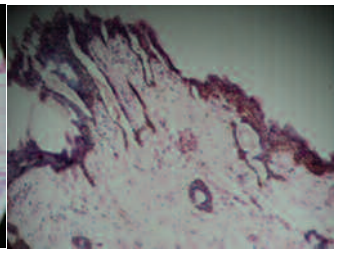

Fig. 6: Section of the skin of the eyelid (H and E, 100X)

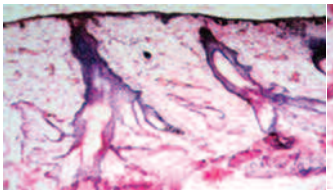

Fig. 7: Skin of the eye brow (H and E, 100X)

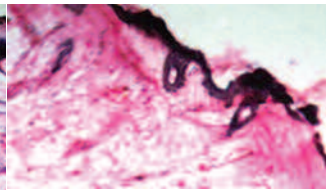

Fig. 8: Lobule of the ear (H and E, 100X)

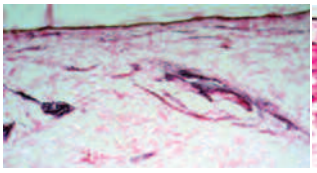

Fig. 9: Skin of anterior abdominal wall (H and E, 100X)

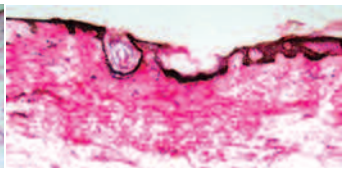

Fig. 10: Skin of the pubic region, (H and E, 100X)

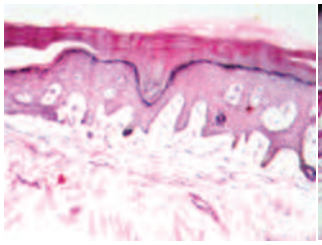

Fig. 11: Palm of hand, (H and E, 100X)

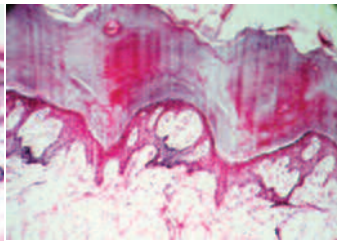

Fig. 12: Sole of foot, (H and E, 100X)

A section of the iris showed a stroma of connective tissue with numerous pigment cells, plenty of minute blood vessels and smooth muscle. The posterior surface (Fig.12) shows a double layer of deeply pigmented epithelium continuous with the ciliary body, extending forwards from the pigment layer of retina.

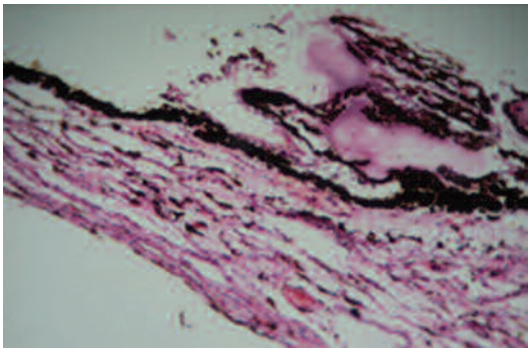

Fig. 12: Section of the iris and ciliary body (H and E, 100X)

Discussion

The gross anatomy and microscopic structure of the skin is regionally diversified, and exhibits many functional correlations. The palmar and plantar skin have thick cornified layer, a prominent pattern of epidermal rete ridges and dermal papillae, numerous eccrine sweat units and nerve endings, but no pilosebaceous units. The palmar skin is corrugated, like the tread of a tyre, and well suited for gripping and grasping objects. The epicritical sensitivity of the fingertips is due to the abundance of touch receptors, which enabled Braille to develop his reading system for the blind. The distensible skin of the eyelids, with its thin dermis, is designed for accommodating the rapid blinking movements necessary to protect the eyes.

The dense pelage that covers the scalp is reflected microscopically in the numerous deeply rooted hair follicles[4]. Morphologically hairs could be straight, wavy, helical or spiral. Straight hairs have their straight follicles oriented vertically to the skin surface. In the blacks the hairs are spiral, as the follicles are curved, and the lower portions are mostly horizontal to the skin surface. Hairs vary in their structure, rate of growth, length and response to stimuli (eg. sex hormones do not affect the development of eyebrows and eye lashes, but profoundly affect other hairy areas)[5]. Foetus is covered by soft, fine, lightly pigmented *'lanugo'* hair, and youngsters have *'vellus'* hairs, covering most of their body. *'Terminal'* (long, coarse, pigmented) hairs have *medulla;* eg., eye brows, eye lashes, scalp, beard, axilla and pubis. Sebaceous glands are mostly associated with hair follicles, forming the pilosebaceous unit. Free sebaceous glands are seen in the dermis of nipple and areola of either sex, labia minora and the inner surface of prepuce[6].

The dermo-epidermal junction[7] reveals three different epithelial cell types resting on a basal lamina: keratinocytes, melanocytes and Merkel cells. The Merkel cells are most heavily concentrated[8] in skin with high hair density and glaborous epithelium of digits and lips, within oral cavity, and outer sheath of hair follicle.

To compare epidermal thickness Robertson and Rees[9] collected confocal images from ten body sites in 39 subjects. Although some epidermal properties varied by site, the most striking finding was the degree of within-site variation, which accounted for between 50% and 74% of the total variation observed.

In the present study the ratio of the thickness of the suprapapillary epidermal plates to the entire epidermal thickness was the highest in the lobule of the ear (1.204), compared to all other areas. The ratio was found to be slightly higher in the sun exposed areas of skin (mean = 0.764), as compared to the sun covered areas (mean = 0.707).

The ratio of the thickness of stratum corneum to the cellular layers of epidermis was studied, and was found to be far higher in the sole of foot (2.818) than the

palm (0.602), as seen in Figs. 11 and 12. This can obviously be attributed to the heavier exposure of sole to friction. It was much lower in the hairy areas of skin.

In vivo reflectance confocal microscopy was performed in ten adults of various skin phototypes[10] with samples from forehead, cheek, inner and outer forearm surfaces, lower back and leg. Epidermal thickness at suprapapillary epidermal plates and rete pegs, the number of epidermal keratinocytes in each epidermal cell layer, as well as the characteristics of dermal papillae were defined. It was observed that the epidermal thickness at rete pegs, but not the suprapapillary epidermal plate, was greater in sun-exposed areas than in sun-protected sites.

The numerical density of granular keratinocytes was greater on the face as compared with all other sites, whereas the surface density of spinous keratinocytes is greater on sun-protected sites in the study by Huzaira M *et al*[10]. Additionally, the number of basal keratinocytes per millimeter length of dermoepidermal junction was greater in sun exposed areas. This is in conformity to our study, which showed the mean keratinocyte number to be 436 in the sun exposed areas and 393 in the covered areas.

Significant regional variation in both the mean thickness and the mean number of cell layers was documented[11] for four selected, sample regions of the body of a group of six adult volunteers, and for two more homogeneous subgroups separated by sex and age. The study showed that there is also marked individual variation within a region that is characteristic and specific for each individual.

In a similar study the thicknesses of the stratum corneum and the cellular part of the epidermis in different races were determined by light microscopic evaluation of skin biopsies by Lock-Andersen J *et al*[12]. They found that epidermal thickness was independent of the skin type and was not correlated to constitutive skin pigmentation.

Conclusions

The histology of skin is amazingly complex, when we consider all the anatomical regions in the same person. As the tissues which constitute it have myriad functions (mechanical protection, photo-protection, immuno-surveillance, nutrient metabolism, repair, etc.), the skin structure also varies from one site to the other. An understanding of this normal variability, with special attention to the exposed and covered areas, and hairy and non-hairy areas, is central to an understanding of cutaneous pathology.

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✪ CASE STUDY

Neuroimaging in Acute stroke - An overview

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Introduction

Neuroimaging is an important part of the assessment of patients with hyperacute stroke. As new treatments that may reverse cerebral ischaemia have been developed, the role of neuroimaging has changed from simply anatomic depiction of early infarction to identification, by means of physiologic (rather than simply anatomic) information, of regions that are at risk for infarction. The goal of such imaging techniques is to monitor the successes and complications of recently developed treatments such as thrombolysis[1].

Stroke is defined as an abrupt onset of a neurological deficit attributable to focal vascular cause. It is the third leading cause of death and is also a major cause of disability in adults. Stroke is generally considered to be of two types, haemorrhagic stroke which can be due to either an intraparenchymal or an extra-axial (subarachnoid) haemorrhage, and ischaemic stroke due to an occlusion of either an artery or a vein.

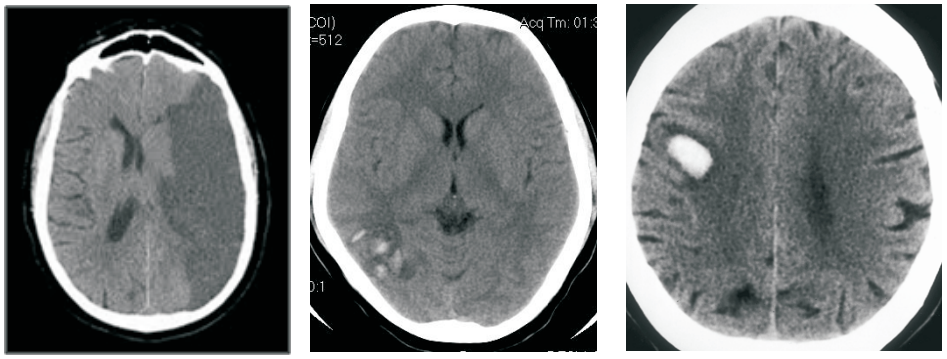

Fig. 1: (a) Arterial infarct (b) Venous infarct (c) Haemorrhage

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CT and MRI protocol in a patient with suspected stroke

A. CT protocol : axial plain CT images, 3 mm sections for posterior fossa, and 5 mm for supratentorial region.

Arterial infarct appears as a wedge shaped hypodensity at the grey-white interface, and remains confined to the arterial territory (Fig. 1). *Venous infarct* usually appears rounded, is often haemorrhagic, occurs in white matter, and is not seen confined to the arterial territory. *Haemorrhage* appears as a hyperdensity on CT.

B. MRI protocol:

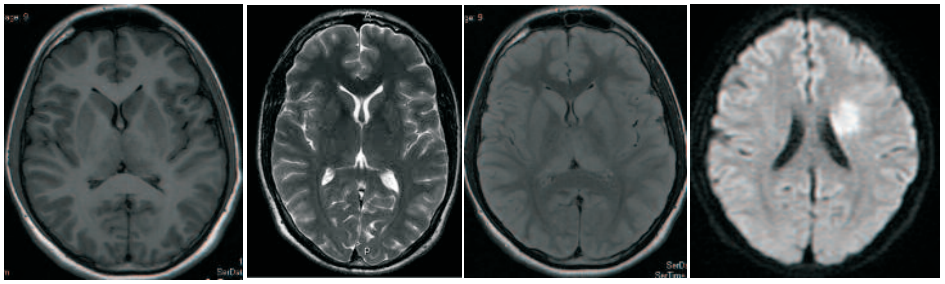

Fig. 2: (a) T1WI (b) T2WI (c) FLAIR (d) DWI

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DWI: is sensitive to restriction of Brownian motion of extracellular water, due to imbalance caused by cytotoxic edema. Normally water protons have the ability to diffuse extracellularly and loose signal. High intensity on DWI indicates restriction of the ability of water protons to diffuse extracellularly. When we look at the DWI-images it is very easy to identify the infarct as it appears bright (Fig. 2). This is why DWI is called *'the stroke sequence'.*

ADC: A diffusion coefficient enables us to differentiate T2 shine through effects or artifacts, from real ischemic lesions. The apparent water diffusion coefficients can be calculated by acquiring two or more images with a different gradient duration and amplitude (b-values). The contrast in the ADC map depends on the spatially distributed diffusion coefficient of the acquired tissues and does not contain T1 and T2 values. A lower apparent ADC is a sensitive indicator of early ischaemic brain, at a stage when ischaemic tissue remains potentially salvageable.

SWAN: This multi-echo 3D imaging technique helps visualize and clearly delineate small vessels and micro bleeds, large vascular structures, and iron or calcium deposits in the brain (Fig. 3). SWAN generates more than twice SNR compared to a conventional T2 producing excellent images and allowing high spatial resolution.

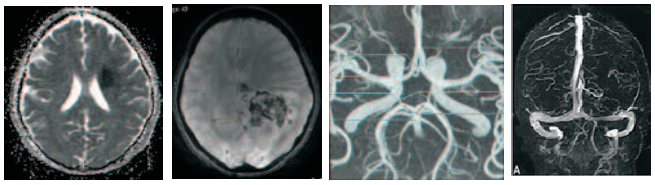

Fig. 3: (a) ADC map (b) SWAN (c) 3D-TOF Angiography (d) Venography

CASE STUDIES

Case 1

A 30 year old female presented with acute onset of right sided weakness.

Clinical diagnosis: Acute infarct in left MCA territory.

Axial CT showed no abnormality. No signal abnormality was noted on FLAIR, but on DWI high signal intensity was noted in left basal ganglia with corresponding low signal on ADC Mapping (Fig. 4). This was suggestive of hyperacute infarct.

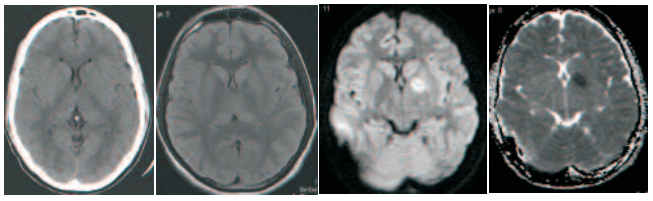

Fig.4: (a) Axial CT (b) FLAIR Axial (c) DWI Axial (d) ADC Map Axial

MRI Diagnosis: hyperacute infarct involving left basal ganglia

Discussion: DWI/ ADC has high sensitivity as well as specificity for detection of hyperacute and acute infarctions. DW imaging and ADC mapping can detect infarct as early as 30 minutes from onset of symptoms.

Case 2

A 40 year old female patient presented with history of sudden onset of right sided hemiplegia, right UMN facial palsy and motor aphasia.

Clinical diagnosis: Left MCA territory infarct

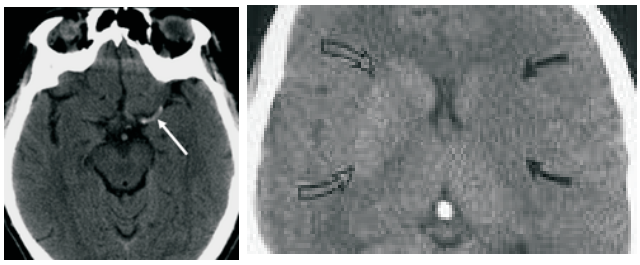

Fig. 5: a) Axial CT b) Magnified CT

Axial CT showed hyperdense left MCA *(dense MCA sign). The magnified view*: showed hypoattenuation of left lentiform nucleus (Fig. 5) with loss of differentiation of left insular cortex *(insular ribbon sign)*.

*CT diagnosis: a*cute infarct involving left MCA territory due to thrombosis of left MCA.

Diffusion restriction was noted in left MCA territory on DWI with low signal on ADC Map, suggestive of acute infarct (Fig. 6). 3D TOF Angiography showed thrombotic occlusion of M2 segment of left MCA.

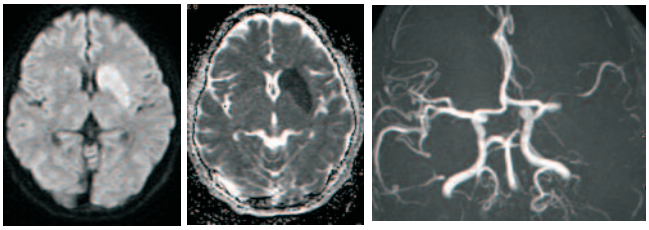

Fig. 6: a) DWI Axial b) ADC Map Axial c) 3D TOF Angiography for COW

MRI diagnosis: Acute infarct involving left MCA territory due to occlusion of M2 segment of left MCA.

Discussion: Identification of hyperacute/ acute infarct on CT requires a high degree of suspicion, a meticulous observation of the above mentioned signs and careful clinical correlation.

MR Angiography is a non-contrast study, so it can be useful in chronic renal failure or other patients contraindicated for contrast study. MRA is sensitive for detecting thrombosis and aneurysm.

Case 3

A 50 year old male patient presented with history of slurring of speech, right side facial palsy and weakness of right upper limb.

Clinical diagnosis: features were suggestive of CVA, probably left MCA territory

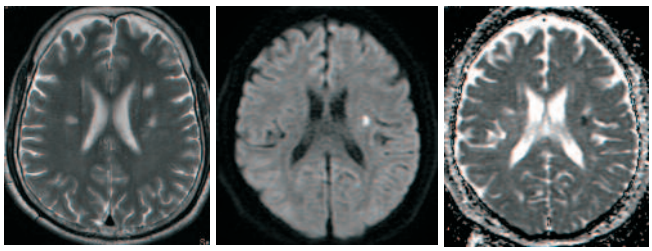

Fig. 7: (a) T2WI Axial | (b) DWI Axial | (c) ADC Map Axial

MRI (Fig. 7) showed a few areas of high signal changes in bilateral corona radiata on T2W image, but only one area in the left corona radiata showed diffusion restriction on DWI with low signal on ADC Map.

MRI diagnosis: Acute lacunar infarct involving left corona radiata, and an old lacunar infarct in right corona radiata.

Discussion: MRI is better for differentiating acute and chronic lacunar infarcts.

Case 4

A 28 year old female patient had a history of IUD (intrauterine death of foetus) three months back. She presented with history of headache, nausea for the past one week. There was an episode of generalized tonic clonic seizures.

Clinical diagnosis: Cerebral venous thrombosis

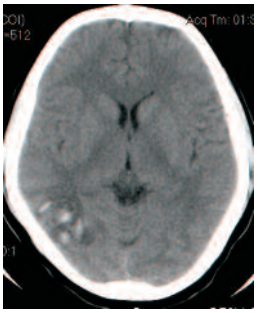

Fig. 8: Axial CT image

On plain CT image discrete areas of hyperdensity were seen in the right temporo-parietal region in the white matter with perilesional oedema (Fig. 8).

CT diagnosis: Intraparenchymal haemorrhage/ haemorrhagic transformation of infarct, seen in right temporo-parietal region.

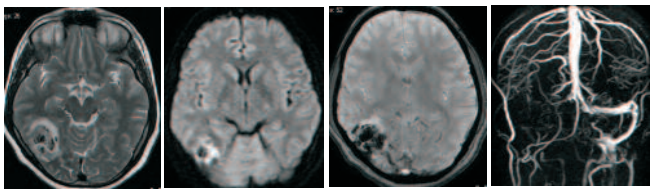

Fig. 9: a) T2WI Axial | b) DWI Axial | c) SWAN Axial | d) Venography

Signal alteration was seen with perilesional oedema in right temporo-parietal region with high signal on DWI and blooming on SWAN sequence, suggestive of haemorrhage (Fig. 9). Venography showed occlusion of right transverse and sigmoid sinuses.

MRI diagnosis: Acute venous infarct involving right temporoparietal region due to occlusion of right transverse and sigmoid sinuses.

Discussion: MRI is as sensitive as CT for detecting acute intraparenchymal haemorrhage. MRI is more sensitive than CT for detecting chronic haemorrhage and microbleeds. MRI venography is a non contrast and non invasive study to detect venous sinus and cortical venous thrombosis.

Case 5

A 54 year old male patient, a known case of diabetes mellitus, presented with sudden onset of headache, and weakness of both upper and lower limbs.

Clinical diagnosis: Medial medullary syndrome

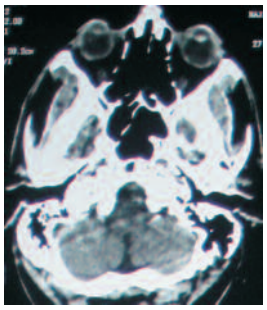

Fig. 10: Axial CT- showed no abnormality

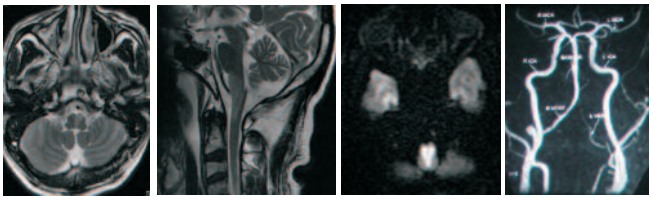

Fig. 11: (a)T2WI Axial | (b) T2WI Coronal | (c) DWI Axial | (d) 3D TOF Angiography

An area of high signal intensity was noted in central part of medulla oblongata with extension into ponto medullary and cervico medullary junction on T2W images with high signal on DWI (Fig. 11). Angiography showed occlusion of left vertebral artery.

MRI diagnosis: Acute infarct involving central part of medulla extending into ponto-medullary and cervico-medullary junction, probably due to occlusion of left vertebral artery.

Discussion: MRI is better for evaluating posterior fossa structures. These structures are obscured on CT by beam hardening artifacts from adjacent bony structures. MRI also has an added advantage of multiplanar imaging which will demonstrate the vertical extent of the lesion easily on sagittal or coronal images.

Case 6

A 34 year old female patient was admitted with a history of sudden onset of severe headache, vomiting and altered sensorium.

Clinical diagnosis: Subarachnoid hemorrhage (SAH)

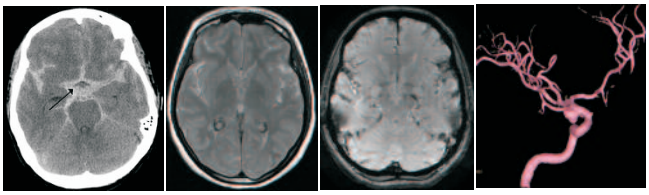

Fig. 12: (a) Axial CT (b) FLAIR Axial c) SWAN Axial (d) Volume rendering angiography

Axial CT showed hyperdensity in basal cisterns and bilateral sylvian fissures suggestive of SAH.

MRI showed subtle high signal intensity in bilateral sylvian fissures and sulcal spaces on FLAIR, blooming in the corresponding areas on SWAN (Fig. 12), suggestive of SAH. Volume rendering angiography depicted the aneurysmal dilatation very well at left ICA bifurcation (cause for spontaneous SAH).

Discussion: SAH is more easily detected on CT i.e., it is obviously seen as hyperdensity involving sulcal spaces or basal cisterns. On MRI it needs to be carefully looked for, and it appears as hyperintensity in sulcal spaces on FLAIR sequence and blooming on SWAN sequence. MR Angiography has an advantage as it is a non contrast, non invasive study to know the cause for non traumatic SAH/ ICH.

Case 7

A 40 year old gentleman, a known case of hypertension, presented with numbness of right arm, and two episodes of focal seizures with secondary generalization.

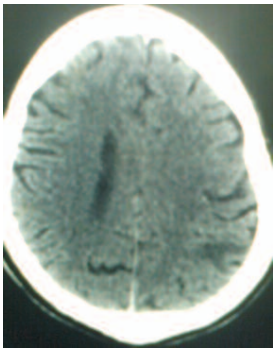

Fig. 13: Plain Axial CT

Axial CT showed ill-defined hypodensity at grey white interface in left parietal region (Fig. 13).

CT diagnosis: CT was suggestive of an infarct in the left posterior parietal region.

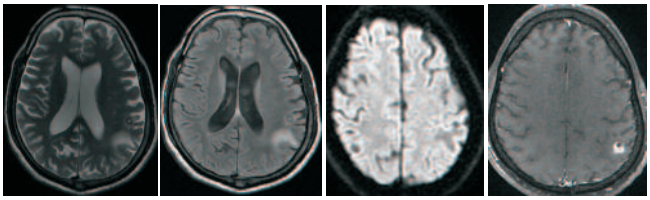

Fig. 14: a) T2WI Axial b) FLAIR Axial c) DW Axial d) Postcontrast T1WI Fat Sat Axial

MRI showed a well defined rounded lesion in the left posterior parietal lobe with perilesional oedema on T2WI / FLAIR images. No diffusion restriction was noted on DWI. On post contrast study, a peripheral ring like enhancement was noted (Fig. 14).

MRI Diagnosis: Ring enhancing lesion in left posterior parietal lobe with perilesional edema, suggestive of neurocysticercosis.

Discussion: MRI gives better tissue characterization and is better for differentiating stroke mimics.

CT vs MRI

Some general features of the two modalities are:

CT	MRI
Faster and better in non co-operative and paediatric patients	Causes motion artifacts and image distortion to greater extent in non co-operative patients
Availability easier	Availability is less
Cost effective	More expensive
Can be used in patients with cardiac pacemakers/ cochlear implants	MRI is contraindicated in these patients

For infarctions imaged within 24 hours, Bryan R *et al.* reported a sensitivity of 58% for CT and 82% for MR imaging[4]. It compared the diagnostic accuracy of computed tomography (CT) and magnetic resonance (MR) imaging in a consecutive series of 691 patients presented to the emergency department with symptoms of acute stroke. The study concludes that in the diagnosis of stroke in the early period (less than 12 hours after presentation), DW MR imaging is superior to conventional MR imaging and CT. Thereafter, DW MR imaging is not demonstrably superior to CT for the evaluation of these patients, remark Mark E. Mullins *et al*[5]. Because DW MR imaging uses fast (echo-planar) imaging technology, it is highly resistant to patient motion, and imaging time ranges from a few seconds to two minutes. As a consequence, DW MR imaging has assumed an essential role in the detection of acute brain infarction[6].

Many previous studies have reported that DW images are very sensitive and specific for the detection of hyperacute and acute infarctions, with a sensitivity of 88% - 100% and a specificity of 86% - 100% [7-9].

Conclusion

MRI offers many advantages over CT in evaluation of an acute stroke. However both modalities are complimentary to each other with each scoring over the other in different clinical situations. Hence referring physician and radiologist should use these modalities judiciously for the benefit of disease management.

Abbreviations used in the article

T1WI	:	T1 Weighted Imaging
T2WI	:	T2 Weighted Imaging
FLAIR	:	Fluid Attenuated Inversion Recovery Sequence
DWI	:	Diffusion Weighted Imaging
ADC	:	Apparent Diffusion Coefficient
TOF	:	Time of Flight
SWAN	:	Susceptibility Weighted Angiogaphy Sequence
MRA	:	MR Angiography
MRV	:	MR Venography
SAH	:	Subarachnoid Hemorrhage
ICH	:	Intracranial Hemorrhage

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✪ TECHNICAL REPORT

Optimized diet design using linear programming

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Abstract

Cost optimization of diets was an issue that even a Nobel Laureate considered worth tackling. George Stigler optimized 15 items from 77 major foods and met all the basic requirements of nutrients as per National Research Council guidelines. Computing facilities can help in the task of this optimization using linear programming with or without 'trial and error' used by Stigler. Linear programming uses an objective function which the equation seeks to minimize. In this article in place of a simple cost minimization, we are trying to minimize the fat load of the diet. MS Excel 'Solver' module was used in this example. Energy content of the diet was sought to be equalized while the content of protein, vitamin A, iron and calcium were maximized. Palatability and preference for some of the items were also used to restricting overuse of some of the 'healthy items'. This approach is designed to be used in practical setting of the dietitian's office, given the time restrictions imposed by the consultation.

Introduction

There was a time when cost was the primary concern in designing optimum diets for populations. In fact it was a Nobel laureate economist, George Stigler, who designed a 15 item diet for a moderately active man weighing 154 pounds, from 77 foods which were available, so that the man's intake of nine nutrients would be at least equal to the recommended dietary allowances (RDAs) suggested by the National Research Council in 1943, with the cost of the diet being minimal[1]. This Stigler diet met the RDAs required for calories, protein, calcium, iron, vitamin A, thiamine, riboflavin, niacin, and ascorbic acid. Annual budget in this case worked out to approximately $0.11 a day in 1939 for a diet comprising of foods such as evaporated milk, cabbage, dried navy beans, and beef liver.

The method which was used to solve this optimization problem was linear programming. Stigler lacked the computing facilities of current specifications so much so that he had to fall back on heuristic *"trial and error"* methods. Linear programming however evolved as a powerful approach to tackling issues of food balancing. The application of this oversimplified approach was predictably restricted to use in child nutrition in countries such as Chad, India and Malawi especially when a fortified food item was to be added to a poor diet [2-4].

Optimization models use an objective function which is an equation restricted by various constraints. This objective function in the examples cited above was the sum total of the cost of the individual items of food. Linear or non-linear approximations are derived by iteration. Lack of familiarity with the Solver component of MS Excel software can be a deterrent for routine clinical application of the same. The custom software programmes available for field use are, however, often non-flexible.

Attention has shifted to chronic diseases world-over, resulting in consensus regarding healthy food[5]. Conventional selection of healthy food materials always result in impractical and high cost solutions. Linear programming, however, helps in finding dietary solutions which do not really result in increased cost of food materials because of the way the problem has been designed. This is achieved by the restriction criteria built

in to check the inclusion of unpalatable items[6,7]. However, cost is not the primary focal point anymore.

This paper deals with the issue of practical application of this method to suit the local needs. We would hope that the dietetics departments of hospitals in the region in general would adopt the solution to provide tailor made diets to the patients who consult them.

Methodology

Linear programming minimizes a linear function (objective function) given a set of constraints which are used to restrict the required daily allowance for each nutrient. The general equation used is as follows:

Cost of the diet = $W_1C_1 + W_2C_2 \ldots + W_nC_n$, where W is the quantity of item and C is the unit cost.

The advantage of this is that instead of cost minimization, we can minimize the most deleterious component of diet while optimizing the amount of the other nutrients which are essential. However, if RDAs were only used for optimizing the diets the solutions sometimes can be impractical suggesting only the most ideal of food items which are not palatable but are healthy. In this context, a variable namely *'maximum allowable limit'* could be used as another criterion, which would restrict some of these unpalatable yet healthy items.

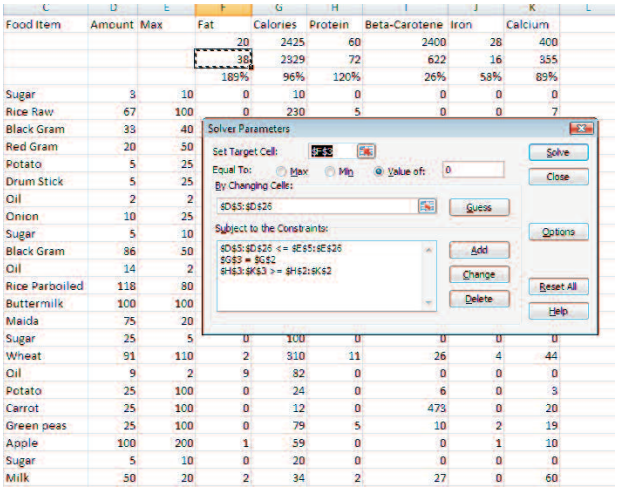

Fig 1: The MS-Excel solver used with the objective function and the constraints

Linear programming was implemented using Microsoft Excel in the present paper[4]. The add-on Solver function was used to minimize the fat content of the diet of an average person (Fig. 1). The MSExcel spreadsheet used here contained an approximate composition of each food as per local practices. Another sheet of the spreadsheet held the nutritional values of each of the components in terms of fat, calories, protein, beta-carotene, iron and calcium (ICMR)[8]. The data entry sheet was used to feed in the diet of a person from a survey conducted. The nutrient content was derived from the amount of dietary item and added for each nutrient separately.

Table 1. The unbalanced diet generated after removal of some of the initial negative items

Food article	Food item	Amount	Max	Fat	Calories	Proten	B-Carotene	Iron	Calcium
Black coffee	Sugar	3	10	0	10	0	0	0	0
Iddli	Rice Raw	67	100	0	230	5	0	0	7
	Black Gram	33	40	0	116	8	13	1	51
Sambar	Red Gram	20	50	0	67	4	26	1	15
	Potato	5	25	0	5	0	1	0	1
	Drum Stick	5	25	0	1	0	6	0	2
	Oil	2	2	2	18	0	0	0	0
	Onion	10	25	0	5	0	0	0	5
Sweet Tea	Sugar	5	10	0	20	0	0	0	0
Uzhunnu Vada	Black Gram	86	50	1	297	21	33	3	132
	Oil	14	2	14	129	0	0	0	0
Rice	Rice Parboiled	118	80	0	407	8	0	1	11
Butter milk	Buttermilk	100	100	7	77	2	10	0	21
Biscuit	Maida	75	20	1	261	8	19	2	17
	Sugar	25	5	0	100	0	0	0	0
Chap-pathi	Wheat	91	110	2	310	11	26	4	44
	Oil	9	2	9	82	0	0	0	0
Veg Kurma	Potato	25	100	0	24	0	6	0	3
	Carrot	25	100	0	12	0	473	0	20
	Green peas	25	100	0	79	5	10	2	19
Apple	Apple	100	200	1	59	0	0	1	10
Sweet Milk	Sugar	5	10	0	20	0	0	0	0
	Milk	50	20	2	34	2	27	0	60
Plantain Thoran	Plantain green	85	100	0	54	1	26	5	9
	Coconut	10	2	4	44	0	0	0	1
	Oil	5	2	5	45	0	0	0	0
Carrot	Carrot	90	30	0	43	1	1701	1	72
RDA				20	2425	60	2400	28	400
Total				38	2329	72	622	16	355
%RDA				189 %	96%	120%	26%	58%	89%

The objective function for minimization in this model was the cumulative fat content of food items consumed by the individual in a day namely $\Sigma\$F_n*\$D_n/100$ where $F is the content of fat in 100 grams of the specific item and $D is the array of amount of food item consumed in grams or ml. This was sought to be minimized by changing $\$D_n:\$D_x$ which is the amount of individual items consumed to ideal values. The constraints were the maximum tolerable amounts of each food item as per the persons' taste or as per prescription, in addition to the RDAs of each of the nutrients selected for optimization. Typically calories were equated with RDA while protein, beta-carotene, iron and calcium were allowed to be maximized as given below:

$\$D_n:\$D_x <= \$E_n:\$E_x$
$\$G_n$ = RDA of Calories
$\$H_n:\$K_n >=$ RDA of all the other nutrients

Where $D is the array (n to x) of amount of food item consumed in grams or ml, $E is the maximum tolerable amount of the item, $G is the amount of calories in the given diet and $H-$K are the nutrient density of protein, beta-carotene, iron and calcium.

In case the solution generated negative values for some of the items consumed by the individual, those items were deleted from the model. In addition to this, some extra items were added to the diet from the nutritional knowledge of the user. For example, the diet shown in table 1 was generated from an initial model which contained some items, which had to be replaced with plantain green and carrot, to balance the content of the micronutrients and to reduce the overall fat content.

Result

The result of the optimization is shown in table 2.

Table 2. A diet balanced by optimization using the MS Excel Solver

Food article	Food item	Amount	Max	Fat	Calories	Proten	B-Carotene	Iron	Calcium
Black coffee	Sugar	10	10	0	40	0	0	0	0
Iddli	Rice Raw	100	100	1	345	7	0	1	10
	Black Gram	40	40	1	139	10	15	2	62
Sambar	Red Gram	50	50	1	168	11	66	1	37
	Potato	25	25	0	24	0	6	0	3
	Drum Stick	25	25	0	7	1	28	0	8
	Oil	1	2	1	13	0	0	0	0
	Onion	25	25	0	13	0	0	0	12
Sweet Tea	Sugar	10	10	0	40	0	0	0	0
Uzhunnu Vada	Black Gram	50	50	1	174	12	19	2	77
	Oil	2	2	2	14	0	0	0	0
Rice	Rice Parboiled	80	80	0	277	5	0	1	7
Butter milk	Buttermilk	100	100	7	77	2	10	0	21
Biscuit	Maida	20	20	0	70	2	5	1	5
	Sugar	5	5	0	20	0	0	0	0
Chap-pathi	Wheat	110	110	2	375	13	32	5	53
	Oil	2	2	2	14	0	0	0	0
Veg Kurma	Potato	100	100	0	97	2	24	0	10
	Carrot	100	100	0	48	1	1890	0	80
	Green peas	100	100	1	315	20	39	1	75
Apple	Apple	200	200	1	118	0	0	7	20
Sweet Milk	Sugar	10	10	0	40	0	0	0	0
	Milk	50	20	2	34	2	27	0	60
Plantain Thoran	Plantain green	85	100	0	54	1	26	5	9
	Coconut	10	2	4	44	0	0	0	1
	Oil	5	2	5	45	0	0	0	0
Carrot	Carrot	90	30	0	43	1	1701	1	72
RDA				20	2425	60	2400	28	400
Total				19	2425	86	2134	23	477
%RDA				93%	100%	143%	89%	81%	119%

The changes effected by the Solver are as follows:

Raw rice as in breakfast was increased while reducing the intake of afternoon parboiled rice meals. Use of black gram was reduced drastically as also oil in many places. Use of wheat in particular and maida to some extent was positively modified by the software. The heuristically added plantain green and carrot were retained by the Solver while increasing the intake of sambar suggesting that iddli-sambar be included in ample amounts in a healthy breakfast. Fruit intake was also encouraged. Simple sugar was preferred instead of oil as an energy source even though we could have restricted use of simple sugars if the subject were to be a diabetic. Overall, the consumption pattern was improved from an overloaded fatty diet to a less fatty, more nutritious diet by the software without drastically changing the composition (Fig.2). An item which could be a source of little more calories along with iron (e.g. jaggery) could balance the diet absolutely, given the RDA suggested for this person. The fact that the time required for optimization is minimal, once the diet is entered into the spreadsheet, is notable.

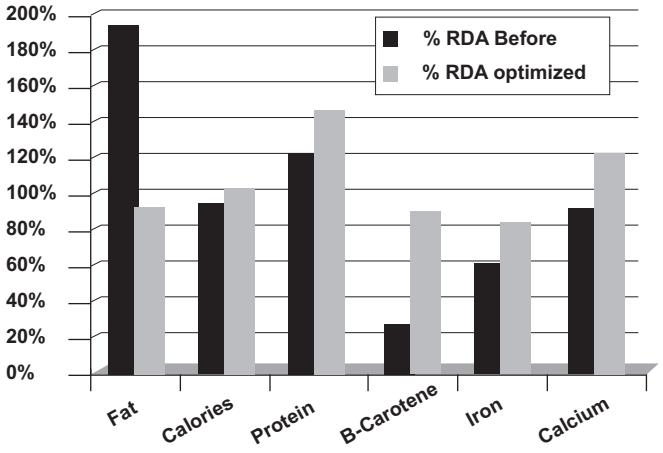

Fig. 2: Effect of balancing of nutrients using the linear programming approach

Discussion

Often the dietitian recommends a diet to a patient in very general terms. This serves only a limited purpose in achieving good compliance in most cases. A more meaningful approach was used in this paper where in the diet of a person was taken and then used algorithmically to find items which do not fit in with the overall requirements. The dietitian then is able to add some items heuristically to serve as a springboard to near-optimal solution. Fine tuning of this diet will serve to make the variety necessary for a seven day cycle for an individual. All the more, a disease condition could be fitted into the model so as to reduce the intake of specific items providing for a healthier diet even for a difficult patient, e.g., suffering from diabetes.

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PUSHPAGIRI MEDICAL JOURNAL

✪ TECHNICAL REPORT

Concept of Rational drug use

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Health is a basic human right and a matter of prime concern for all humans. In today's health care delivery, which is primarily based on the physicians, there is a pressure for quick relief, due to lack of time (prolonged treatment additionally escalates the cost of treatment), and due to the general expectation of speedier outcome in all fields of life. In a country like India, where limited budget is allocated for the healthcare, especially for medicine procurement, it is vital to optimize this expenditure, as a National policy. It is widely known that quite unsuitable, irrational and non-productive use of many medicines is commonly practised in many of the developing countries including India[1].

According to WHO *"Rational use of medicines requires that the patients receive all medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, at the lowest cost to them and their community"*[2]. The National Health Policy 2002 of India has stressed the need on rational medicine use.

Rational medicine use has three important aspects:

1. Appropriate medications for the respective clinical ailment
2. Proper dose regimen to meet requirements of the patient for an appropriate duration of time
3. Pharmaco-economics or cost aspects of the treatment.

Concept of rational medicine treatment involves following six **"RIGHTS"**:

- ✓ RIGHT choice of the medicine
- ✓ Available at the RIGHT time
- ✓ In the RIGHT dose
- ✓ At the RIGHT interval
- ✓ For the RIGHT length of time
- ✓ At the RIGHT cost

Before prescribing a particular medicine, we need to obtain answers on its efficacy, safety, cost and availability. Examples of irrational prescribing include over-prescribing, under- prescribing, multiple prescribing and inappropriate prescribing. All stake holders, including the consumers (patients), the prescribers (doctors), the manufacturers (pharmaceutical companies) and the Government are responsible for the current irrational use of drugs in the following manner:

I. Patients

- ○ Lack of awareness about the proper use of medicines
- ○ Non-compliance with medicine prescription
- ○ OTC (over the counter) purchase, self medication with previous prescriptions
- ○ Overuse and misuse of antimicrobials, overuse of 'relatively safer' medicines
- ○ Multiple consultations without giving past history of medicine consumption and mixing treatments

II. Doctors

- ○ Lack of training in basic principles of rational drug use
- ○ Influence of promotional practices of pharmaceutical companies
- ○ Patient overload restricting proper attention to individual patients
- ○ Poor diagnostic facilities in rural areas and uncertain diagnosis

A prescription study carried out in Goa[3], including both Government hospitals and private practitioners, revealed the following facts:

1. Prescription writing was unsatisfactory
2. The information necessary to identify the prescriber, like the name and registration number was lacking

3. Information to identify the patient like name, age, sex and address was deficient
4. Polypharmacy was found in 50% of cases.

Some examples to demonstrate the irrational prescriptions are:

a. A 35 year old man has a history of yellowish purulent urethral discharge for two days. Gram staining showed evidence of gram negative diplococci. The treatment given was:

Tab. Cephalexin 500 mg 8 hourly x 5 days

From the case history it is very clear that it was a gonococcal infection. Cephalexin belongs to first generation Cephalosporins, which have very weak action against gram-negative strains. So this is an irrational prescription.

b. Combination of NSAIDS with muscle relaxants

This combination is irrational, because NSAIDS reduce body temperature causing sweating and heat dissipation. Muscle relaxants also reduce body temperature due to their anticholinergic properties. Hence the combination of these can result in dangerous reduction of body temperature.

c. Combination of NSAIDS

Advertisements like 'Ibuprofen for pain and Paracetamol for fever' are seen frequently. The combination is irrational because synergism is not seen between these two drugs which act on the same enzyme system. It merely adds to the adverse reactions and cost of treatment.

III. Manufacturers

- Production of poor quality medicines
- Irrational combinations
- Neglected ethical issues

IV. Government

- Lack of stringent laws
- Inappropriate licensing of drugs

Irrational use of drugs leads to decrease in the quality of medicines leading to increased mortality and morbidity, wastage of limited financial resources, increased incidence of adverse drug reactions and drug resistance.

Fixed dose combinations in India

Combination products also known as fixed dose combinations (FDC's) are combinations of two or more active drugs present in a dosage form. The Food and Drug Administration, USA defines a combination product as *"a product composed of any combination of a drug and a device, or a biological product and a device, or a drug and a biological product, or a drug, device, and a biological product"*[4].

The FDCs marketed in India are mostly irrational. Some of the commonly prescribed drug combinations in India are:

- Nimesulide and Paracetamol combination for many paediatric use[5]. This combination doesn't give any added advantage, other than the cost and adverse reactions.
- The rampant use of quinolones and nitroimidazoles (examples: Norfloxacin + Metronidazole, Ciprofloxacin + Tinidazole, Ofloxacin + Ornidazole) for gastrointestinal, pelvic and dental infections. These combinations don't have any supportive scientific data[6,7].

Promotion of rational drug use

- Standardizing diagnostic and treatment protocols will help the doctors to reduce the number of drugs prescribed and offer optimized treatment plan
- Educational approaches like conducting CMEs, training programmes, group discussions, seminars and workshops within the scientific community
- Creating social awareness by the mass media communication and distribution of printed education material
- Self monitored prescription practice by doctors to avoid polypharmacy
- Intervention by regulatory authorities like the FDA and DCI (Drug controller of India)
- Promotion of the Essential drug concept

Conclusion

The effective interventions for improving rational use of drugs should come from all the stakeholders. There is need for a political will from decision makers so that these interventions can be implemented countrywide with the same zeal and fervor. The steps taken in this direction will be helpful to reduce morbidity and mortality associated with the irrational drug use. It will improve the utilization of the scarce financial resources, leading to improved availability of appropriate drugs at affordable prices.

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✪ TECHNICAL REPORT

Impact of Diagnostic Virology on Health care in the 21st century

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Introduction

In May 1993, an outbreak of an unexplained pulmonary illness occurred in the southwestern part of the US. A young, physically fit Navajo man suffering from shortness of breath was rushed to a hospital in New Mexico and died soon after. Medical personnel reviewing the case discovered that the man's fiancée had died a few days before with similar symptoms. Within a month of the appearance of the first case of this new clinical syndrome, the etiological agent was identified as a previously undescribed hantavirus serotype, *Sin Nombre virus* (SNV). In perspective, it took several decades for the first hantavirus serotype, *Hantaan virus* (HTNV), to be isolated, whereas the SNV was identified, isolated and characterized within a matter of weeks. Availability of sophisticated serological and molecular diagnostics helped investigators fish for the etiological viral agent[1,2].

With the emergence of new viral diseases in the past decade diagnostic virology has assumed great importance in patient management and disease surveillance, even in the absence of appropriate therapeutic and prophylactic options.

Virology - A young science

Virology developed as a science only after the successful isolation of polioviruses in cell culture by Enders and colleagues in 1949[3]. Approximately 50 new infectious disease agents have been identified in the last 40 years, majority of them being viral in origin[4]. Their identification and characterization reflects scientific advances in diagnostic microbiology.

The Indian scenario

In India, there are very few diagnostic virology laboratories. Many of the viral infections, like measles, rubella, dengue, to mention a few, are clinically diagnosed without laboratory confirmation. In addition there are many misconceptions regarding viral diagnostics. Many clinicians believe identification is useless as there is no treatment for most viral infections. Additionally, viral diagnostic assays are rumored to be slow and expensive.

About 67% of around 30,000 hospitals in India are in the private health sector, and they account for approximately 790 million users, compared to 290 million users of the public sector[5,6]. Only a very small percentage of the population has some kind of health insurance and the out-of-pocket spending for health care in India is among the highest in the world[7,8]. Therefore most patients are reluctant to pay for tests in case of self-limiting viral infections. Fear of positive results and distrust of the testing systems are other reasons for their unwillingness to undergo testing. Viral infections thus remain undiagnosed and at times of clinical uncertainty the patient seems satisfied with *"It's probably a virus".*

In a study from China, done over a eleven year period, accuracy of clinical diagnoses of measles was only 40% while that for rubella was 100%[9]. Certain clinical syndromes and results of routine laboratory tests are very nonspecific and a clinical diagnosis alone may not suffice. Furthermore, if the specific viral etiologies are not confirmed by laboratory testing, the true incidence of viral infections in a particular geographical region is difficult to determine.

Many viruses cause different clinical syndromes in different parts of the world. While the SNV causes pulmonary distress in the Americas, HTNV, causes renal disease in Asia and Europe[10]. Accurate laboratory diagnosis helps ensure appropriate patient management avoiding unnecessary antibiotic use, thereby reducing emergence of antibiotic

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resistance. Most of the available antivirals have a narrow spectrum of activity and correct identification of the viral agent is essential. Viral identification helps epidemiological monitoring; during outbreaks it serves to institute prompt preventive public health measures. Overall, it reduces wastage of meagre health resources.

Diagnostic Virology today offers sophisticated serological and molecular assays with good performance indices and shorter turn around time.

Conclusion

World over, emerging viral infections are a cause of concern for public health authorities. It is impossible to predict the emergence of viruses. The virus laboratory service has to recognize the needs of the medical community and provide cost effective, rapid, reliable diagnostic techniques in the battle against these invisible invaders.

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✪ QUIZ

Radiological spotters in Paediatrics

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Question:

Spot the diagnosis from the Radiological appearance:

Figure 1: CT head of a three month old baby. The only complaint was a head tilt noticed by the parents.

Figure 2: The eight month old baby presented with global developmental delay.

Figure 3: CT head of an eight year old boy with seizure disorder and facial naevus.

Figure 4: A six year old girl from New Delhi presenting with a focal seizure.

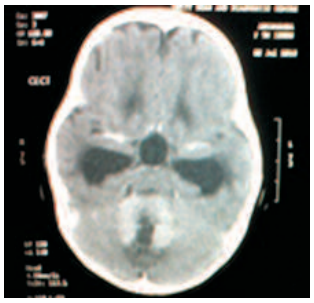

Fig. 1

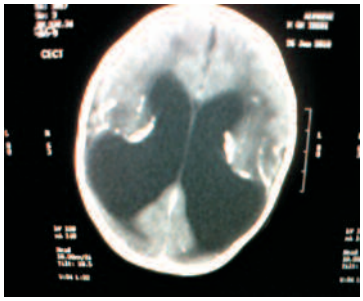

Fig. 2

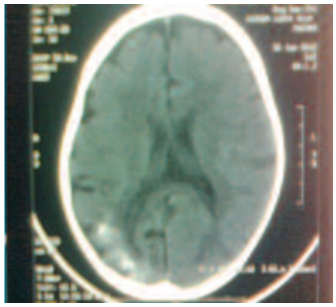

Fig. 3

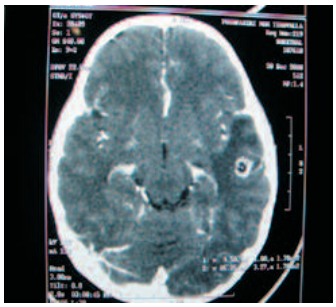

Fig. 4

Answers:

Figure 1: Posterior fossa tumour; an unusal clinico-radiological presentation.
Figure 2:The widespread intracerebral calcifications with the gross hydrocephalus suggest intrauterine infection, most probably toxoplasmosis. The mother had a history of fever with rashes during the first trimester of pregnancy.

Figure 3: Probably an easy radiological picture to diagnose. '*Rail track calcification*' characteristic of *Sturge Weber syndrome* (port wine facial naevus from birth, most commonly in the area of distribution of ophthalmic division of trigeminal nerve, associated with cerebral calcifications which develop during childhood; may be associated with epilepsy and contralateral hemiplegia as well)

Figure 4: The '*ring enhancement*' is characteristic of Neurocysticercosis! A close differential of the radiological appearance is tuberculoma. She responded to treatment with Albendazole.

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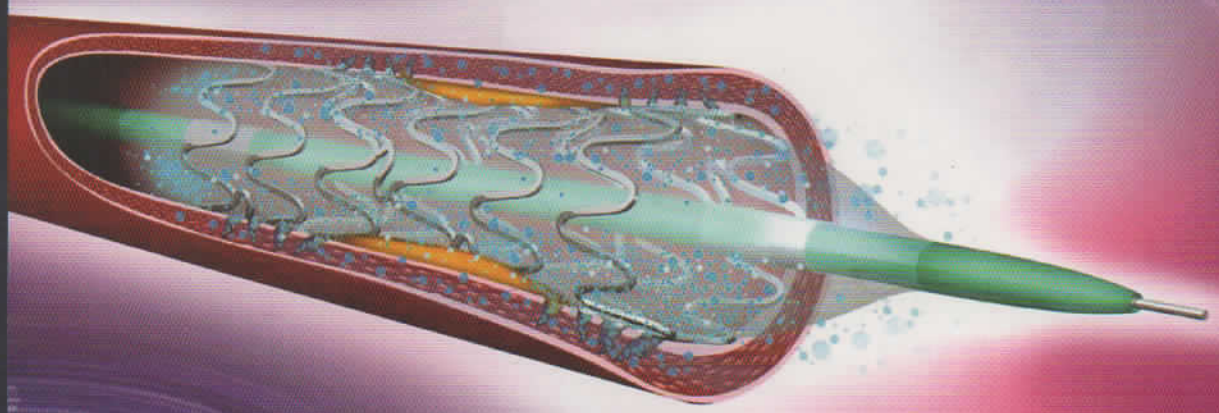

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