ISSN 0379-038X
eISSN 2454-5635

Annals of the National Academy of Medical Sciences (India)

Official Publication of National Academy of Medical Sciences (India)
under the Aegis of Ministry of Health and Family Welfare, Govt. of India

Number 2 • Volume 55 • Pages 63-116 • April 2019

OPEN ACCESS

Thieme

Ann Natl Acad Med Sci (India)

Volume 55 • Number 2 • Pages 63–116 • April 2019

ISSN 0379-038X
eISSN 2454-5635

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Annals of the National Academy of Medical Sciences (India) is published 4 times a year in January, April, July, and October by Thieme Medical and Scientific Publishers Private Limited, A — 12, Second Floor, Sector - 2, Noida - 201301, Uttar Pradesh, India. Tel: +91-120-4556600, Fax: +91-120-455-6649.

Subscription: Open access journals available online for free at http://open.thieme.com.

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Annals of the National Academy of Medical Sciences (India) is indexed in DOAJ. Thieme Medical Publishers is a member of the CrossRef initiative.

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Typesetting: DiTech Process Solutions Pvt. Ltd. Mumbai, India

Printing and Binding: Avantika Printers Pvt. Ltd.

Printed in India

Volume 55, Number 2/2019

Annals of the National Academy of Medical Sciences (India)

Thieme
Delhi • Stuttgart • New York • Rio de Janeiro
Thieme Medical and Scientific Publishers Private Limited
A - 12, Second Floor, Sector - 2, Noida - 201301
Uttar Pradesh, India
Tel: +91 - 120-4556600

online www.thieme-connect.com/products

Editorial

Turning Point in the Journey of *Annals of the National Academy of Medical Sciences (India)*

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Ann Natl Acad Med Sci (India) 2019;55:63–64

Deep N. Srivastava

It is indeed a matter of pride for the Academy as its official journal *Annals of the National Academy of Medical Sciences (India)* is venturing into a newly chartered path of a long journey for good. The main aim of a journal is to provide a platform to biomedical scientists and researchers from different fields. It helps in contributing toward the dissemination of health care information at the national and international levels. With this new venture, we hope to take the academic endeavors of publication of the journal to a global level.

National Academy of Medical Sciences (India) was established on April 21, 1961 as a registered society, the "Indian Academy of Medical Sciences" under the Societies Registration Act XXI of 1860, with the objective of promoting the growth of medical sciences. It was inaugurated on December 19, 1961, New Delhi, by Pandit Jawaharlal Nehru, the first Prime Minister of India. The Academy was renamed as "National Academy of Medical Sciences (India)" on November 16, 1976, on the recommendations of a Working Group, set up by the Government of India. The National Academy of Medical Sciences (India) is a unique institution that fosters and utilizes academic excellence as its resource to meet the medical and social goals of the country.

Over the years, the Academy has recognized the outstanding achievements of Indian scientists in the field of medicine and allied sciences and conferred Fellowships and Memberships. Fellows and members are selected through a peer-review process that involves screening by the Advisory Panel of Experts and the Credential Committee elected by the Council and Fellows through voting.

The Academy also elects very eminent persons as Honorary Fellows. The list of eminent persons who have been conferred Honorary Fellowship of the Academy since inception includes Pandit Jawaharlal Nehru, Dr. BC Roy, Maj. Gen. SL Bhatia, Col. RN Chopra, Dr. HM Lazarus, Dr. Jivaraj N Mehta, Dr. AC Ukil, Dr. A. Lakshamanswami Mudaliar, Dr. NA Purandare, Maj. Gen. SS Sokey, Dr. Sushila Nayar, Smt. Indira Gandhi, Dr. VTH Gunaratne, Dr. Karan Singh, Dr. Ihsan Dogramaci, Dr. FC Robbins, Dr. U Ko Ko, Dr. Dharmendra, Dr. PK Sethi, Shri PV Narasimha Rao, Prof. Rolf Luft, and Dr. CP Thakur; all luminaries of medical, biomedical, and social fields.

The Academy has been fortunate to have very eminent medical persons, namely, Drs. VR Khanolkar (the first President), CG Pandit, KL Wig, RV Rajam, AK Basu, S Padmavati, PN Chhuttani, BK Anand, B Ramamurthi, BN Sinha, HD Tandon, RK Gandhi, P Siva Reddy, JS Bajaj, Snehalata Deshmukh, BK Sharma, Mathangi Ramakrishnan, NK Ganguly, Hari Gautam, PK Dave, Prema Ramachandran, KK Talwar, CS Bhaskaran, and Mukund S Joshi, as its Presidents.

A special mention is required for Dr. APJ Abdul Kalam, the former President of India, who is considered a scientist par excellence for his contribution to Missile and Rocket technologies. He was a distinguished elected Fellow of the National Academy of Medical Sciences (India) for his unique health care contribution by providing the metal alloy used in missile technology and designing crutches for small children with special needs. Earlier, a 7-year-old child who found it difficult to walk with a 7-kg steel crutch started running after using the crutches designed using Dr. Kalam's metal alloy having 80 times more strength than steel but weighing less than 1.5 kg. This was a unique contribution of Dr. Kalam whose vision made use of the missile alloy for the welfare of children with special walking needs.

This is the second issue of 2019 published by our new collaboration with the world-reputed Thieme Medical and Scientific Publishers. It would be refreshing for the readers to go through the history of the journal. The *Annals of the National Academy of Medical Sciences (India)* has a long journey dating back to 1964 when the first issue was published. The nomenclature of

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DOI https://doi.org/10.1055/s-0039-1698612
ISSN 0379-038X.

the journal at that time was *The Annals of the Indian Academy of Medical Sciences* after the name of the academy. Henceforth, as the academy was renamed from Indian Academy of Medical Sciences (IAMS) to National Academy of Medical Sciences (India) in November 1976, the journal was also renamed as *The Annals of the National Academy of Medical Sciences (India)*.

One of the goals of National Academy of Medical Sciences (India) is to promote excellence in medical/biomedical/health science education and improve public health. Therefore, our journal acts as a unique multipurpose platform that helps the Academy in subserving its various objectives. The journal caters to both grass root level research and latest updates in medical sciences and technologies. It is an exclusive journal as it has several multispecialty domains and caters to all clinical and paraclinical specialties with cutting-edge research to disseminate knowledge to all and everyone who wants to seek and improve global health.

Different issues of the journal have been getting published online since 2013 and past issues are available since 2005 onward on the website of National Academy of Medical Sciences (India). The past issues from 1964 will be made online in a phased manner. Also, the print copies of these are available at the National Academy of Medical Sciences (India) office and can be obtained on request.

The Editorial Board is constituted by the Council of National Academy of Medical Sciences (India). The council plans to promote international contribution as dissemination of knowledge knows no boundaries. Thieme Medical and Scientific Publishers is an award-winning international medical and science publisher serving professionals for more than 125 years and National Academy of Medical Sciences (India) has full faith that the *Annals of the National Academy of Medical Sciences (India)* will flourish with its new facelift and achieve its goal of global presence. We hope the readers would whole-heartedly contribute to the growth of the journal.

Conflict of Interest
None declared.

Acknowledgments
The help rendered by Dr. Shilpa Sharma, MNAMS, Associate Professor, Department of Pediatric Surgery, AIIMS, New Delhi and Dr. K.K. Sharma by way of providing significant inputs in preparing this editorial is highly appreciated and acknowledged.

Smoking and Tobacco Use: Ill Effects on Reproductive, Maternal, Newborn, Child Health, and Adolescent (RMNCHA) Program—A Review

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Ann Natl Acad Med Sci (India) 2019;55:65–73

Abstract

Most people are aware that tobacco causes cancer, heart disease, chronic obstructive pulmonary disease, and major health problems, leading to high morbidity and mortality; however, many are not aware of its ill effects on the reproductive health of men and women as well as their children. This article has summarized the current research evidence from literature search to date, including prevalence of tobacco use, types of tobacco use, its effects on male and female fertility, pregnancy and their progeny in utero, neonatal period, childhood, adolescence, and subsequent well-being, with both active and passive smoking and smokeless tobacco use. Although antitobacco campaigns show horrifying visuals linked to tobacco use, not much progress has been made in controlling its use. Publicizing these harmful effects on pregnancy and progeny, making public aware, screening women coming for infertility or antenatal care on any form of tobacco use, and helping them to quit tobacco use may help the National Tobacco Control program, as parents are more concerned if they learn that there is harm to their fertility and progeny. Indirectly, it will help to improve reproductive, maternal, neonatal, child, and adolescent health.

Keywords

- smoking
- reproductive health
- fertility
- maternal health
- perinatal outcome
- miscarriage
- smokeless tobacco use
- pregnancy
- passive smoking

Introduction

Globally, rates of smoking and tobacco use among women are increasing, whereas smoking rates in men show a slow decline. The use of tobacco in middle- and low-income countries is rising and is usually linked to low-income and low-educational status.[1] India is increasingly facing a double burden of disease, and the burden attributed to noncommunicable diseases (NCDs) is growing. Tobacco use is identified as a major NCD behavioral risk factor contributing to several chronic diseases, including cancer, lung diseases, and cardiovascular diseases. India, along with other countries, has endorsed the target of a 25% reduction in premature mortality from NCDs by 2025, and 30% reduction in tobacco use will significantly contribute to achieve this goal.

The use of tobacco in any form, including exposure to second-hand smoke (SHS), adversely affects the functioning of most organ systems of our body. Tobacco use has harmful effects on women through *all* stages of their lives, starting from childhood through adolescence and reproductive life, extending even into the postmenopausal decades. Most people are aware of the ill effects of tobacco such as respiratory, coronary, and vascular disease, chronic obstructive lung disease, and several types of cancers. However, the adverse effects on reproductive health including increased risk of fetal loss and higher incidence of preterm and low birth babies are rarely publicized. This article reviews the ill effects of smoking and tobacco use in the context of the Government of India Reproductive, Maternal, Newborn, Child Health, and Adolescent (RMNCHA) program.

Materials and Methods

A literature search was performed in PubMed and Medline using key terms such as "tobacco use," "smoking and reproductive health," "tobacco and pregnancy," "tobacco and

DOI https://doi.org/10.1055/s-0039-1694071
ISSN 0379-038X.

neonatal outcome," "exposure to passive smoking during pregnancy," "tobacco and child and adolescent health." All research articles, observational and epidemiological studies, systematic reviews, and meta-analyses focusing on the ill effects of tobacco use in any form on reproductive health have been reviewed, and the observations have been categorized into specific areas to enable the reader to have a comprehensive overview of this issue. As research in this field is limited and a vast range of reproductive health issues have been covered, it is not possible to carry out a systematic review. All relevant literature published on this issue has been analyzed.

Results

There are several epidemiological studies published on the ill effects of tobacco use on reproductive health from several countries including India. Besides, some systematic reviews and prospective cohort studies have also evaluated the effect on pregnancy and its outcome. Few research papers have analyzed the adverse effects of tobacco at a molecular level. After reviewing epidemiology of tobacco use and forms of tobacco use globally and in India, the results have been categorized under specific subheadings, focusing on the ill effects on the reproductive health of women with fertility issues, influence on pregnancy and its outcome, problems in neonates, infants, children, and adolescents, and well-being during adult life due to direct and indirect tobacco exposure in utero.

Epidemiology of Tobacco Use in Women

Despite the evidence of the negative effects of tobacco use, the centers for Disease Control and Prevention (CDC) in the United States reports that 18% of women older than 18 years smoked cigarettes in 2009.[2] This rate of smoking has remained largely unchanged over the past 5 years, thus falling short of the Healthy People 2010 goal of a smoking rate of 12% or less.[2] More than 80% of "current" smokers start before age 18, and lower levels of education and economically backwardness increase the prevalence of tobacco use in women.

There is a paucity of epidemiological data on women in developing countries. Nonetheless, numerous surveys worldwide and in India show a greater prevalence of tobacco use among the less educated and illiterate. In a large population-based study in Mumbai,[3] the odds ratios (ORs) for any kind of tobacco use among the illiterate as compared with the college-educated were 7.4 for males and 20.3 for females after adjusting for age and occupation. Overall, school dropouts are more likely to take to tobacco use in childhood and adolescence.

As per the Global Adult Tobacco Survey (GATS), India, 2010, India has alarmingly high rates of tobacco consumption.[4] Almost 275 million Indian adults, nearly 35% of the population, consume some form of tobacco. The key findings of GATS highlight that 20.3% of adult women use tobacco products and more than 90% women tobacco users consume smokeless tobacco (a large number of these users are in the reproductive age group). The average age at initiation of tobacco use was 17.8 years, with 25.8% of females starting tobacco use before the age of 15 years. Besides the use of smokeless tobacco, exposure to passive smoking is very common in India. Currently, the tobacco industry is trying to target and attract women aggressively into tobacco use by projecting smoking as something modern and fashionable. Even antitobacco lobbies give a lot of emphasis on curbing tobacco use for preventing lung and oral cancer, and very little attention is being paid to its ill effects on reproductive health women and their progenies.

Different Forms of Tobacco Use

The most common form of tobacco addiction is smoking. Cigarettes are very popular and a glamorized form of tobacco use in most countries including India. Hand-rolled "bidis" are also popular among women of our country, especially those who are illiterate with low socioeconomic status. In recent years, tobacco products have changed, and several others have been developed or are gaining popularity. There are many flavors of cigarettes, cigars, and other forms of tobacco that are available for sale. Menthol cigarettes increase the likelihood and degree of nicotine addiction in new smokers and make smoking cessation more difficult.[5] The more recent forms of smoking alternatives include a gel strip impregnated with nicotine that melts on the tongue and an electronic or e-cigarette, a battery-powered device that heats cartridges of liquid containing nicotine to create a mist, which users inhale.

Smokeless tobacco products are mistakenly believed to be a safer and may be a more convenient alternative to cigarettes where smoking is prohibited. In India, various types of chewing tobacco products and common forms of smokeless tobacco use are paan with tobacco, bajjar, gudhaku, mishri, and laldantmanjan and creamy snuff used as dentifrice for cleaning teeth. One form of smokeless tobacco popular with young women is "snus," a flavored self-contained tobacco pouch that is placed between the cheek and gum and does not require spitting.

Use of oral snuff and smoking tobacco with a water pipe (hookahs and chilim) are some other forms of tobacco use seen among the rural Indians. Hookahs, or tobacco water pipes, are popular among youth or young adults. When using a hookah, inhalation is usually deeper and smoking sessions are longer than with a typical cigarette. This leads to higher concentration of toxins after hookah smoking compared with cigarette smoking.[6]

Many Indian women are also involved in tobacco farming or "bidi" rolling. Additionally, there may be others who are employed in cigarette manufacturing companies. These are examples of occupational exposure to tobacco. Most modern cities have too many vehicles on road emitting smoke. The air pollution is yet another manner in which women can be exposed to health hazards.

"Passive smoking" or exposure to SHS is another way a woman may be at risk even when she herself does not smoke, as husband or other relatives smoke in her vicinity, with some of them heavily.

Ill Effects of Tobacco Use on Reproductive Health

Tobacco smoking has a negative influence on female (as well male) fertility and is even known to cause health issues for postmenopausal women, such as osteoporosis.

Smoking and Fertility

It is clearly established that smoking can have a negative impact on female fertility. Women who smoke take longer to conceive than women who do not smoke.[7] The greater the quantity of cigarette smoked, the longer a woman is likely to take to achieve pregnancy.[8] It is suggested that tobacco consumption affects uterine receptivity; this effect is more likely with heavy smokers.[9] Interestingly, even comparatively low levels of smoking do seem to have a significant impact on female fertility. There is also a higher rate of ectopic pregnancies in smokers.[10]

There is evidence to suggest that smoking reduces the success rates of fertility treatment.[11] Women undergoing assisted reproductive technology (ART) treatment demonstrate a significant negative effect associated with smoking.[12,13] In a study evaluating 200 in vitro fertilization (IVF)/intracytoplasmic sperm injection cycles, the endometrial thickness in smoking patients was significantly less than nonsmoking patients.[14]

There have been reports of substantial reduction (nearly 50%) in implantation rates among smokers compared with nonsmokers.[15] A study involving IVF cycles with oocyte donors showed that ovarian response was significantly reduced in donors who smoked. However, the oocyte quality, pregnancy rate, and live birth rates were not affected by smoking.[16] A dysregulation of reproductive and hormonal systems caused by maternal smoking reduces the probability of pregnancy in both healthy women and those undergoing ART treatment.[17]

Smoking in men results in erectile dysfunction, lower sperm quality, and decreased testosterone levels, thus lowering the chances of pregnancy. Some of the early reports suggest that smoking during pregnancy has an impact on protamine, a protein essential in sperm production that can lead to fertility problems.[18] Men who smoke have lower sperm count, higher proportion of malformed sperms, and reduced sperm motility.[19] A meta-analysis of studies published since 1980 found that 40 to 80% of current smokers were impotent compared with 28% men in general population.[20]

Furthermore, a growing body of research suggests that maternal smoking may have a negative impact on the fertility of both female and male offspring.[21,22] Smoking during pregnancy reduces the number of germ cells and somatic cells that form in the developing fetus.[23]

Ill Effects on Maternal Health

Smoking during Pregnancy

In the United Kingdom, by March 2012, the proportion of women smoking at the time of delivery was 13%. This equates to approximately 83,000 infants born to smoking mothers each year.[24] The 2010 Infant Feeding Survey also reports that nearly 26% of mothers smoked in the 12 months before or during their pregnancy. These figures are down from 33% in 2005.[25] Nearly one (54%) of two women who smoked before pregnancy managed to stop once they became pregnant. But sadly, 12% (one out of eight) mothers-to-be continued to smoke throughout their pregnancy. U.S. data from 27 states by the Pregnancy Risk Assessment and Monitoring System[26] shows that ~10.7% of women reported smoking during the last 3 months of pregnancy; however, of women who smoked 3 months before pregnancy, 54% (one out of two) quit *during* pregnancy, though 44% relapsed to smoking again within 6 months after delivery.

In contrast, a significant fall was noticed in England, with only 14% of mothers reporting to be smoking at delivery in England in 2010. Smoking rates, though, vary significantly throughout the United Kingdom.[27] Those who were young (under the age of 20 years) at the time of conception were significantly more likely to smoke before or during pregnancy compared with older mothers (over the age of 35 years).[28]

Studies have shown that during pregnancy, women consciously reduce the use of tobacco products, alcohol, and caffeine,[29] though it may not make significant changes in their lifestyle or dietary pattern.[30]

In an editorial published in the Indian Journal of Medical Research,[31] it has been reported that Indian women generally do not smoke, though the situation may differ from state to state.[32] In India, reproductive health services do not address tobacco problem at all. But, the prevalence of smokeless tobacco use among women in India is quite high and recent data show that smokeless tobacco use during pregnancy[33,34] causes nearly the same adverse impact as tobacco smoking. A recent survey has shown that 23% women were exposed to SHS and 6.1% smoked during pregnancy.[35]

Adverse Impact on Pregnancy

According to a CDC report, the health hazards of smoking during pregnancy[26] include more likelihood of having a miscarriage or an abortion, problems with the placenta including placental abruption or placenta previa, prematurity and growth restriction in baby, stillbirth or longer stay in the hospital, risk of sudden infant death syndrome (SIDS or cot death), and certain birth defects such as a cleft lip or cleft palate. There is a recent report evaluating the effect of smoke extract on placental macrophage function,[36] which may be responsible for the adverse pregnancy outcome.

Miscarriage

Miscarriage is usually due to genetic defects induced by nicotine. Smoking may also alter the endometrium, making it more difficult for implantation to take place. There is some evidence that a father who smokes in excess of 20 cigarettes per day may increase the chances of miscarriage because his sperm may get damaged. Some studies indicate that men who smoke have a higher incidence of chromosomal abnormalities in their sperm.[19] Besides, exposure to SHS increases the abortion risk in mother.

A meta-analysis and a 2014 systematic review has reported an increased risk of miscarriage in active smokers, with risk increasing proportionately to the number of cigarettes smoked.[37] Early pregnancy loss is higher in women who

smoke and conceive following ART treatment.[38] A study from the University of Newcastle, New South Wales, Australia,[39] reported that current smokers and ex-smokers had an increased risk of miscarriages compared with women who had never smoked, with the highest risk occurring in heavy smokers (adjusted ORs for those smoking 20 or more cigarettes per day: 2.0).

Fetal Growth Restriction and Low Birth Weight

Maternal smoking is a major risk factor for low birth weight and small for -gestational age babies.[40-43] Swedish researchers have shown that babies born to women who smoke throughout their pregnancy are on average 162 to 226 g lighter than babies born to nonsmoking mothers.[44] This was also documented in research performed in Spain.[45] Another study reported that maternal smoking could be an independent risk factor in nearly 30% of growth-restricted neonates.[46] Researchers have documented that smoking during pregnancy leads to smaller head circumference and slower growth of the fetal head.[47-49]

Preterm Births

Recent research in Sweden examined the relationship between maternal smoking and preterm birth. It was found that compared with nonsmokers, moderate smokers had a twofold increase in risk of preterm labor; this risk increases to two and a half times among heavy smokers.[50] An experimental study of amnion exposed to cigarette smoke condensate has shown alteration in the retinoid pathway in amnion-derived epithelial cells. These play a significant role in pathophysiology of membrane rupture and preterm birth.[51] Mouse exposed to e-cigarette have shown altered DNA methylation and lung cytokine expression in their offspring, similar to mechanisms described for preterm birth.[52]

Congenital Malformations

There is an increased risk of congenital defects in the offspring of smokers.[53] The most commonly reported birth defects include orofacial clefts (cleft lip or cleft palate),[54-56] neural tube defects (defects of the defects of the brain, spine, or spinal cord),[57,58] cardiovascular/heart defects, musculoskeletal defects, limb reduction defects, missing/extra digits, clubfoot, craniosynostosis (fused skull bones that may affect brain growth), facial defects, eye defects, gastrointestinal defects, gastroschisis, anal atresia, hernia, and undescended testes.[59]

A meta-analysis of 23 articles showed a higher risk of neural tube defects in neonateswhen mothers smoked (OR: 1.05), and this further increased with exposure to passive smoking.[60] Evaluation of cryptorchidism in Down's syndrome has shown that 55% of these were children of mothers who smoked during pregnancy. Prevalence of cryptorchidism increased 3.89 times in children exposed to paternal smoke.[61]

Adverse Effects on Neonatal Health

Tobacco use during pregnancy not only harms in utero development of fetus but also continues to have adverse effects on neonate, infant, child and adolescents. Some of these in utero exposed babies continue to manifest some problems even during adult life.

Perinatal Mortality and Sudden Infant Death Syndrome

It is estimated that about one-third of all perinatal deaths including stillbirths and early neonatal deaths in the United Kingdom are caused by maternal smoking.[62,63] Evidence has demonstrated that babies born to women who smoke during pregnancy are around 40% more likely to die within the first 4 weeks of life than babies born to nonsmokers.[43,64] A meta-analysis of risk factors in 886,505 women from nine states of India showed that tobacco chewing women (% of total) had higher odds of having stillbirth (OR: 1.1; 95% confidence interval [CI]: 1.02–1.21) after excluding other confounding factors.[65] Lessons learned from epidemiological and experimental animal model studies confirm these observations.[66]

More than one-quarter of the risk of death due to SIDS is attributable to smoking during pregnancy and exposure to SHS, particularly in the home.[67,68] McDonnell-Naughton et al report that the risk of cot death has trebled in infants whose mothers smoke both during and after pregnancy.[69] Postnatal parental smoking is cited as an important risk factor for SIDS. Indeed, the greater the number of cigarettes smoked, the higher the risk of SIDS.[70] It is likely that nicotine from tobacco smoke (including its derivatives) easily reach the cerebrospinal fluid in the fetus to cause ependymal damage (the lining providing a protective barrier and filtration system separating the brain from cerebrospinal fluid). The best way to reduce the risk of SIDS or cot death is to maintain a smoke-free home and vehicle at all times.[71]

Smoking and Breastfeeding

Longer periods of abstinence from smoking are linked to better initiation of breastfeeding. Women who have quit smoking for at least a month are more likely to initiate breastfeeding.[72] Additionally, women who quit smoking tend to continue breastfeeding for a longer period of time than those who continue to smoke.[73] Indeed, breastfeeding is still recommended by the National Health Service and the American Academy of Pediatrics, among others, because of its beneficial effects on the baby, even if the mother continues to smoke. It is important therefore that the health care professionals combine smoking cessation and relapse-prevention advice with lactation counseling in women who smoke to maximize success of smokers' efforts to initiate breastfeeding.

Adverse Effects on Child Health

Effects on Childhood Growth Development and Behavior

One study found that maternal smoking during pregnancy is linked to high fetal testosterone. This leads to an increased risk of autism, childhood attention deficit/hyperactivity disorder (ADHD), conduct disorder, and antisocial behavior.[74] Numerous other studies have demonstrated a link between maternal smoking and ADHD.[75,76] Data from a recent study also incriminate SHS in causing ADHD.[77]

A population-level study of Finnish children documented that the risk of psychiatric morbidity was significantly

higher among children of mothers who smoked during pregnancy.[78] Studies have found that smoking during pregnancy and exposure to SHS in early childhood were "quite strong" predictors of conduct problems, antisocial behavior, and crime later in life.[79] This finding is supported by other studies exploring the relationship between maternal smoking during pregnancy and behavior problems in childhood and adolescence,[80,81] including smoking (particularly among girls)[82] and other substance use.[83]

Maternal smoking has been associated with an increased risk of learning difficulties.[84] Prenatal exposure to environmental tobacco smoke in Chinese children has been associated with hyperactive behavior (OR: 1.51) compared with those born to nonexposed mothers. A meta-analysis of offspring with prenatal exposure to maternal smoking has shown a significant association with childhood ADHD.[85] Pre- and postnatal exposure to tobacco results in higher sleep problems in girls at 3 years of age.[86]

In an evaluation of scholastic achievements of offspring of mothers who smoked during pregnancy, childhood in 4th, 7th and 10th grade revealed 5 to 7% lower score compared with children of nonsmoking mothers after controlling for other factors affecting childhood performance.[87]

Ill Effects on Child Health

There is some evidence to suggest that pre- and postnatal SHS contributes to insulin resistance in children.[88] There is strong evidence that childhood obesity can be related to smoking during pregnancy.[89] Two meta-analyses of 7 and 14 studies, respectively, found that for children of mothers who smoked during pregnancy, there was a 47 to 50% increase in the odds of being overweight in childhood.[90,91]

A meta-analysis of 11 articles analyzing 4,833 children with strabismus concluded that antenatal smoking during pregnancy is significantly associated with strabismus in offspring (OR: 1.46; 95% CI: 1.32–1.60) when mother smoked less than 10 cigarettes per day and increased further (OR: 1.79; 95% CI: 1.39–2.31) if she smoked more than 10 cigarettes per day.[92]

A meta-analysis evaluating 14 case–control studies involving 3,114 children with neuroblastoma showed an association with tobacco use during pregnancy (OR: 1.22).[93]

Adverse Effects on Adolescent Health

Adolescent Health Risks

Prenatal multidrug exposure including tobacco has been correlated with adolescent cognition and attention disorders and with higher rates of substance abuse.[94] An analysis of seven databases evaluating prenatal tobacco exposure and puberty timing observed that it decreases the age of menarche in girls.[95] Gestational tobacco exposure has also been associated with adolescent tobacco dependence and higher use of e-cigarettes.[96]

Late Manifestations in Adult Life

Both maternal smoking and paternal smoking have been associated with low sperm counts in the sons. Sons of smoking fathers have 51% lower sperm count.[97]

It is reported that exposure to cigarette smoke in early fetal developmental can result in certain epigenetic changes in the lungs of the offspring. These can then be transferred to following generations, resulting in adult onset of respiratory disease.[98] There is some evidence of an association between maternal smoking, early childhood exposure to SHS, and the development of emphysema in adulthood. The preceding findings suggest that the lungs may not recover completely from the effects of early life exposure, even when the offspring continues to be nonsmoker in adult life.[99,100]

Perinatal exposure to environmental tobacco smoke has been associated with altered DNA methylation in mice. This epigenetic finding could represent a potential biomarker for adult respiratory disease.[101] Another experiment exposing mice to e-cigarettes has shown altered DNA methylation and lung cytokine expression in their offspring.[52] This may be responsible for pulmonary dysfunction at a later age.

Several researchers have also found that adults exposed to tobacco smoke in utero had a more adverse cardiovascular disease risk profile.[102] Some evidence suggests that prenatal exposure to tobacco smoke may be associated with benign breast disease later in life.[103]

Passive Smoking and Pregnancy

Passive smoking is perhaps more relevant to Indian setting as the number of women smoking while pregnant is far less, with high exposure to SHS. However, SHS is associated with similar maternal and fetal risks as is active smoking. SHS exposure during pregnancy has been correlated with lower quality of life and higher incidence of postpartum depression in women, besides its ill effects already discussed.[104] According to a report from U.S. Surgeon General, second-hand tobacco smoke is a mixture of at least 4,000 chemical compounds,[105] many of which are likely to be reproductive toxins.[15] Nonsmoking women exposed to other people's tobacco smoke during pregnancy are more likely to have lower weight babies.[106,107]

Several other researchers have reported that nonsmoking women who are exposed to SHS are at an increased risk of infertility or have difficulty becoming pregnant,[108] giving birth prematurely of stillbirth,[109,110] spontaneous abortion,[111] and having a baby with congenital malformations. Additionally, some evidence suggests that female fertility can be damaged in utero if the woman's mother was exposed to SHS while pregnancy.[21] Exposure to SHS can also be damaging in terms of successful pregnancy outcomes for women undergoing IVF or other ART treatment.[10,112,113] ADHD has also been linked to SHS exposure in the home, in addition to maternal smoking during pregnancy.[114] Exposure to parental SHS in the home and vehicle is strongly associated with middle ear disease in children.[115] There is some evidence to suggest that prenatal and postnatal SHS may cause leukemia,[116] especially acute lymphoblastic leukemia.

It must be appreciated that research on the reproductive effects of SHS exposure is relatively new compared with that on the effects of active smoking. More epidemiologic research is likely to reveal additional negative health effects, as well as the mechanisms whereby they occur and the dose–response relationships involved.

Smoking and Oral Contraception

It is generally known that women using combined oral contraceptives are at an increased risk of heart disease. However, since the risk of heart disease in young women is low, the benefits of using the pill generally outweigh the risks for young women who do not smoke. This is not the same with women who smoke. In addition, pill users who smoke are also at a risk of venous thromboembolism and arterial thrombosis.[117-119] It is, therefore, important that all women who take the contraceptive pill be counseled against smoking and advised on the use of alternative method of contraception.

Smoking and Menopause

Women who smoke seem to attain menopause at an early age,[120] with the natural menopause occurring up to 2 years earlier in smokers. The likelihood of earlier menopause is related to the number of cigarettes smoked; those smoking more than 10 cigarettes a day have an increased risk of early menopause.[121] It must be emphasized that stopping smoking may lower the risk of early menopause. Research suggests that polycyclic aromatic hydrocarbons found in tobacco smoke can trigger premature egg cell death, which may, in turn, lead to earlier menopause.[122] Another study suggests that chemicals in tobacco smoke alter endocrine function, which, in turn, affects the release of pituitary hormones. This endocrine disruption is thought to contribute to adverse outcomes, including earlier menopause.[123]

Postmenopausal women who smoke have lower bone density than women who never smoked. Women who smoke have an increased risk of hip fracture compared with never smokers. Cigarette smoking also causes skin wrinkling that could make smokers appearance less attractive and prematurely old.

Conclusion

Smoking (or tobacco) seems to adversely impact the health of women in *all* stages of their life, starting from birth to senescence. There is a growing body of evidence that smoking causes "preventable" harm to women's health, with the ill effects being most profound during pregnancy and immediate puerperium.

The adverse impact of smoking is linked to the number of years of smoking and number of cigarettes smoked each day, and when done during pregnancy, it has a far-reaching adverse impact on the health of her progeny. In India, passive smoking or SHS is also very important.

Knowing the profound ill effects of tobacco, it is worth spending large sums of money on helping people stay away from tobacco addiction. Smoking cessation is possible with the right support and help from health care professionals along with government agencies and self-help groups. Pregnancy and childbirth provide the best opportunity when women are most likely to be motivated to quit smoking (for the sake of the child). By dissuading people from the use of tobacco (in any form), we can prevent several illnesses and substantially reduce the overall disease burden. This translates into better health and improved quality of life for our citizens and would lead to huge savings in government expenditure. Thus, screening for smoking and tobacco use and measures to stop should be integral components of the RMNCHA program in India. Tobacco cessation training needs to be imparted to the care providers, and there is a need to discuss the synergistic role of tobacco control with the basic goal of reducing maternal and child mortality.

In light of the serious health consequences and the strong motivation of pregnant women to ensure the health of their newborns, efforts to help pregnant women quit smoking (and to prevent postpartum relapse) should be accorded a high priority in public health programs focusing on women and children. A mechanism needs to be developed to integrate tobacco control prevalence indicators and cessation advice in the health care delivery system for women.

Conflict of Interest
None declared.

Acknowledgments
A national consultation on tobacco use and its implications on the health of women and their children was organized by the author at Fortis Memorial Research Institute in collaboration with World Health Organization, Ministry of Health and Family Welfare (Government of India), and Indian Council of Medical Research on World No Tobacco Day in 2013. The author is grateful to all the resource persons who participated in the consultation.

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Multiparametric Magnetic Resonance Imaging of the Prostate: An Update

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Ann Natl Acad Med Sci (India) 2019;55:74–83

Abstract

Multiparametric magnetic resonance imaging (mp-MRI) has emerged as an important tool for the detection and characterization of prostatic lesions. It now plays a quintessential role in the surveillance, diagnosis, and staging of prostate cancer (PCa), as well as for the detection of local recurrence. As reliance on serum prostate-specific antigen has declined in the recent times, mp-MRI has emerged as the go-to tool for urologists all over the world. Hence, for the clinician, it has become necessary to be well versed with the technique, image interpretation, and fallacies of mp-MRI. Since mp-MRI has the advantage of better contrast resolution, combining PSMA PET (prostate-specific membrane antigen–positron emission tomography) with MRI could provide additional functional information. However, due to the absence of enough evidence supporting its routine use, mp-MRI still has the unsurpassed role in the initial diagnosis and local staging of PCa.

Keywords
- multiparametric MRI
- prostate cancer
- PIRADS

Introduction

Multiparametric magnetic resonance imaging (mp-MRI) has emerged as an important tool for the detection and characterization of prostatic lesions. It now plays a quintessential role in the surveillance, diagnosis, and staging of prostate cancer (PCa), as well as for the detection of local recurrence. As reliance on serum prostate-specific antigen (PSA) has declined in the recent times, mp-MRI (T2-weighted [T2W] images, diffusion-weighted imaging [DWI], dynamic contrast-enhanced [DCE] MRI, and magnetic resonance [MR] spectroscopy [MRS]) has emerged as the go-to tool for urologists all over the world. Hence as radiologists, it has become necessary to be well versed with the technique, image interpretation, and fallacies of mp-MRI. This review is aimed at providing a brief overview of prostatic MRI, its indications, and basics of sequences used, with emphasis on recent updates in MRI of the prostate.

PCa is one of the most commonly diagnosed malignancies in men. The age-adjusted incidence rate in India is 37 per 100,000 men per year.[1] Difficulty in accurate staging and prediction of disease progression has made the management of PCa a complex issue. Traditionally, urologists have relied on digital rectal examination (DRE), PSA levels, and transrectal ultrasound (TRUS) with sextant biopsy for the diagnosis of PCa.[2] MRI, in the present scenario, has become indispensable for not only staging of prostatic cancer but also for its surveillance, detection, and follow-up. Radiologists can be easily intimidated by prostate MRI examinations. Knowledge of glandular anatomy, the use and interpretation of various MRI sequences, and, finally, the reporting of correct findings is challenging for an amateur reader. Although the technical details of imaging protocols are beyond the scope of this paper, the standard imaging sequences that constitute multiparametric prostate imaging will be discussed along with their utility. The aim of this review is to discuss, in brief, the fundamental anatomy of the prostate and the techniques of mp-MRI and to provide a guide for the interpretation and reporting of mp-MRI scans.

Normal Anatomy of the Prostate

The prostate is grossly divided into three anatomical regions: the base, the midgland, and the apex. The base forms the

DOI https://doi.org/10.1055/s-0039-1694077
ISSN 0379-038X.

broad and superior most limit of the prostate and is located below the urinary bladder neck. The narrower apex rests below on the pelvic floor. Each anatomical region consists of a left side and a right side, thus dividing the prostate into six parts or sextants. Biopsy samples are obtained from each sextant, and this organization helps in clinic–radiologic–pathological correlation.

The anterior fibromuscular stroma, the transition zone (TZ), the central zone (CZ), and the outer peripheral zone (PZ) form the four histological zones.[3] The nonglandular anterior fibromuscular stroma may contribute to up to one-third of the prostatic mass. It may be replaced by glandular tissue in adenomatous enlargement of the prostate. However, it is rarely invaded by carcinoma. The TZ surrounds the urethra proximal to the verumontanum and contains 5% of the glandular tissue. It is the TZ that accounts for the increase in size of the prostate in benign prostatic hyperplasia (BPH) by increasing the percentage of the gland volume. It is estimated that only 20 to 30% of PCas originate in this zone. The CZ expands in a cone shape around the ejaculatory ducts to the base of the bladder and contains approximately 20% of the glandular tissue. Only 1 to 5% of adenocarcinomas arise in the CZ, although it may be infiltrated by tumors arising from the PZ. The PZ forms the bulk of the glandular tissue (70–80%), and 70 to 75% PCas arise from this zone.[4]

On T1-weighted (T1W) images, the entire prostate gland appears uniform with intermediate signal intensity (SI). Hence, the zonal anatomy of the prostate cannot be made out on T1W images.[2] The location and differences in SI on T2W images often help in distinguishing TZ from the CZ on MR images (►**Fig. 1**). The anterior fibromuscular stroma is seen as dark on both T1 and T2W images. The PZ, on the other hand, is bright on T2W images, having SI comparable to the adjacent periprostatic fat. It is bound by a T2 hypointense capsule. Both CZ and TZ tend to be of lower T2 SI than the PZ possibly because of more compact smooth muscle and lesser glandular elements. Age-related expansion of TZ seen in BPH, however, may result in compression and displacement of the CZ.[5]

The "prostate capsule," which is a thin, dark rim surrounding the prostate gland on T2W images, serves as an important landmark for the assessment of extraprostatic extension (EPE) of cancer. It is incomplete anteriorly and apically and contains an outer band of concentric fibromuscular tissue that is inseparable from the prostatic stroma. Thus, the prostate lacks a true capsule. The prostatic pseudocapsule (sometimes called "surgical capsule" when seen at enucleation of an adenoma) on T2W MRI, is a thin, dark rim at the interface of the TZ with the PZ, which appears so due to compressed prostate tissue.

The proximal urethra cannot be visualized on MR unless there is a Foley catheter in situ or a transurethral resection has been performed. The verumontanum appears as a T2 hyperintense structure in the midline posterior to the urethra. The vas deferens and seminal vesicles are best seen on axial and coronal images.[2]

The neurovascular bundles (NVBs) to the prostate are formed by the sympathetic and parasympathetic nerves that supply the corpora cavernosa and the closely associated arterial branches from the inferior vesicle artery. Together, these course posterolateral to the prostate bilaterally, at 5 and 7 o'clock positions. Small nerve branches that surround the prostate periphery and penetrate through the capsule at the apex and base form a potential route for the EPE of cancer. The NVBs are best seen on axial images.[2]

Indications for Prostate MRI

MRI has been used for the assessment of the prostate since the 1980s, when it was used largely for the staging of biopsy-proven prostate carcinoma. The locoregional spread of the disease was evaluated based on T1W and T2W pulse sequences, which helped describe the morphology of the prostate.[6]

In the recent times, however, mp-MRI has been developed to significantly improve the sensitivity and specificity of MRI for carcinoma prostate. mp-MRI integrates anatomical, functional, and physiological assessments using T2W images, DWI, dynamic contrast enhancement, and MR proton spectroscopy.

Consequently, prostate MRI is now being used for the detection of tumors and their localization and characterization and for the prognostication as well as assessment of suspected recurrent disease. It may even be employed for taking image-guided biopsies and targeted therapy.[7,8]

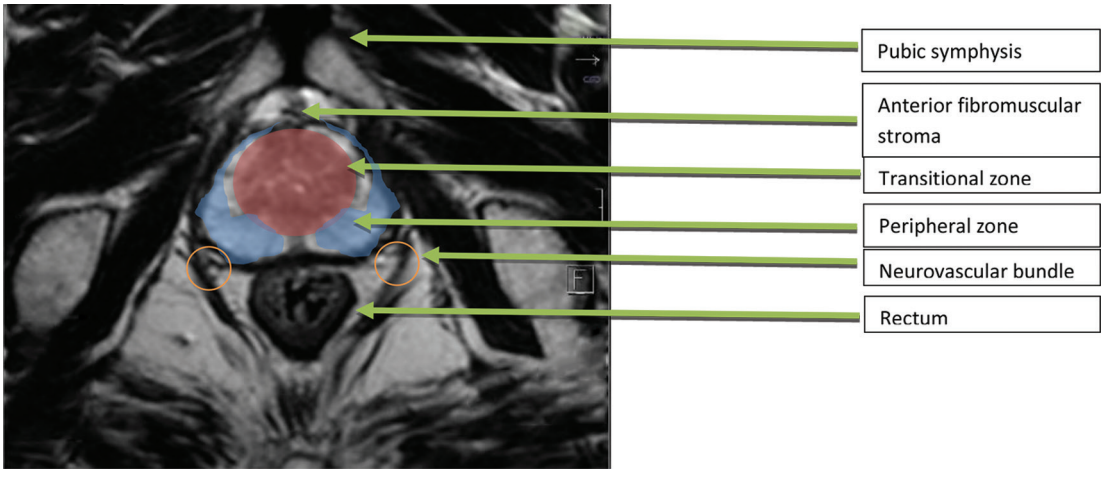

Fig. 1 Normal anatomy of the prostate.

The extensive use of mp-MRI, however, faced several impediments. The European Society of Urogenital Radiology (ESUR) drafted guidelines along with a scoring system to standardize its use. The scoring system is known as Prostate Imaging Reporting and Data System version 1 (PIRADS v1).[8] This effort generated interest in the use of mp-MRI for the prostate. Moreover, it provided validation and consistency to imaging findings, which encouraged widespread use. Nonetheless, the system had limitations in several clinical scenarios. To resolve the deficiencies, the American College of Radiology, the ESUR, and the AdMeTech Foundation improved upon PIRADS v1 in the form of PIRADS v2 (2015). PIRADS v2 is designed to "promote global standardization and diminish variation in the acquisition, interpretation, and reporting of prostate mp-MRI examinations."[6] It provides minimum acceptable technical parameters for performing a prostate mp-MRI and standardizing the terminology and content of radiology reports. The basic aim of PIRADS is to reduce the variability in imaging interpretation and to enhance communication between radiologists and the referring clinicians.

Despite the updated version, the limitation of use of PIRADS for the treatment of naïve prostate glands remains. Thus, its use for the detection of suspected recurrence or progression is not validated.

Clinical Considerations and Technical Specifications

Clinical Considerations

Timing of MRI following Prostate Biopsy

Hemorrhage and postbiopsy changes can possibly confound MRI interpretation. Hemorrhage appears as bright on the T1W images and is generally seen in the PZ or in the seminal vesicles following a TRUS-guided biopsy. Two general approaches can be followed to avoid this potential pitfall. Although hemorrhagic changes can persist for months following a biopsy, they generally resolve within 6 weeks. Hence, ideally, an MRI should be performed at least 6 weeks after a biopsy.[6] However, since waiting for 6 weeks may not always be feasible, an initial T1 sequence may be performed as a screening. If there is evidence of hemorrhage, the MRI may be postponed after discussion with the urologist. If postponing the MRI is not an option, it must be remembered that the possibility of finding a malignant lesion at the site of postbiopsy hemorrhage is low. In such a situation, it is imperative to rule out malignancy at locations other than those showing hemorrhagic change.[9]

Patient Preparation

The use of enema for rectal emptying is controversial. The presence of air/stool in the rectum can cause distortion of MR signal and compromise DWI quality. However, enemas also promote peristalsis, resulting in increased motion-related artifact. Antispasmodics such as glucagon and scopolamine can reduce these motion-related artifacts; however, their use must be weighed against the cost and possible adverse effects associated with their use.

Though there are no guidelines at present, evacuation of the rectum by the patient prior to the MRI generally obviates the need for enema.

If air is seen on the initial MR images, it may be worthwhile to perform the MRI with the patient in the prone position or to use a suction catheter for evacuation.[6]

Patient Information

As is repeatedly emphasized, knowledge of the patient's history and clinical findings is always beneficial while interpreting images. It is important to record the patient's recent serum PSA level and PSA history. If a biopsy has been performed, the results of the biopsy including the number and location of positive cores and corresponding Gleason scores are of immense value to the reporting radiologist.

Technical Specifications of Equipment

Three sequences are essential for a prostate mp-MRI according to the PIRADS v2. These include T2W, DWI, and DCE. The role of MRS is controversial, but we will still cover it in this review. Apart from being used for the confirmation and localization of clinically significant malignancy, mp-MRI also has the potential of being used as a screening modality. However, cost and time are the two limiting factors. As a corollary, the supervising radiologist should be vigilant about not including unnecessary sequences as it not only affects the patient compliance and acceptance but also reduces the machine throughput.

The field of view should be reduced to include the relevant structures only. However, at least one pulse sequence should include area up to the aortic bifurcation. This allows for the evaluation of pelvic nodes.[6]

Field Strength: 3T or 1.5T

With increasing field strength, there is a linear increase in the signal-to-noise ratio (SNR). Hence, employing a 3T magnetic field instead of a 1.5T one means that the spatial ratio and temporal resolution both can be increased. The downside is that increasing the field strength also increases power deposition, artifacts related to susceptibility, and signal heterogeneity. However, the advantages of 3T scanners over 1.5T significantly outweigh the disadvantages. PIRADS v2 recommends the use of 3T for prostate MRI. The only indication for using a 1.5T scanner is when a patient has an implant that is either compatible only with 1.5T or is in a location that could result in significant artifacts during imaging, such as a hip prosthesis.[6]

Endorectal Coils or Surface Coils

Endorectal coils (ERCs) offer the advantage of increased SNR with the obvious disadvantage of patient discomfort and poor acceptance apart from possible problems such as deformation of the gland and artifacts. The increased spatial resolution is especially advantageous while using lower SNR sequences such as DWI and high temporal resolution DCE. It also scores over external phased array radiofrequency (RF) coils in obese patients.[6]

At 1.5T, ERC was indispensable for obtaining high-resolution diagnostic quality imaging. However, at 3T, surface coils

can provide equally good quality imaging. Some of the 1.5T scanners that employ a relatively high number of external phased array coil elements and RF channels (e.g., 16 or more) may be capable of achieving adequate SNR in many patients without an ERC as multiple factors including receiver bandwidth, coil design, and efficiency of the RF chain.[6]

PIRADS v2 recommends optimization of protocols and coils to obtain the best possible image quality, taking into account the cost, availability, and patient preference. No specific recommendation has been made regarding the use of ERC/surface coils.

Computer-Aided Evaluation Technology

Computer-aided evaluation (CAE) can enhance lesion detection and discrimination performance of amateur radiologists who have little or no experience in reading prostate MRIs. However, CAE using specialized software or a dedicated workstation is not required for prostate mp-MRI interpretation.[6]

Multiparametric MRI

T1- and T2-Weighted Images

T1W images are obtained to detect the presence of hemorrhage within the prostate or seminal vesicles and to outline the anatomy of the region.

T2W imaging is the best imaging sequence to delineate the prostatic anatomy, for the detection and categorization of lesions, and for the EPE and nodal assessment.[10]

T2W imaging is the dominant sequence to be assessed in the TZ. Features of malignancy in the TZ are noncircumscribed, ill-defined, homogeneously hypointense lesions that have been variously described as erased charcoal or smudgy fingerprint appearance. Other features of malignancy include spiculated margins, lenticular shape, absence of a complete hypointense capsule, extension of the lesion into adjacent structures such as the urethral sphincter, and anterior fibromuscular stroma. Though no single feature is not diagnostic of malignancy, the likelihood of malignancy increases with the presence of more number of features.

TZ is composed of variable amounts of glandular (T2 hyperintense) and stromal (T2 hypointense) elements, and this makes the overall signal of the TZ heterogeneous. Hence, detection of malignancy is especially challenging. Areas where benign stromal elements predominate can mimic clinically significant malignancy.

In the PZ, clinically significant cancer tends to occur as a well-defined, round, focal hypointense lesion. However, mimics such as hemorrhage, prostatitis, glandular atrophy, and benign hyperplasia can mimic malignancy.

A relatively specific sign of malignancy is extension of the lesion across anatomical boundaries. T2W images can help discern extension of the lesion within the gland (across regional parts of the prostate) as well as into the seminal vesicles/adjacent fat and NVB.

Three-dimensional (3D) axial acquisition can help improve the spatial resolution with isotropic voxels. However, the soft tissue contrast and in-plane resolution tend to be inferior to routine 2D acquisition. At our institute, we do not routinely acquire 3D datasets.

Diffusion-Weighted Imaging

One sequence that has had a significant role in the increased use and popularity of mp-MRI is DWI. It is based on the principle of free, random motion of water molecules. DWI includes an apparent diffusion coefficient (ADC) map and high *b*-value images (►**Table 1**).

The ADC map is a representation of the ADC values of each voxel in the image. It uses two or more *b*-values and a monoexponential model of signal decay with increasing *b*-values to calculate ADC values. Clinically significant cancers have restricted diffusion as compared with normal tissue and appear hyperintense on high *b*-value images and hypointense on ADC maps. Quantitatively, ADC values correlate inversely with the tumor grade, and though attempts have been made to provide cutoffs for ADC values for predicting malignant lesions, there is considerable overlap between benign prostatic nodules and low- and high-grade malignant lesions. Though a threshold of 750 to 900 um^2/second has been suggested to differentiate benign from malignant prostatic lesions in the PZ, qualitative visual assessment remains the most commonly employed and used technique.

DWI of the prostate is unique. It uses high *b*-value images (>1,400 seconds/m^2) that are not routinely used in imaging of other body parts. DWI is highly sensitive to motion

Table 1 PIRADS v2 assessment for T2W image

Peripheral zone	
Score	**Lesion characteristics**
1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or noncircumscribed, rounded, moderate hypointensity Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to the prostate and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5 cm in greatest dimension or definite extraprostatic extension/invasive behavior
Transition zone	
Score	**Lesion characteristics**
1	Homogeneous intermediate signal intensity (normal)
2	Circumscribed hypointense or heterogeneous encapsulated nodule(s) (BPH)
3	Heterogeneous signal intensity with obscured margins, includes others that do not qualify as 2, 4, or 5
4	Lenticular or noncircumscribed, homogeneous, moderately hypointense, and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5 cm in greatest dimension or definite extraprostatic extension/invasive behavior

Abbreviations: BPH, benign prostatic hyperplasia; PIRADS, Prostate Imaging Reporting and Data System; T2W, T2-weighted.

and is a time-consuming imaging technique. As the *b*-value increases, the spatial resolution decreases. At such high *b*-values though, only the areas with restricted diffusion show signal and appear bright. This increases the conspicuity of lesions especially in the subcapsular location at the base and apex of the gland as well as adjacent to the anterior fibromuscular stroma.

High *b*-value images can be obtained in two ways: by directly acquiring a high *b*-value sequence (time consuming) or by extrapolating data acquired at lower *b*-values to create the ADC maps. The extrapolation time has two advantages: less time and less artifact. This is achieved by avoiding the longer echo times required to accommodate the strong gradient pulses required for higher *b*-value acquisitions.

If only two *b*-values can be acquired, the lower *b*-value should be set at 50 to 100 seconds/mm^2 and the higher *b*-value should be 800 to 1,000 seconds/mm^2. High *b*-value images (>1,400 seconds/mm^2) can be extrapolated. For more accurate ADC calculation and extrapolation of high *b*-value images, additional *b*-values may be obtained between 100 and 1,000 (►**Table 2**).

Dynamic Contrast-Enhanced MRI

DCE MRI involves acquisition of scans just before, during, and after contrast injection to study the enhancement characteristics of lesions. Rapid T1W gradient-echo scans are obtained every few seconds with injection of a bolus of gadolinium-based contrast. PCas show early enhancement compared with normal tissue with washout. However, prostate malignancy shows variable and heterogeneous contrast kinetics. Some tumors may show early washout, whereas others may show contrast retention. Enhancement is neither a sign of malignancy nor does the absence of enhancement exclude a diagnosis of prostate malignancy.

The importance of DCE lies in the fact that it can pick up small lesions, which may show focal early enhancement. Any small lesion showing focal early enhancement should be carefully looked at in the corresponding T2W images and DWI. However, its role in the characterization of lesions is limited and subordinate to T2W images and DWI.

Positive early enhancement can be compared with the adjacent normal prostatic tissue. It usually occurs within 10 seconds of appearance of contrast in the femoral artery.

Table 2 PIRADS v2 assessment for DWI

Score	Lesion characteristics
1	No abnormality on ADC and high *b*-value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high *b*-value DWI
4	Focal markedly hypointense on ADC and markedly hyperintense on high *b*-value DWI, <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5 cm in greatest dimension or definite extraprostatic extension/invasive behavior

Abbreviations: ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; PIRADS v2, Prostate Imaging Reporting and Data System Version 2.

Contrast enhancement for a lesion is reported as either positive or negative. Positive DCE refers to focal enhancement of a lesion that is earlier or simultaneous with enhancement of normal prostatic tissue and corroborating with findings on T2W images and/or DWI. Negative DCE is defined by the absence of early enhancement or diffuse enhancement not corresponding to a focal finding on T2 and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2W images.

Diffuse enhancement in the prostate is usually associated with prostatitis. Infiltrating malignancy may also show diffuse enhancement, but these lesions show corresponding signal changes on T2W images and DWI as well. At times, histologically sparse PCas are intermixed with benign prostatic tissues. These tumors tend to be occult on T2W images and DWI and may be apparent only on DCE. However, these are usually lower grade malignancies, and the enhancement may be due to concurrent prostatitis.

The easiest and the most commonly used technique for interpretation of DCE is direct visual assessment. The various DCE time points at each slice location are assessed either by manual scrolling or using cine mode. It is recommended to use fat suppression or subtraction technique to improve lesion pickup. Using a parametric map which color-codes enhancement features within a voxel (such as slope and peak) can also assist image interpretation. However, any suspicious finding on a parametric map or subtracted images should be confirmed on the source images.

Another technique used for the interpretation of dynamic contrast enhancement is plotting the SI of the lesion versus time: curve typing. However, given the heterogeneity in enhancement characteristics of PCa, this has not proven to be too useful. Perfusion parameters like K^{trans} (wash-in) and K_{ep} (washout) have been used to assist in diagnosis. As of now, not enough published literature is available to recommend the use of perfusion parameters for the diagnosis of prostate malignancy (►**Table 3**).

PIRADS V2 Reporting

PIRADS, like the already established BI-RADS, aims at standardizing assessment and reporting of mp-MRI for PCa. It uses a 5-point scale to categorize the probability of malignancy. The aim of PIRADS is to pick up all clinically significant malignancies while reducing unnecessary biopsies.

Clinically significant PCa has been defined as pathologically proven PCa with Gleason score ≥ 7 (including 3 + 4 with prominent but not predominant Gleason 4 component), volume ≥ 0.5 mL, and/or EPE.

The PIRADS assessment is based on a combination of T2W, DWI, and DCE findings, with the relative importance of these sequences differing according to the zone of the gland (►**Figs. 2–6**).

Biopsy should be considered for all PIRADS 4 and 5 lesions, whereas PIRADS 1 categorizes no-touch lesions. Lesions that are PIRADS 2 or 3 require correlation with PSA/DRE and other clinical details for their management. Depending on the clinical and laboratory findings as well as the local preferences

Table 3 Magnetic resonance imaging sequence parameters

	T2W	DWI	DCE
Sequence	TSE/FSE	Free-breathing spin-echo EPI with spectral fat saturation (TE ≤90 ms, TR ≥ 3,000 ms)	2D/3D T1 GRE sequence TR < 100 ms, TE < 5 ms
Plane of imaging	Axial, coronal, sagittal	Axial	Axial
Slice thickness	3 mm (no gap)	≤4 mm	3 mm (no gap)
FOV	12–20 cm (to encompass the entire prostate gland and seminal vesicles)	16–22 cm	Encompass the entire prostate gland and seminal vesicles
In-plane dimension	≤0.7 mm (phase) × ≤0.4 mm (frequency)	≤2.5 mm (phase and frequency)	≤2 × ≤2 mm
			Temporal resolution: ≤15 s (<7 s is preferred) Total observation time ≥2 min

Abbreviations: DCE, dynamic contrast enhancement**;** DWI, diffusion-weighted imaging; EPI, echo planar imaging; FOV, field of view; FSE, fast spin echo; GRE, gradient echo; T2W, T2-weighted; TE, echo time; TR, repetition time; TSE, turbo spin echo**.**

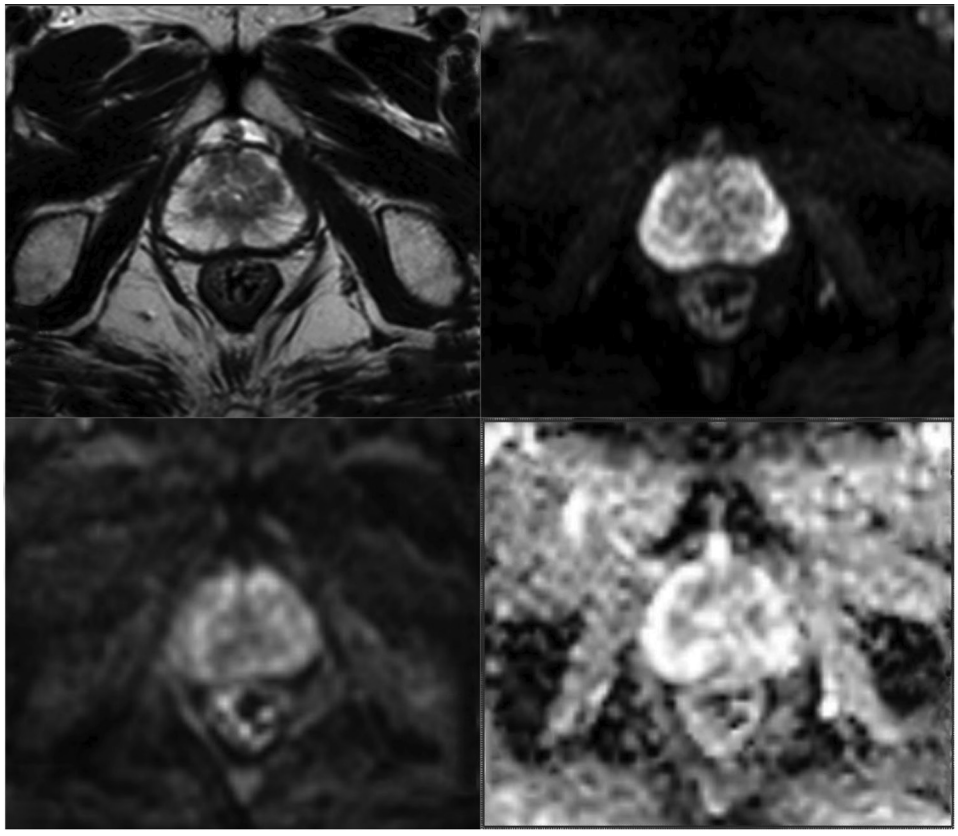

Fig. 2 Uniform high signal intensity T2 and low signal intensity on high *b*-values DWI and high signal on ADC-PIRADS 1.

and technical expertise, these lesions can either be biopsied or followed up (►**Table 4**).

Out of the aforementioned three sequences, T2W imaging and DWI are the mainstay for assessment. DCE plays the role of an adjunct (►**Fig. 7**). Early enhancement within a lesion points toward a malignant lesion; however, it may be disregarded if a finding is a definite PIRADS 1 or 2 lesion based on the T2W images and DWI. Similarly, lack of early enhancement can be disregarded in lesions that are PIRADS 4 or 5 based on T2W images and DWI. However, DCE can tilt the scales in PIRADS 3 lesions where it assumes the role of a referee. For example, in a PIRADS 3 lesion in the PZ according to DWI, a positive DCE increases the likelihood of the finding being malignant, and the resultant finding can be upgraded to PIRADS category 4 (►**Table 5**).

In case the dominant sequence (DWI in the PZ and T2 in the TZ) is technically inadequate, PIRADS category "X" should be assigned and the sequence should be repeated. In case that is not possible, assessment can be made with other pulse sequences with a clear mention of the limitation in the report.

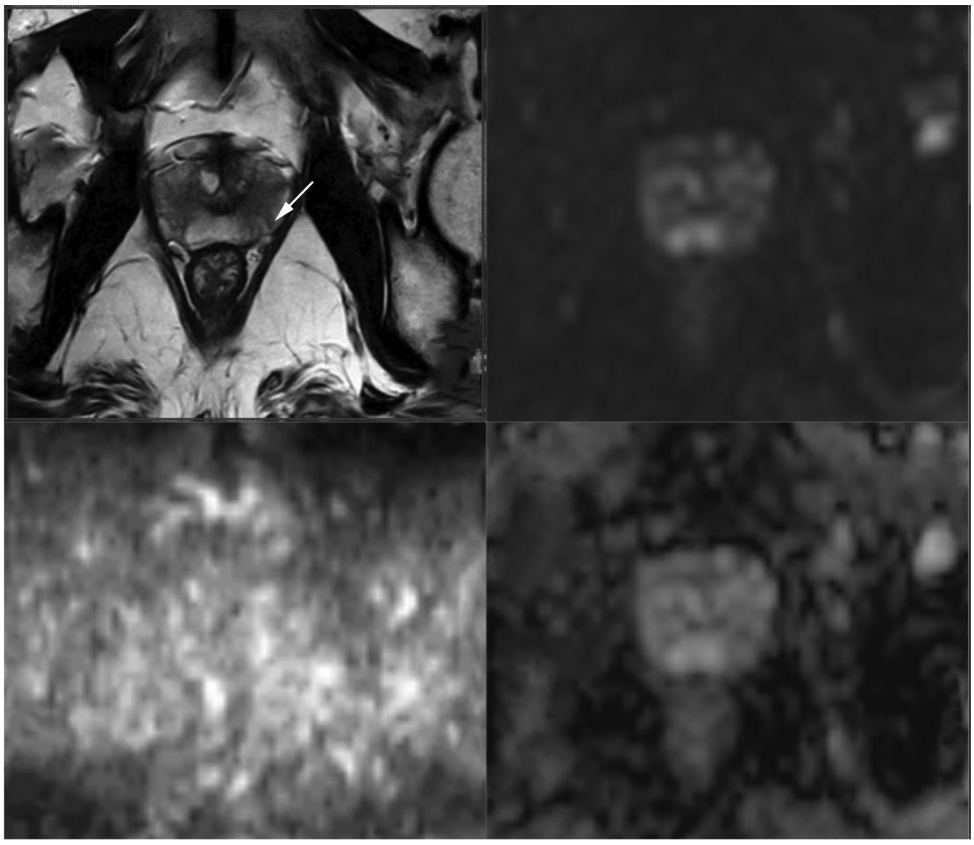

Fig. 3 Linear and wedge-shaped T2 hypointensities with indistinct margins without diffusion restriction–PIRADS 2.

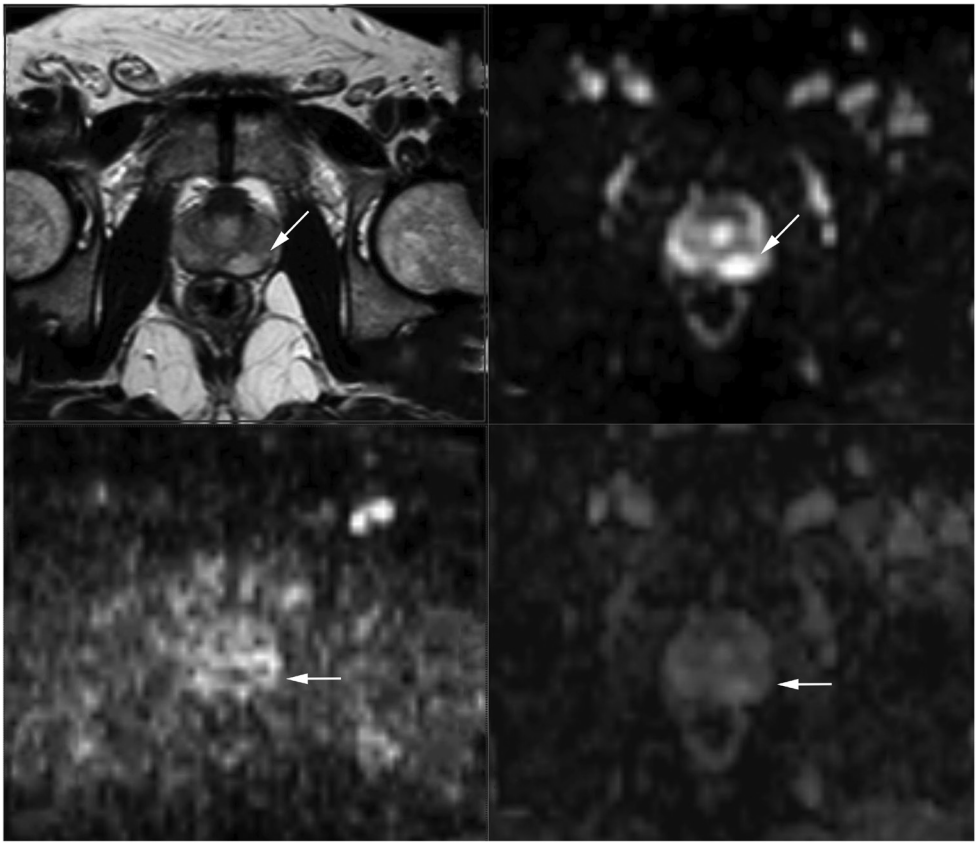

Fig. 4 T2 hypointense lesion with mild hyperintensity on high *b*-value DWI images with focal mild hypointensity on ADC in the left lateral peripheral zone (arrows)–PIRADS 3.

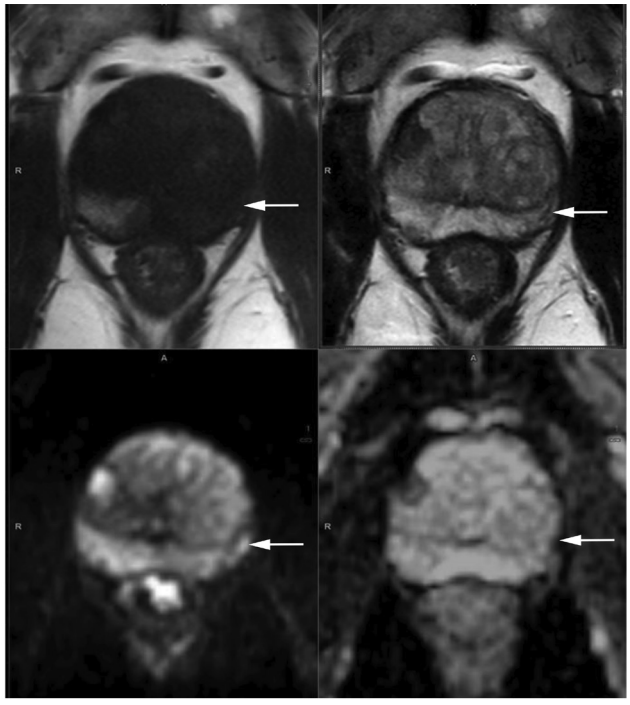

Fig. 5 Only an ill-defined T1 and T2 hypointensity in the left lateral peripheral zone. However, focal markedly hyperintense on high b-value DWI and hypointense area on ADC in left lateral peripheral zone measuring less than 1.5 cm (arrow)-PIRAD 4.

Assessment without Adequate Dynamic Contrast Enhancement

In PZ and TZ, it is determined by DWI assessment category (►**Table 6**). If both DWI and DCE are not available, only EPE should be assessed for the purpose of staging.

Measurement of the Prostate Gland

The volume of the prostate gland can either be calculated by automated segmentation or manually by measuring the maximum dimensions in all three planes using the following formula:

(Max anteroposterior diameter) × (Max transverse diameter) × (Max longitudinal diameter) × 0.52.

This helps calculate the PSA density–PSA/prostatic volume.

Mapping Lesions

As prostatic malignancy can be multifocal, up to four findings with a PIRADS assessment category of 3, 4, or 5 may each be assigned on the sector map, and the index (dominant) intraprostatic lesion should be identified. The index lesion is the one which has the highest PIRADS assessment category. PIRADS v2 recommends that up to four findings with an assessment category of 3, 4, or 5 can be identified and reported. In case there are more than four lesions with suspicious findings, the four with the highest PIRADS assessment

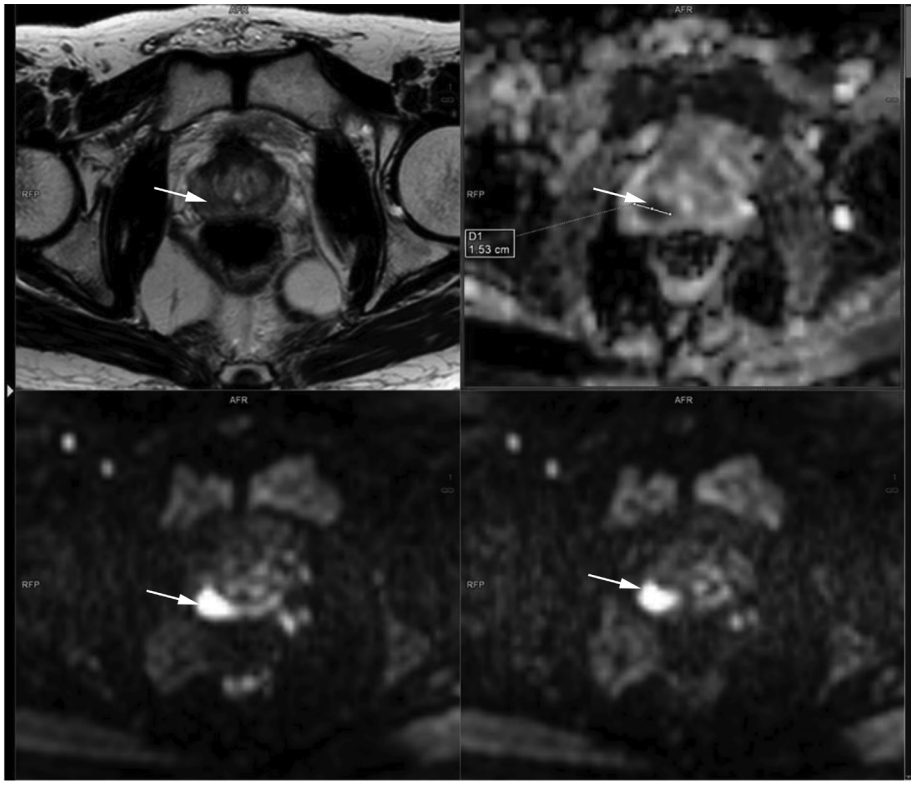

Fig. 6 A focal well-defined T2 hypointense region in the right peripheral zone, showing marked diffusion restriction appearing hypointense on ADC and hyperintense on high b value DWI with early enhancement on DCEI measuring more than 1.5 cm. Features are consistent with a PIRADS 5 lesion. The lesion shows >1 cm smooth contact with the adjacent capsule, a sign of EPE. Note the difference between PIRAD 4 (< 1.5 cm) and PIRAD 5 (>1.5 cm) lesions are only size. Moreover, any capsular or NVB invading lesions are PIRAD 5 irrespective of size.

Table 4 PIRADS v2 and the risk of malignancy

PIRADS 1	Very low (clinically significant cancer is highly unlikely to be present)
PIRADS 2	Low (clinically significant cancer is unlikely to be present)
PIRADS 3	Intermediate (the presence of clinically significant cancer is equivocal)
PIRADS 4	High (clinically significant cancer is likely to be present)
PIRADS 5	Very high (clinically significant cancer is highly likely to be present)

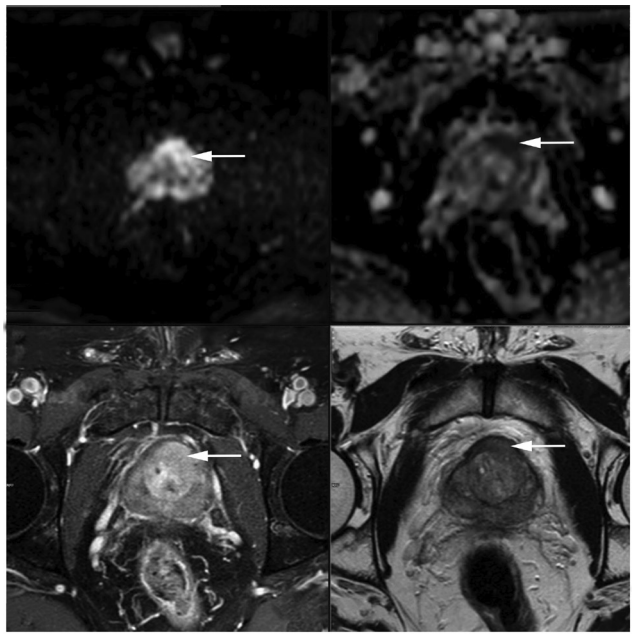

Fig. 7 A focal lesion in the left anterior fibromuscular stroma with extension into the adjacent central zone showing marked diffusion restriction appearing hyperintense on DWI, hypointense on ADC map showing early enhancement on DCEI and well-defined T2 hypointensity (arrows) s/o PIRAD 5 lesion highly suspicious of malignancy.

Table 5 PIRADS v2 final assignment of score

Peripheral zone		
DWI	**DCE**	**Final PIRADS score**
1	Any	1
2	Any	2
3	–	3
	+	4
4	Any	4
5	Any	5
Transition zone		
T2W	**DWI**	**Final PIRADS score**
1	Any	1
2	Any	2
3	≤ 4	3
	5	4
4	Any	4
5	Any	5

Abbreviations: DCE, dynamic contrast enhancement; DWI, diffusion-weighted imaging; PIRADS, Prostate Imaging Reporting and Data System; T2W, T2-weighted.

Table 6 Assessment of PIRADS v2 without DWI

Peripheral zone and transition zone		
T2W	**DCE**	**Final PIRADS score**
1	Any	1
2	Any	2
3	–	3
	+	4
4	Any	4
5	Any	5

Abbreviations: DCE, dynamic contrast enhancement; PIRADS, Prostate Imaging Reporting and Data System; T2W, T2-weighted.

category should be reported. In case there are two lesions with the same PIRADS assessment category, the lesion that shows EPE should be the index lesion even if it is smaller in size. If neither lesions show EPE, then the larger lesion is considered the index lesion.

It is advised that benign findings such as cysts may be reported but is optional. They not only help as landmarks to guide subsequent biopsy or in follow-up but also help provide clarification to clinical colleagues who may see the lesion on films and have difficulty in interpretation. Ideally, the image number and series on which the measurement is made should be reported.

Measurement of Lesions

According to the PIRADS v2, the largest dimension of a suspicious finding should be reported with a mention of the plane (axial/sagittal/coronal) on which the measurement is made. Furthermore, for PZ lesions, the measurement should be made on ADC images, and for TZ lesions, measurement should be made on T2W images. However, in case lesion measurement is difficult on these sequences, it should be made on the sequence that best shows the lesion.

Staging

To differentiate stage T2 EPE (tumor confined to the gland) from stage T3 EPE, MRI is a useful investigation. On MRI, it is essential to inspect the apex of the gland well. Invasion of the external urethral sphincter by cancer leads to a risk of surgically damaging the sphincter and results in urinary incompetence. Tumor in the apex of the gland may also need special considerations for radiation therapy.

At times, obvious signs of EPE may be present, such as direct tumor extension into the bladder base or seminal vesicles with breach of the capsule. However, when there is no gross EPE, certain surrogate signs can predict EPE. The presence of a prostatic contour bulge or irregularity of prostatic margins, loss of normal rectoprostatic angle, asymmetry in the region of the NVBs, and a tumor-capsule contact length more than 1 cm can indicate EPE. Similarly, extension of malignancy into the seminal vesicle may be indicated by the features of seminal vesicle invasion including signal abnormality within the seminal vesicles in the form of T2 hypointensity, which may be focal or diffuse and/or abnormal contrast enhancement and/or restricted diffusion. Morphologically, loss of angle between the base of the prostate and the seminal vesicle may also be an indicator of seminal vesicle invasion.

The other important structures to be analyzed on MRI are the pelvic and retroperitoneal lymph nodes, that is, the common femoral, obturator, external iliac, internal iliac, common iliac, pararectal, presacral, and paracaval, and para-aortic lymph nodes. However, currently, the detection of abnormal lymph nodes is limited to size, morphology, and enhancement pattern. Although it is known that metastatic lymph nodes are not always enlarged, lymph nodes over 8 mm in size in the short axis are usually considered suspicious. One should also assess the images for the presence of skeletal metastases.

Imaging Pearls

- For proper correlation and synchronization between sequences, ensure that the imaging plane, location, and slice thickness for all sequences (T2W, DWI, and DCE) are the same.
- All signal abnormalities are not malignancies. In the PZ, signal alteration on T2W/DWI that is indistinct, linear, lobar, or diffuse, and not rounded may be secondary to prostatitis rather than malignancy.
- The ability of MRI to reliably detect and characterize malignancy in the PZ is more than that in the TZ.
- Homogeneous and heterogeneous nodules in the TZ that are round and well circumscribed are common in men above the age of 40 years. Irrespective of diffusion restriction and/or enhancement, they are considered to be benign BPH. They may sometimes harbor a malignancy but the probability is very low.
- Findings on DWI should always be correlated with those on T2W, T1W, and DCE imaging.
- Not all that appears dark on ADC images is malignant. Blood products, areas of fibrosis or dense fibromuscular stroma, and calcifications can be hypointense on T2 and ADC maps; however, they tend to be hypointense on high*b*-value images as well.
- BPH nodules are the most common benign finding that can masquerade as malignancy. Some of these nodules in the TZ are not clearly encapsulated and may show diffusion restriction. Also, some of these nodules can get extruded into the PZ and be well encapsulated and circumscribed with diffusion restriction. This is a limitation of mp-MRI.
- Signs of extracapsular extension:
  - Asymmetric prostate capsular bulge with irregular margins.
  - Obliteration of the rectoprostatic angle.
  - Asymmetry of NVB.
  - Tumor encasement of the NVB.
  - Seminal vesicle invasion.

In conclusion, mp-MRI has emerged as an important tool for the detection and characterization of prostatic lesions. It now plays a quintessential role in the surveillance, diagnosis, and staging of PCa, as well as for the detection of local recurrence. As reliance on serum PSA has declined in the recent times, mp-MRI has emerged as the go-to tool for urologists all over the world.

Conflict of Interest

None declared.

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Clinical Practice of Palliative Care: Current Concepts and Future Perspectives

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Ann Natl Acad Med Sci (India) 2019;55:84–91

Abstract

Pain is a distressing symptom having biological, psychological, and social consequences. A large number of cancer patients are in advanced stages of the disease and for these patients the only positive and realistic option is pain management and palliative care. These patients have complex needs that have to be taken care of in order to improve the quality of life of such patients and their family members. Surgical treatment along with chemotherapy and radiotherapy is the mainstay for the treatment of cancer, but these modalities also have limitations. The main aim behind palliative care is to allay the sufferings of a terminally ill patient by responding to pain using multimodal analgesia including opioids. According to WHO step ladder, other symptoms like breathlessness, fatigue, delirium etc., are also needed to be managed adequately along with psychosocial and spiritual support. Along with it patients and his family members should be well explained that palliative care is a multidimensional approach directed to the best possible care for that stage of their illness, which may not be curative in nature. There are multiple obstacles in the growth of palliative care in India. Nonetheless we have overcome many such hurdles and there has been a noticeable change regarding palliative care in the mindset of health care providers in the last 2 decades.

Keywords
- palliative care
- clinical practice
- current concepts

Introduction

WHO defined palliative care "as an approach that improves the quality of life of patients and their families facing the problem associated with life threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems: physical, psychosocial, and spiritual."[1,2]

Palliative care is for everyone and anyone during any stage though mostly terminal stage of a serious ailment. It can also be planned concurrently with surgical excision or chemotherapy or radiotherapy or all three combined together. Obviously it includes hospice care services and is surely not having any relationship with prognosis.[3]

The palliative care is required in number of terminal diseases. The transition between the aggressive treatment to cure or to prolong a good quality of life and palliative care may not be clear and both should be considered in conjunction, each becoming dominant at a given time.

Palliative care is an interdisciplinary approach involving physician, nursing staff, social workers, priest/father of church and various other specialties that focus on enhancing the quality of life for patients of any age, who are living with any critical illness and also their families. Patients receiving palliative care can have various types of symptoms like breathlessness, delirium, nausea, vomiting, constipation, respiratory infection, pain, which need to be addressed individually and patiently.[4]

Palliative care and concepts of "hospices" are nothing new to the western world and is already very well established in the western hemisphere, but in developing nation like India it is very much in infancy, may be because developing nations

DOI https://doi.org/10.1055/s-0039-1697241
ISSN 0379-038X.

have huge challenges to first manage communicable diseases like malaria, dengue, swine flu, enteric fever, etc.

In India the palliative care is getting established with whatever limited support that has been provided by the government of India. On the other hand, the only state and the very first state where it got established almost a decade back was state of Kerala, which has set an important benchmark for other states in India to follow.[5]

Heart disease, respiratory diseases, diseases of digestive system and alcohol-related diseases such as liver problems or cancer, homeless populations, prisoners, sex workers, and individuals with substance use disorders have been cited as major chronic diseases causing morbidity and mortality among patients.[6,7]

Historical Aspects of Palliative Care

The pioneering works of Dame Cicely Saunders in the United Kingdom drew the attention of the Medical Community and the public to the evolution of palliative care in 1967. She framed an ideal model of care for the patients suffering from terminal cancer and who are close to death. She has been the role model and great source of inspiration for various health care providers involved in the setting up of palliative care units. The first hospital palliative care team was established in St. Thomas Hospital in London in 1977. Since then rapid progress has been made in developing palliative care as a discipline in the health care delivery.[8]

In India the earliest centers for delivery of palliative care were established in few places like Ahmedabad, Bangalore, Mumbai, Kerala state in the late 1980s and early 1990s. In other states palliative care was initiated with the opening of pain clinic and palliative care services under the department of anesthesiology. Now the Kerala network has more than 60 units covering a population greater than 12 million and is one of the largest networks in the world.[9]

Palliative care in India is still at an early stage of development and is facing numerous challenges. It is estimated that less than 3% or may be more of India's cancer patients have access to adequate pain relief.[10] The government of India initiated a National Cancer Control Program in 1975, modified in 1984, to make pain relief one of the basic services to be provided at primary health care level. This policy was however not translated into a large scale service provision. Access to the availability of opioid and other drugs is the most important practical issue in the establishment of palliative care in India.

Approximately 30% of the world population suffers from pain. Pain survey's reliable estimates indicate that the chronic pain prevalence is somewhat closer to 19.3% in India.[11] In a study conducted by Dureja and Saxena et al, they concluded that the overall point prevalence of chronic pain in India was 13%, and the mean intensity of pain on numeric rating scale scale was 6.93 in India.[12]

There has been a steady progress in the field of palliative care in the past few years. According to a report by Worldwide Hospice Palliative Care Alliance, India has moved from Group 2 countries (making capacity to building activities) to Group 3B for having generalized palliative care provisions.

Diversity and complexity of health problems pose challenges in access to good palliative care more so in people experiencing homelessness.[13]

Evaluation and Management of Common Physical Symptoms

Pain

Pain is a very prominent and distressful symptom in patients presenting at the end of life. The effective relief of pain in a palliative patient depends mainly on a comprehensive assessment to identify the different physical, psychological, social, and spiritual aspects that are specific to each patient, and optimally intervene on a multidisciplinary level.

Cancer pain is a greatly feared symptom in all the patients. A recent meta-analysis reported pooled prevalence rates of 55% for cancer-related pain in patients who were receiving disease modifying treatment and 64% in those with advanced metastatic or terminal disease.[14] An accurate, thorough, and systematic assessment of cancer pain is crucial to identify the underlying etiology and decide a treatment plan. For cancer pain management, we need to know the cancer patient's life expectancy and the exact staging of the cancer pathology. In case the survival chances are low and life expectancy is not much, one can have the freedom of taking higher degree of risks for providing optimum pain relief. On the other hand, if chances are bright for recovery or subsiding of cancer pathology, then spiritual, psychological, and cognitive support and steps for enhancement of quality of life should be undertaken.

Metastatic disease most commonly occurs in the bones, lungs, and liver. Therefore these patients would have pain which may be located at multiple areas of the body including the pain due to bone metastasis or of neuropathic origin.[15,16] Ineffective pain relief further worsens the cancer burden.

Palliative care involves assessing and managing pain that is persistent, may have multiple etiologies, one or more of which are incurable, is impairing function, increasing dependency, and invokes fear of further suffering and death. The pain must be assessed in detail to know which component of pain prevails in a particular patient. Pharmacological management is one of the main modality for the treatment of pain. The choice of pharmacological agent depends on the primary pathology of the patient as well as underlying comorbidities as all the medications have different action and potential side effects. Along with it there is variability between patients in terms of response to a particular drug.

A thorough assessment of pain in palliative care helps in the development of strategies to manage the pain and enhance quality of life. These may include: (1) regular analgesic administration according to the WHO analgesic ladder; (2) use of appropriate pharmacological and nonpharmacological adjuvant therapies; (3) a wide range of strategies to improve mood, morale, general health, and resilience; and (4) open discussions about pain and sufferings to assist in appropriate pain interpretation.

WHO Analgesic ladder: The WHO analgesic ladder is a method to guide symptomatic pain relief[17] (►**Fig. 1**).

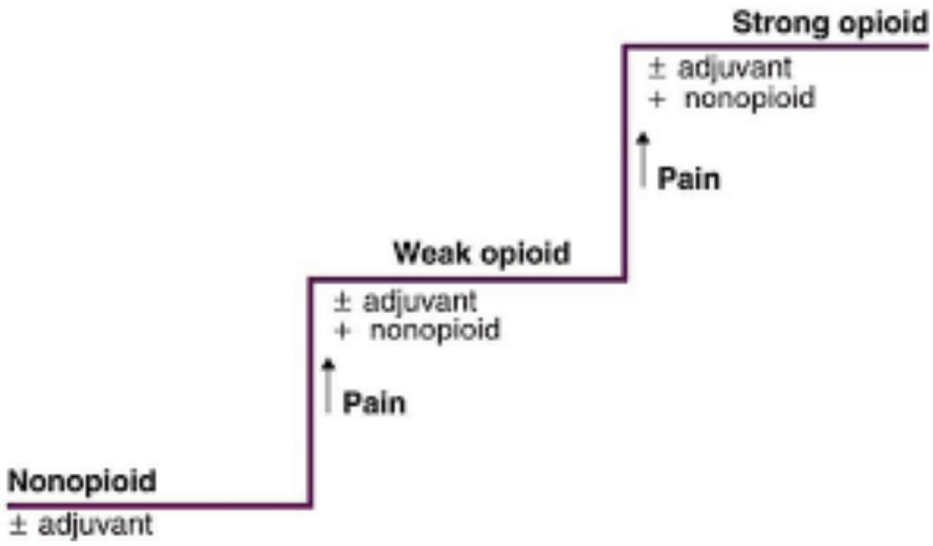

Fig. 1 Three step analgesic ladder (fourth step is interventional pain management).

Step 1: Nonopioid ± Adjuvant.
Step 2: Weak opioid + nonopioid ± adjuvant.
Step 3: Strong opioid + nonopioid ± adjuvant.
Step 4: Interventional/neurolytic pain procedures.

A nonopioid is used for analgesia in the first step of the ladder. This is usually paracetamol at a dose of 1 gram every 6 hours. If it is not effective at this dose we move to Step 2. For Step 2, a weak opioid such as codeine is added to the analgesic used in Step 1. This usually means adding codeine to the regular paracetamol already being taken. The recommended dose of codeine is 30 to 60 mg every 4 hours up to a maximum of 240 mg daily. In the Step 3, among the strong opioids morphine remains the "gold standard" as it has been the most extensively studied, and is available in a wide range of formulations and routes.

If peroral use of oral opioids is not possible then it can be administered transdermally, for example, transdermal fentanyl patch (25 µg/h, 50 µg/h, etc.) and transdermal buprenorphine patch (5 mg/h, 10 mg/h). Another option is that of subcutaneous infusion of opioids. For the management of breakthrough pain, intranasal fentanyl sprays or buccal fentanyl tablets or sublingual tablets can be utilized.[18] For an adult who has pain on the regular weak opioid used in Step 2, an appropriate starting dose of oral morphine is 5 mg every 4 hours. Later sustained release preparations can also be used. Laxatives are generally prescribed along with morphine to avoid constipation caused mainly through peripheral opioid receptor.[19] Other side effects associated with the use of opioids are nausea, vomiting caused by direct stimulation of the chemoreceptor trigger zone, or the vestibular apparatus and through the inhibition of gut motility.[20]

Most opioids are metabolized in the liver by glucuronidation and/or demethylation catalyzed by cytochrome P450 isoenzymes. It is administered carefully in patients with renal impairment due to one of its active metabolites, M3G, which is dependent on kidney for excretion and hence may lead to opioid-related toxicity. So in patients with compromised renal function lipophilic opioids that do not have active metabolites (e.g., fentanyl) should be considered. Hydromorphone and oxycodone are also to be used with caution followed by close monitoring of the patient.[21,22]

Long-term usage of opioids in cancer pain may produce hypogonadism and hyperprolactinemia which may ultimately lead to fertility problems. Long-term use may also predispose to chronic fatigue and osteoporosis due to hormonal changes.[23-25] In cases where long acting preparations and opioids with immunosuppressive properties (e.g., morphine) were used the incidence of infection and hospitalization was higher.[26] Components of ►**Fig. 2** can be very well utilized in cancer pain patients while prescribing them on opioid therapy. Few of the screening tools like opioid risk tool, risk efficacy and screener and opioid assessment for patient with pain revised can be brought into practice to elicit some amount of information as monitored in ►**Fig. 2**.[27] The dose of opioids shall be on the higher side if the intensity of cancer pain increases or there is a fresh development including the addition of neuropathic component in cancer pain or if the patient is cachectic (so the bioavailability of the opioid goes down or if there is a possibility of drug interaction).[28] Requirement for increased doses of opioids may also reflect opioid tolerance or opioid-induced hyperalgesia. This can be managed by altering the opioid or its route of administration or by adding ketamine.

Caraceni et al have brought out revised evidence-based recommendation on behalf of the European Association for palliative care for the relevant use of various opioids in the management of cancer pain.[30]

Opioids have been combined with antidepressants or antiepileptic drug in tumor-related cancer pain. A recent systematic review concluded that these combination did not significantly improve pain relief compared with monotherapy.[31]

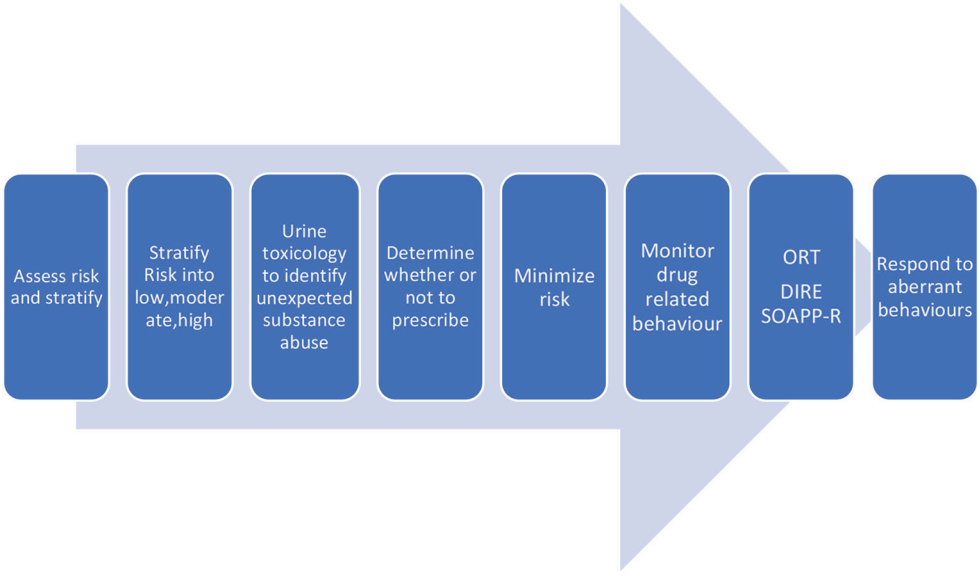

Fig. 2 Basic components for monitoring cancer pain patients who are on opioids.[29]

Adjuvants

These medications have effects on specific types of pain syndromes, such as neuropathic or inflammatory pain. Examples are antidepressants and antiepileptic drugs. Tricyclic antidepressants for example amitriptyline, duloxetine, and venlafaxine are commonly used. Anticonvulsants such as gabapentin and pregabalin are used for pain control as well. Amitriptyline is effective in the dose range of 10 to 75 mg/d especially for targeting the neuropathic component of cancer pain. Their anticholinergic effects are the main side effects. Recently duloxetine and venlafaxine have also been used for neuropathic component of cancer pain. Duloxetine has no anticholinergic effect but may produce nausea, vomiting, and is especially beneficial for elderly patient.[32]

Gabapentin and pregabalin inhibit voltage-gated calcium channels. They have strong affinity for alpha 2 delta 1 receptors located on voltage-gated calcium channels. They are mainly excreted by renal route hence dosage needs to be adjusted according to creatinine clearance rate and they have no known drug interaction and on long-term use they may produce gain in body weight. Oral gabapentin is administered in the dose range of 300 to 3,600 mg/d in three divided doses, though in Indian patients usually the upper limit is 1,800 mg/d. Oral pregabalin is administered in dose range of 75 to 600 mg/d in two divided doses, though in Indian patient population the upper limit is 300 to 450 mg/d.[33]

Corticosteroids are prescribed in a variety of clinical conditions where inflammation is causing pain such as neuropathic pain, cerebral edema, spinal cord compression, bone or visceral pain. Long duration therapy should be avoided due to side effects (►**Table 1**).[34,35]

Interventional pain management should be considered as adjunct to comprehensive medical management in intractable cancer pain patients. The neuroablative procedures involve the use of chemical agents (alcohol 50–100% and freshly prepared phenol 6–10%), heat (radiofrequency), cold (cryoablation), compression, and surgery.[36] Neurolytic blockade of peripheral nerves produces short-term pain relief. Intercostal neurolysis has a median duration of 3 weeks.[37] Other options are percutaneous cervical cordotomy and radiofrequency ablation. It reduces perception of temperature in addition to pain. Its value in mesothelioma is well documented.[38] Continuous programmable intrathecal pumps containing preservative-free morphine, with or without clonidine are also used but their cost is highly exorbitant.[39]

Nonpharmacological Methods of Pain Management

Nonpharmacological modalities can be used with a pharmacological approach to pain management. These strategies can be very effective in relieving pain and providing comfort while empowering the patient and family to deliver pain relief in a safe manner. Nonpharmacological modalities include, but are not limited to, relaxation techniques, superficial heating or cooling, acupuncture, TENS and spiritual support, and pacing.[40]

Recently the frequency of palliative chemotherapy and the rate of invasive procedures have increased in patients with end-stage gynecologic cancer who were treated aggressively without hospice management over 2011 to 2015 as compared to previous years.[41]

Neuropathic component of cancer pain is still a serious problem affecting day to day life of cancer patients because of the wide variety of underlying causes and the paucity of clear data for its diagnosis and treatment. With the advancement in palliative care in the form of new technologies and therapies, cancer patients have a longer survival; so symptoms like neuropathic pain need to be well treated to improve the quality of life of these patients.

According to International Association for study of Pain (IASP) neuropathic pain is defined as the pain arising from a lesion or disease affecting the somatosensory system.[42] Neuropathic pain manifests as a regional distribution of pain

Table 1 Pharmacokinetic information for opioids, antidepressants, and gabapentinoids in managing neuropathic component of cancer pain[29]

Drugs	Metabolic pathway	Active metabolite	Remarks
Opioids			
Buprenorphine	CYP3A4; UGT 1A1/1A3	Norbuprenorphine	
Fentanyl	CYP3A4	No	
Hydromorphone (not available in India)	UGT 1A1	No	Creatinine clearance rate (CCR) to be monitored
Methadone (not available in India)	CYP 1A2/2B6/2C19/2D6/3A4	No	QT-time long and variable half-life
Morphine	UGT 1A1/2B7	M6G	Accumulation in kidney failure
Oxycodone (not available in India)	CYP 3A4/2D6	Oxymorphone	CCR to be monitored. CYP3A4 inducers reduce and inhibitors increase effect
Antidepressant			
Amitriptyline	CYP 2D6/2C19/3A4	Nortriptyline	Single nucleotide polymorphism
Nortriptyline	CYP2D6	10-Hydronortryptyline	Single nucleotide polymorphism
Duloxetine	CYP2D6/1A2	No	Single nucleotide polymorphism
Venlafaxine (not available in India)	CYP2D6	*o*-Desmethyl venlafaxine	Single nucleotide polymorphism
Gabapentinoids			
Gabapentin	No liver metabolism	No	CCR to be monitored
Pregabalin	No liver metabolism	No	CCR to be monitored

along a peripheral innervation. Patients may describe this pain as burning, prickling, tingling, or they may have unusual sensations ranging from numbness to lancinating sensations. Using combinations of drugs with different mechanisms of action may provide effective treatment.[43,44]

Breathlessness

Breathlessness is common in people with advanced cancer or cardiorespiratory or neurological disease. It generally occurs by complex interaction among chest walls, lungs, upper airways, and central nervous system. Once reversible causes have been addressed, management focuses on nonpharmacological interventions, aimed at increasing comfort. Pharmacological treatment includes low dose morphine, and if appropriate, benzodiazepines (if anxiety) or oxygen treatment (if hypoxemic). The effectiveness of treatments will vary between patients, so a flexible approach to management is required (►**Table 2**).

Nonpharmacological strategies[46] targeted to improve the comfort of palliative care patient include the following:

- Altering the position of the patient to the maximum comfortable position, for example, elevating the head and trunk, or lying with the affected lung downward if only one lung is pathological to decrease ventilation perfusion mismatch.
- Chest physiotherapy and deep breathing exercises.
- Cognitive behavioral therapy[47] in the form of relaxation exercises.
- Using a humidifier.
- Decreasing room temperature.
- Elimination of irritants such as smoke or allergens which further irritate the airway.
- Opening a window for ventilation.

Table 2 Reversible causes and their relevant management of breathlessness[45]

Anemia	Blood transfusion
Acidosis	HCO_3
Bronchospasm	Bronchodilator therapy
Pneumonia	Antibiotic therapy
Pulmonary embolus	Anticoagulate
Pneumonitis	Steroids
Atrial fibrillation	Antiarrhythmic
Congestive cardiac failure	Diuretic
Pericardial tamponade	Drainage
Carcinomatous lymphangitis	Steroids
Lung metastases	Chemotherapy/hormonal therapy

- Providing a window to see outside has a positive impact on the patient.
- Positive counseling and reassurance.

Systemic opioids (oral morphine) are safe and effective treatment for breathlessness in advanced stages of chronic obstructive pulmonary disease patients. Low dose benzodiazepines can be used as an adjuvant therapy to allay anxiety. Oxygen is not administered universally to all patients with breathlessness; only patients with established hypoxemia (PaO_2 < 55 mm Hg) are likely to benefit by oxygen therapy. Benefits of oxygen therapy in a hypoxic patient are reduction of hypercapnia and polycythemia thus leading to better sleep and comfort for the patient.[48]

In patients who are not significantly hypoxemic, there is currently no evidence that oxygen reduces breathlessness.[49]

A Cochrane review found no overall improvement in breathlessness among patients with cancer using oxygen; however, some individuals felt better breathing oxygen.[50]

Malignant pleural effusion is also a leading cause of breathlessness. For treatment of malignant pleural effusion, recently Bhatnagar et al observed that with an indwelling pleural catheter along with talc administration, there are greater chances of pleurodesis.[51]

Fatigue

Fatigue may be defined as "a subjective, unpleasant symptom which incorporates total body feelings from tiredness to exhaustion, creating an unrelenting overall condition which interferes with a person's ability to function to their normal capacity." It has a major impact on the quality of life of the patient.[52]

There is no single preferred assessment tool but for clinical purposes a numerical scale can be followed. This can be a numerical 0 to 10 scale or fatigue scoring system based on palliative care assessment tool as described below[53]:

1: no fatigue.
2: fatigue present but not affecting daily life.
3: fatigue present and having moderate effect on daily life.
4: fatigue present and having overwhelming effect on daily life.

Treatable cause of fatigue must be managed first, for example, anemia, infection, drug side effect, insomnia, and depression. Drug management of fatigue may include the use of corticosteroid, psycho stimulants, or antidepressants.[54]

Nonpharmacological measures in the form of physiotherapy, psychological support, occupational therapy can always be used.

Psychological Symptoms like Delirium, Confusion, Anxiety, and Depression

Delirium is one of the common and most serious neuropsychiatric symptom seen in terminally ill patients. It is associated with high degree of morbidity and stress both for the patient and the family members. In Cochrane database of systemic review, delirium is described using a variety of terms such as agitation, acute confusional state, encephalopathy, organic mental disorders, and terminal restlessness.[55]

In a recent study by Bush et al, the authors observed the incidence of delirium and associated symptoms from 43% in general cancer population to 85% in the patients in terminal stage of their illness.[56]

According to Cherny et al, three clinical subtypes of delirium described are as follows[45]:

1. Hyperactive subtype—hyperaroused, hyperalert, agitated.
2. Hypoactive subtype—hypoaroused, hypoalert, or lethargic.
3. Mixed with alternating features of both.

Common precipitating events include sepsis, medication side effects, and metabolic aberrations (particularly hypercalcemia, hyponatremia, uremia, dehydration, brain metastases, or cerebrovascular events).

Pain physicians always face the dilemma to intervene in reversing delirium, and according to Yennurajalingam et al following are the components of a possible strategy to be adopted to manage delirium[57]

- Identify the underlying cause (if possible) and assess its impact on the patient's quality of life.
- Rank the distress of delirium in the context of the patient's overall symptom complex.
- Assess the potential problems associated with correcting the underlying causes and consequent impact on the quality of life (e.g., using intravenous line for antibiotics and patient pulling out).
- Consider the advantages and disadvantages of intervention versus no intervention.
- One must discuss the treatment options with the palliative care patient (if mild cognitive impairment) and the family, to allow informed decision-making and ultimately the development of a consensus on the appropriate level of intervention.

Various medications for the management of agitation and delirium in the end stage of the disease include antipsychotics of newer class such as olanzapine 5 mg, quetiapine, and aripiprazole.

They tend to have lesser extrapyramidal side effects than earlier generation antipsychotics such as haloperidol, chlorpromazine, levomepromazine, or risperidone. In addition, benzodiazepines may be needed for faster control of agitation and anxiety.

Spiritual Support

The philosophy and practice of palliative care operate upon an understanding of a person as a whole along with his disease. It is reflected in the multidimensional approach of the biopsychosocial model. One cannot provide whole-person care without giving consideration to the relevant spiritual needs held by the patients with serious illness. Palliative care providers are also called to be advocates for the spiritual and religious rituals of patients and families, especially at the time of death.[58]

As defined by the Hospice and Palliative Nurses Association, "spiritual distress refers to a disruption in one's beliefs of value system, a shaking of one's basic beliefs."[59]

Anandarajah and Hight observed that "spiritual distress and spiritual crisis" occur when a person is "unable to find sources of meaning, hope, love, peace, comfort, strength, and connection in life or when conflict occurs between their beliefs and what is happening in their life."[60]

Conclusion

Overall management of cancer pain remains suboptimal even in the best possible center in a developed country, so one can imagine the status of palliative care in a developing country like India. There is no doubt that these patients keep suffering for a number of months and years due to a variety of causes, before they get any opportunity to finally visit a pain and palliative care center, where oral strong opioids are available or before a neurolytic interventional pain procedure can be offered.[61] It is essential that timely and early referrals for cancer pain management are sent to pain and palliative care centers for achieving a satisfactory pain relief.

It has been suggested by Linklater et al and Kay et al that joint consultation clinics should be held between the department of palliative medicine and pain medicine, so that patients are assessed in depth and well managed as large number of procedures with wider dimension can be carried out than in those hospitals without these kinds of associations.[62,63]

Liaison between various specialties with specialists interested in cancer pain management (palliative care, oncology, radiotherapy, pain specialists, orthopedics and general surgery, etc.) will allow for a variety of palliative pain control options to be considered.

As of today, palliative care currently provided to the people experiencing homelessness does not meet the core requirements of palliative care due to bottlenecks regarding timely identification, care for the social network, and the assessment and management of physical symptoms and psychosocial and spiritual care needs.

Recently La Cruz et al concluded that patient education is of paramount importance and is intensively required to minimize stealing and inappropriate use and at the same time ensuring genuine access to opioids for real needy cancer pain patients in palliative care while taking steps to stop the entry of these drugs into the non-needful strata of the society.[64]

Today, we are 10 years ahead of the IASP Global Year against cancer pain (2008–2009) and still cancer pain management remains a mammoth task ahead; but integrating our efforts on palliative care, as mentioned above with the Indian holistic system (yoga, meditation, etc.) may optimally connect the mind, body, soul and shall go a long way in mitigating the pain and enhancing the quality of life of such patients.

Conflict of Interest
None declared.

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Small Dense Low-Density Lipoprotein: Biomarker or Potential Drug Target?

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Ann Natl Acad Med Sci (India) 2019;55:92–97

Abstract

Ischemic heart disease is currently an epidemic affecting individuals worldwide. Increased incidence along with earlier onset of disease has led to the constant search for biomarkers that will help in earlier identification and treatment of at risk individuals. Small dense low-density lipoprotein (sdLDL) is the atherogenic subtype of low-density lipoprotein (LDL). It is smaller in size and higher in density in comparison to other LDL subtypes. Higher levels of sdLDL have been found to be associated with increased incidence of ischemic heart disease and adverse outcomes. Properties including decreased resistance to oxidative stress and prolonged residence time in the circulation account for its increased atherogenic potential. Hence intervention approaches targeting sdLDL directly in at risk individuals may be beneficial.

Genetic, lifestyle, and environmental factors affect sdLDL levels. But the main determining factor is the level of triglycerides (TGs). Higher TG levels are associated with higher levels of very low density lipoprotein (VLDL) 1 and sdLDL. Various drugs have been used for targeting sdLDL with varying outcomes; drugs tried out include statins, fibrates, niacin, cholesterol ester transfer protein inhibitors and sodium-glucose co-transporter-2 inhibitors. Future prospects include modification of enzymes involved in fatty acid and TG synthesis, for example, lipoprotein lipase and acyl CoA carboxylase. However, further research is still necessary to draw clear guidelines for sdLDL reduction therapy in coronary artery disease treatment and prevention.

Keywords

- ischemic heart disease
- small dense low-density lipoprotein
- atherogenicity
- drug target

Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD) and coronary artery disease (CAD), is a major cause of morbidity and mortality worldwide. According to the 2016 Heart Disease and Stroke Statistics update of the American Heart Association, in the United States, 15.5 million people ≥20 years of age have CHD.[1] The prevalence increases with age for both men and women. In India the prevalence of CHD has increased fourfold in the past 40 years.[2] The Registrar General of India reported that CHD-related adult deaths have increased from 26% in 2001 to 2003 to 32% in 2010 to 2013.[3] Gupta et al reported that cardiovascular risk factors among Indians increase exponentially in the age group of 30 to 39 years.[4] Covering 24.8%, CVD is the leading cause of death throughout India, including both rural and urban areas.[5]

Increasing incidence combined with earlier onset has led to the constant search for biomarkers which will help in identifying at risk individuals at an early stage. Small dense LDL (sdLDL) is the smaller and denser subtype of LDL. Higher levels of sdLDL have been found to be associated with increased incidence of cardiovascular events.[6] Hence sdLDL estimation could be used as a means of identification of high-risk individuals. Early intervention using drug therapy for reduction of sdLDL levels could ultimately lead to a better outcome for these people.

DOI https://doi.org/10.1055/s-0039-1697239
ISSN 0379-038X.

Cardiovascular Risk Assessment

Risk factors which increase the probability of CHD include diabetes, hypertension, central obesity, physical inactivity, smoking, psychosocial factors, dyslipidemias, and genetic predisposition. The INTERHEART study reported that more than 90% of the risk factors for CHD were measurable and modifiable.[7] Among the lipoproteins, traditionally high-density lipoprotein (HDL) is considered as "good cholesterol" and LDL as "bad cholesterol." Longitudinal studies had established the role of LDL as a risk factor for CHD occurrence, recurrence, and fatal outcome. Clinical trials proved that control of elevated LDL in high-risk patients was a very cost effective and efficient means of cardiovascular risk reduction.[8] Hence lipid profile, in particular LDL, is routinely used by clinicians as a tool for cardiovascular risk assessment.

Other studies, however, found that LDL is not elevated in all those patients suffering from CAD.[9] Moreover, though lipid lowering agents are widely used in clinical practice as a treatment component in CAD, the risk reduction after lipid lowering therapy has been found to be not more than 30% in most of the clinical studies.[10]

These findings led to the search of risk factors in addition to those previously known which could contribute to the development of atherosclerosis and CAD, that is, the "beyond cholesterol" concept.[11] Evidence started pointing toward the fact that it is in particular the sdLDL which is responsible for its atherogenic property.[12]

LDL and Its Subtypes

LDL is the main cholesterol carrying lipoprotein. It is broadly defined as lipoprotein fraction with density 1.019–1.063 g/mL.[13] Structurally, it consists of a core of cholesterol esters surrounded by a coat of phospholipids and protein (Apo B100 mainly). LDL delivers cholesterol to the cells, where it is utilized for synthesis of membranes, steroid hormones, etc. Krauss and Blanche used density gradient ultracentrifugation and separated LDL particles of normal subjects according to their size and density.[14] Austin et al (1990) conducted a study on 301 subjects. They separated LDL using gradient gel electrophoresis and identified two distinct patterns, Pattern A with a predominance of large buoyant LDL particles (density 1.019–1.044 g/mL), and Pattern B consisting of mainly small dense particles (density 1.044–1.063 g/mL)[15] (►**Fig. 1**).

Pattern B (sdLDL) has been found to be associated with number of diseases including CHD, obesity, metabolic syndrome, acute ischemic stroke, and Type 2 diabetes mellitus (DM).[16,17] High sdLDL itself is a component of "atherogenic phenotype," consisting of high TGs, low HDL, and high sdLDL. This is now recognized as a distinct dyslipidemia linked to various genetic loci.[18] Accordingly, sdLDL concentration was accepted as a risk factor for cardiovascular events by National Cholesterol Education Program (NCEP III).[19]

Atherogenicity of sdLDL

The next question which arises is "Why is sdLDL atherogenic?" Small dense LDL differs from large buoyant LDL in certain properties. First, sdLDL has lesser affinity for the LDL receptor than other LDL subtypes. This leads to reduced LDL uptake and as a result, prolonged existence in the circulation. Second, sdLDL has greater affinity for arterial wall proteoglycans. The result is increased retention in the subendothelial space and hence greater opportunity for promoting atherogenic changes. These properties are a result of conformational changes in the Apo B part of sdLDL. These changes alter the properties of sdLDL; the result being decreased receptor-mediated uptake and increased proteoglycan affinity.[20] Desialylation of sdLDL also contributes to this property.[13]

Oxidized LDL is well known for its atherogenicity. LDL oxidation takes place in the circulation; it leads to the generation of specific epitopes which are recognized by receptors and induce immune response and inflammation. The altered lipid composition and lesser content of antioxidative vitamins reduce the resistance of sdLDL to oxidative stress and hence increase its atherogenic potential.[13]

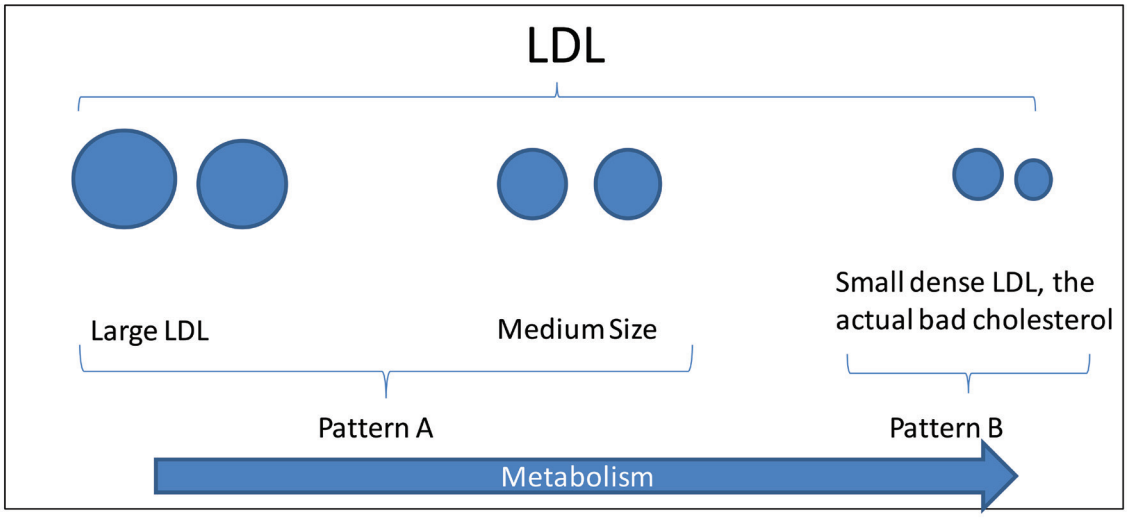

Fig. 1 Low-density lipoprotein and its subtypes. LDL, low-density lipoprotein.

Numerous studies have proven the atherogenic potential of sdLDL. Nishikura et al in a prospective cohort study of 7 years concluded that sdLDL is a promising biomarker to predict future cardiovascular events in the secondary prevention of stable CAD.[6] In the Quebec Cardiovascular Study which was a prospective cohort study of 13 years, it was concluded that sdLDL is a strong independent predictor of ischemic heart disease (IHD).[21] The Framingham Offspring Study which was a prospective cohort study on 1,680 women and 1,508 men concluded that sdLDL is a very strong predictor of IHD in women, whereas in men it is the sdLDL/LDL ratio which is a stronger predictor.[17]

What Determines the Distribution between Large Buoyant and Small Dense LDL?

SdLDL is a subtype of LDL, so the basic synthetic pathway is the same. Triglyceride (TG)-rich very-low-density lipoprotein (VLDL) is synthesized in the liver and released into the circulation. TGs are acted upon by lipoprotein lipase and hepatic lipase producing intermediate-density lipoprotein and LDL. Simultaneously, LDL is acted upon by cholesterol ester transfer protein (CEPT) which removes cholesterol esters from LDL in exchange for TGs which it brings in from other lipoproteins. The distribution of LDL among large buoyant and small dense subtypes depends on various factors. The trait of sdLDL predominance or the atherogenic lipoprotein phenotype (high TGs, low HDL, and high sdLDL) is a distinct dyslipidemia linked to various genetic loci with a heritability of 35 to 45%.[18]The prevalence of this trait is higher in older men and postmenopausal women. Other factors include diet, obesity, exercise, drugs, abdominal adiposity, and hormonal status[20] (►**Fig. 2**).

However, the major factor determining LDL subtype distribution is the level of TGs. Studies have shown that pattern B subclass distribution is not seen till TG levels exceed 1.5 mmol/L or 120 mg/dL. Fifty percent of the variation in LDL size is determined by TG levels. When TG levels are high, it leads to increased synthesis of TG-rich VLDL1. Lipolysis of VLDL1 produces LDL particles with prolonged residence time of around 5 days in the circulation compared with LDL derived from smaller VLDL precursors which remain in the circulation for around 2 days. This smaller LDL has sufficient time to be remodeled by CETP; LDL loses cholesterol esters and gains TGs. If this happens to a certain degree, next exposure of TG-rich LDL to hepatic lipase (HL) promotes a particle shift to smaller denser range. Hence the levels of activity of CETP and HL also influence LDL subclass distribution[22] (►**Fig. 3**).

sdLDL as a Drug Target

The importance of sdLDL as a predictive biomarker in CAD is well established and its atherogenic potential understood. Numerous studies are now being performed using different approaches of modifying the lipid profile. Instead of LDL, targeting sdLDL alone or along with high TGs and low HDL as a part of the atherogenic triad, can probably give a better outcome. Different approaches have been tested for reducing sdLDL with variable results.

Fibrates

Since high TGs are a direct influencing factor on sdLDL levels, TG reduction was one of the earliest approaches tried out.

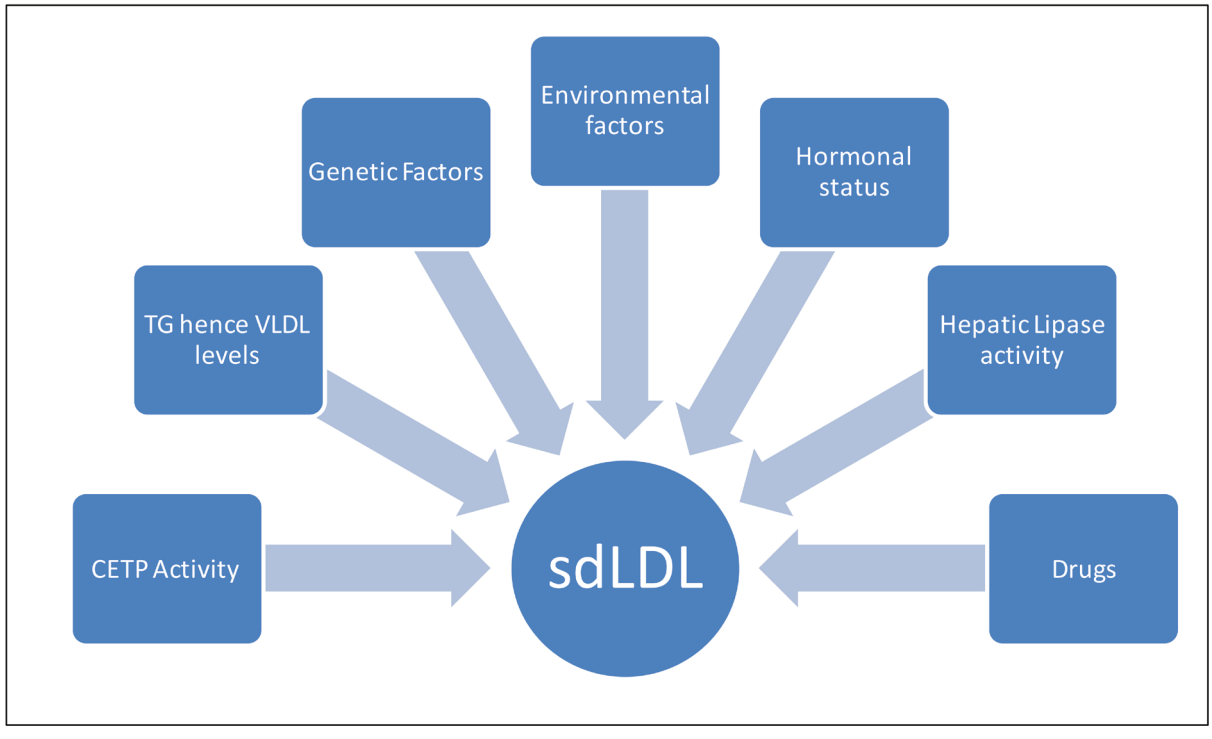

Fig. 2 Factors influencing SdLDL levels. CETP, cholesterol ester transfer protein; SdLDL, small dense low-density lipoprotein; TG, triglycerides; VLDL, very-low-density lipoprotein.

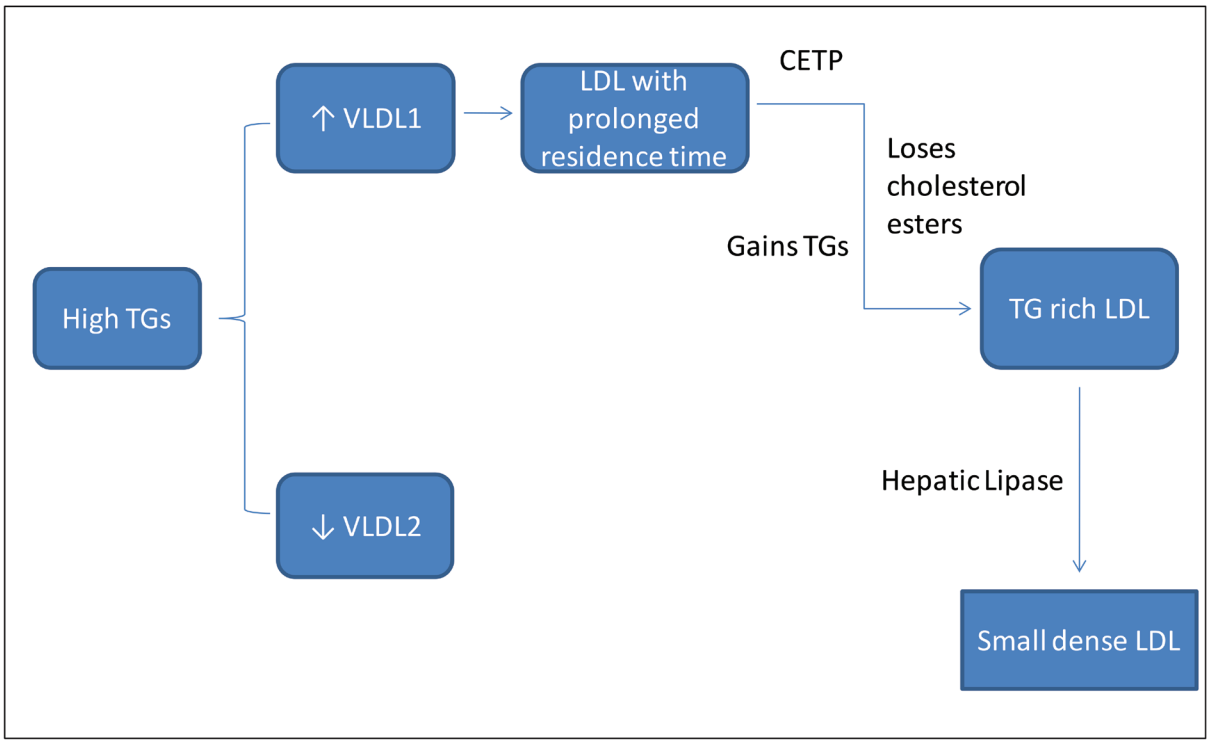

Fig. 3 Pathway of small dense low-density lipoprotein synthesis. CETP, cholesterol ester transfer protein; LDL, low-density lipoprotein; TG, triglycerides; VLDL, very-low-density lipoprotein.

Fibrates are peroxisome proliferator activated receptor α agonists. They increase muscle and hepatic fatty acid oxidation and reduce lipogenesis. In addition, they increase lipoprotein lipase (LPL) activity and reduce VLDL levels through decreased synthesis and increased clearance. The effect is reduced TG levels, modest elevation of HDL, and shift of sdLDL to large buoyant LDL (lbLDL) while total LDL remains the same. Though apparently fibrates appear to be a good treatment modality, disappointing results were obtained in clinical trials in regard to CVD prevention. Drugs that have been tested include fenofibrate, bezafibrate, and gemfibrozil.[23-25] Meta-analysis of the fibrate outcome trials has revealed that significant positive outcome is obtained in hypertriglyceridemic patients, who are but not in those who are normotriglyceridemic.[26] At present, fibrates are being used as an add on to statins in high-risk patients with baseline high TG levels.[27]

Niacin

Niacin reduces TG levels by decreasing TG synthesis and accelerating Apo B degradation leading to decreased secretion of VLDL, LDL, and sdLDL. High-dose niacin increases HDL.[28] Immediate release of niacin causes flushing and worsens glycemic control in Type 2 DM patients. Slow release forms are hepatotoxic and less efficient in raising HDL levels. Extended release forms have favorable effect on the lipid profile without being hepatotoxic or worsening glycemic control.[27] However, no additional benefit of adding niacin to statins has been demonstrated in any clinical trial for improving CVD outcome.[29]

CETP Inhibitors

CETP mediates transfer of TGs from TG-rich lipoproteins to HDL and LDL in exchange for cholesterol esters. This is the main pathway of reverse cholesterol transport and hence, cholesterol breakdown and excretion through the liver. Use of CETP inhibitors, for example, torcetrapib increases HDL levels but also impairs reverse cholesterol transport, hence curbing its benefit.[27] Until now good results have not been obtained using CETP inhibitors. Newer more potent drugs are being developed. Anacetrapib is one such drug which increases HDL, reduces LDL and Apo B 100, and increases the LDL TG/cholesterol ratio, LDL size, and Apo B 100 clearance.[30,31]

Statins

Statins inhibit the enzyme HMG CoA reductase; hence they control the rate limiting step of cholesterol synthesis. They are highly effective in reducing LDL; they also reduce TGs and raise HDL. Rosuvastatin in high doses is highly effective in reducing sdLDL levels.[32] Fukushima et al used atorvastatin to reduce LDL in patients with acute coronary syndrome and metabolic syndrome and found that the sdLDL reduction was 5.5 times greater than ACS patients without metabolic syndrome.[33] Choi et al, however, reported that though statins reduce the absolute levels of both sdLDL and lbLDL, they are not effective in reducing the proportion of sdLDL to total LDL.[34]

Sodium-Glucose Co-transporter-2 Inhibitors

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a group of drugs used in the treatment of Type 2 DM. They reduce blood glucose by inhibiting glucose re-absorption in the proximal tubules of the kidney. Clinical trials have revealed that SGLT-2 inhibitors reduce TGs and increase not only HDL but LDL as well. Hayashi et al in a study on the effect of the SGLT2 inhibitor dapagliflozin on the lipid profile of

Type 2 diabetics reported that dapagliflozin reduced the levels of sdLDL by 20% and increased ldLDL by 18% keeping the total LDL levels the same. They postulated that the reduction in sdLDL levels was brought about by reducing TG levels and increasing insulin sensitivity.[35]

Future Prospects

LDL reduction and subtype redistribution is an area of constant research. Interventional methodologies are being developed which will target the primary pathophysiological aspects of the atherogenic dyslipidemia complex and will lead to HDL increase and LDL subclass modification as a secondary effect. Together this will lead to a better outcome for those patients at risk of CAD. Some of the ongoing research areas are discussed below.

LPL activity is one of the factors influencing sdLDL levels. In patients with homozygous loss of function mutations leading to severe hypertriglyceridemia, gene therapy has a good outcome.[36] Strategies other than gene therapy are also being explored. APOC3 is an inhibitor of LPL. Inhibition of APOC3 using antisense therapy may reduce sdLDL levels.[37] ANGPTL are another group of proteins which inhibit LPL. Antibody-mediated blockade of ANGPTL3 has given good outcome in animal models.[38]

Other methods being tried out include inhibition of certain enzymes of lipid metabolism. Monoacylglycerol acyl transferase and diacylglycerol acyl transferase are enzymes involved in TG synthesis.[39] Acetyl CoA carboxylase catalyzes the rate limiting step in the fatty acid synthesis. Drug-mediated inhibition of these enzymes may decrease lipogenesis and increase lipid oxidation. Clinical trials are going on for these drugs.[40]

ETC-1002 (bempedoic acid) is another drug under investigation. It inhibits adenosine triphosphate (ATP) citrate lyase and activates AMP-activated protein kinase, thus reducing fatty acid synthesis and increasing its oxidation. A major benefit of this drug is that it reduces LDL levels regardless of the TG levels.[41,42] However, further clinical trials are required to assess its efficacy and safety as a combination drug.[27]

Whatever the treatment strategy being developed in the future, the importance of lifestyle modification in lipid lowering should not be ignored. Diet, exercise, and maintenance of healthy body weight have a positive effect on atherogenic dyslipidemia. Improved-insulin sensitivity and hormonal balance which accompanies lifestyle changes are thought to bring about this effect.[43-45]

Conclusion

Small dense LDL is the atherogenic component of LDL. It is a predictive biomarker for CAD. Lipid lowering drugs are being routinely used as a treatment component in high-risk patients for primary and secondary prevention of CAD. But the outcome is not always favorable, in spite of significant LDL reduction. Targeting the atherogenic dyslipidemia complex stressing on sdLDL reduction may be the solution. Various drugs have been shown to be effective in reducing sdLDL. However, further research is necessary to draw clear guidelines for sdLDL reduction therapy in CAD treatment and prevention.

Conflict of Interest
None declared.

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Viral Encephalitis: A Hard Nut to Crack

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Ann Natl Acad Med Sci (India) 2019;55:98–109

Abstract

Viral encephalitis is inflammation of brain that manifests as neurological complication of viral infections. There are quite a good number of viruses, for example, human herpes virus, Japanese encephalitis, and enteroviruses that can result in such a dreadful condition. Geographical location, age, gender, immune status, and climatic conditions also contribute to the establishment of this disease in an individual. Clinical signs and symptoms include fever, headache, altered level of consciousness, changed mental status, body ache, seizures, nausea, and vomiting. Effective management of this disease relies on timely diagnosis that in turn depends on apt and suitable investigation techniques. Traditional investigations have thinned out these days owing to the fact that advanced molecular technologies have been introduced to the diagnostic field. Treatment of viral encephalitis mainly involves symptomatic relieve from fever, malaise, myalgia along with measures to reduce viral load in the patient. This review mentions about all the possible aspects of viral encephalitis starting from etiology to the management and preventive measures that include immunization and vector control.

Keywords
- encephalitis
- viral infection
- pathogenesis
- molecular techniques
- management

Introduction

Central nervous system (CNS) is apex authority system of human body and hence it is secured within an exceedingly sophisticated barrier system. This highly complex barrier system sometimes fails to protect CNS and a wide variety of pathologic elements especially viruses manage to reach out CNS.[1] CNS infection is a broad term that might include one or combination of following anatomical sites: meninges (meningitis), brain (encephalitis), and spinal cord (myelitis), or simultaneously in multiple regions (meningoencephalitis, encephalomyelitis).[2]

What Is Encephalitis?

The word "Encephalitis" is an amalgamation of two words, one being a Greek word "enkephalon" that means brain and the other one is a Latin word "itis" that means pertaining to inflammation. Thus, encephalitis stands for inflammation of the brain.[3] To be more precise, it refers to inflammation of brain parenchyma and is usually associated with a spectrum of signs and symptoms including fever, headache, clouding of consciousness, seizures, personality change, focal neurological deficits, and coma.[4-9] Sometimes it can also be associated with brain dysfunction and noteworthy morbidity and mortality.[10] Statistic data suggest that ~5 to 10 per 100 000 residents per year suffer from encephalitis in urban countries; and is one of the alarming threats to the society.[11-13]

A syndrome that is present worldwide and is often associated with encephalitis is "Acute encephalitis syndrome" (AES).[14] It is mainly caused by viral infection and presents with acute-onset of certain symptoms such as fever, altered mental status and/or seizures, disorientation, delirium, or coma in a patient irrespective of his age. AES is a huge burden to public health, as it frequently leads to considerable morbidity and mortality.[5,14-17]

There are over 100 factors that can cause encephalitis.[18] Inflammation of parenchymal tissue may result due to direct infection, or due to a postinfectious process, or due to a noninfectious condition such as anti-N-methyl-d-aspartate receptor (NMDA) encephalitis associated with antibodies against subunits of the NMDA receptor.[9,19,20] For convenience of description, various causes can be grouped under two broad categories: (a) infectious etiological factors that include various microbes and (b) noninfectious etiological factors that

DOI https://doi.org/10.1055/s-0039-1697767
ISSN 0379-038X.

include chemicals and antibodies. ►**Table 1** enumerates various causative agents of encephalitis.[5,7,14,21-23] Since among all, viral infection of CNS is a major cause of encephalitis[1,24-26] this review will revolve mainly around viral encephalitis (VE). This review will shed some light on detailed profile of VE including its etiological agents, epidemiology, pathogenesis, clinical signs and symptoms, current diagnostic aids, management, and its preventive measures.

Viral Encephalitis

Though VE is an unusual complication of viral infection, viral infection is one of the prime causes of encephalitis.[27-30] Literature reports around 100 viruses that are believed to cause encephalitis.[31] Viral infection can strike any part of CNS, but it often causes meningitis and encephalitis. The ambit of vital findings includes fever, headache, altered mental status, sometimes accompanied by seizures and focal neurologic abnormalities.[32]

Table 1 Various causative agents of encephalitis

Infectious etiological factors	Noninfectious etiological factors
Bacterial • *Mycobacterium tuberculosis* • *Mycoplasma pneumoniae* • *Listeria monocytogenes* • *Borrelia burgdorferi* • *Brucella* species • *Leptospira* species • *Legionella* species • *Tropheryma whipplei* (Whipple's disease) • *Nocardia actinomyces* • *Treponema pallidum* • *Salmonella typhi* • Rickettsiae causing Rocky Mountain spotted fever Endemic and epidemic typhus Q fever Ehrlichiosis	Chemical/toxins Immune-mediated disorders • Anti-N-methyl-d-aspartate receptor encephalitis • Antibodies against voltage-gated potassium channel complex
Fungal • *Cryptococcus* • Aspergillosis • Candidiasis	
Parasitic • Human African trypanosomiasis • Cerebral malaria • *Toxoplasma gondii* • Schistosomiasis • *Naegleria fowleri* • *Balamuthia mandrillaris* • *Acanthamoeba* spp. • *Baylisascaris procyonis*	
Viral causes (mentioned in ►**Table 2**)	
Prions causing • Creutzfeldt-Jakob disease	

Etiology and Epidemiology

A wide variety of viruses that are presented in ►**Table 2** have been implicated to cause encephalitis.[6,21,26,33-40] Fortunately with increased vaccination rates and discovery of new vaccines, the rates of encephalitis due to previously common pathogens including measles (Morbillivirus), mumps (Rubulavirus), and poliovirus (Picornavirus) have declined over the past 60 years.[25,41] On the basis of etiology and pathogenesis, in general VE can be divided into four classes based on causes and pathogenesis[42]:

- Acute VE
- Postinfectious encephalomyelitis
- Slow viral infections of CNS
- Chronic degenerative diseases of CNS

Ascertainment of accurate epidemiology of VE is next to impossible because of variation in climatic and geographic conditions across the world. The annual cases of VE have been reported within the range of 7/100000 to 1/ 500000.[26,39,43,44]

Globally, majority of studies have concluded that herpes simplex virus (HSV) is the most prevalent cause of VE.[4,12,25,43,45-56] The pathogenic agents of VE vary from country to country. In Western countries such as France, England, and the United States, human simplex virus-1(HSV-1) has come up as the most prominent cause of sporadic VE.[39] West Nile virus (WNV) is the most common cause of epidemic encephalitis in the United States.[4,12,21,39,45,57-60] The available data also suggests that in Asian countries the primary pathogen of VE is Japanese encephalitis virus (JEV).[61-63] In a year, ~10,000 patients suffer from encephalitis caused due to JE.[64,65]

Table 2 Some important etiological agents of viral encephalitis

- *Human herpes simplex virus* (HSV)*:* HSV-1, HSV-2, Varicella-Zoster virus, cytomegalovirus, Epstein–Barr virus, human herpes virus 6 and 7
- *Adenoviruses:* serotypes 1, 6, 7, 12, 32
- *Influenza A*
- *Parvovirus (B19)*
- *Astroviruses*
- *Enteroviruses*: EV 9,70 and 71, echo- and coxsackieviruses, poliovirus
- *Measles, mumps, and rubella viruses*
- *Rhabdoviruses*: Australian bat *lyssaviruses*, rabies
- *Flaviviruses:* Japanese B encephalitis, West Nile encephalitis virus, dengue virus, Powassan virus, and Zika viruses
- *Tick-borne encephalitis viruses*
- *Bunyaviruses*: Toscana virus, La Crosse strain of California virus
- *Reoviruses*: Colorado tick fever virus
- *Retroviruses*: Human immunodeficiency virus
- *Alphaviruses*: Chikungunya virus, Venezuelan equine, eastern equine, western equine.
- *Henipavirus*: Nipah virus, Hendra virus
- *Bornavirus*: Variegated squirrel bornavirus 1 virus

To contradict above statement, a study done among Chinese children suffering from VE has reported that JEV was least involved in causing this disease.[40] Following herpes group of viruses, Varicella zoster virus (VZV) is the second most common cause of VE.[4,24,43,45,46,49,52-54,66,67] Literature has documented that around 1.8 cases per 10 000 cases of varicella zoster infection have led to VE.[68]

Apart from aforementioned viruses, human enteroviruses are also one of the prominent causes of VE in world.[46,55,62,63,69-71] Enteroviruses have many serotypes among which, enterovirus 17 has gained more attention because of its vital role in causing VE.[72] In India, JE has claimed more number of VE cases to its credit and is followed by herpes viruses, enterovirus, measles virus, mumps virus, dengue, Chandipura virus, and Rubella virus.[73-76]

The spectrum of severity of this disease is influenced by various following factors:

Age and gender variation: The highest incidence of VE is seen among younger age group patients and elderly people.[4,39,49,77,78] Studies have reported that number of male patients diagnosed with VE is more when compared with female patients. Verma et al reported that JE had more inclination toward male who belonged to younger or older age groups.[79]

Role of immune status: Patients who have compromised immune system are at greater risk of acquiring disseminated disease with the incidence upto 36%.[65] Immunocompromised patients are exclusive victims of cytomegalovirus infection, though VZV infection has also been reported.[39,80]

Seasonal distribution of VE and meningitis: Certain viruses have specific favorable set of atmospheric conditions for its growth and proliferation. Therefore, it blooms out in certain sessions and causes more damage. Human enteroviruses infection is believed to be more pervasive in summer and autumn, thus resulting frequent number of cases of VE during this session of the year.[40]

Pathogenesis

The first step toward VE begins with breach in CNS protective barriers. There are essentially two routes mentioned below through which viruses can gain access to the CNS and cause infection.[2,5,81]

1. Through blood supply:
    a. By directly damaging endothelial cells and creating passage through the junctions.[25]
    b. Or through anatomic structures that are less secured and have low strength defense such as the choroid plexus and circumventricular organs.[82,83]
    c. Or with the assistance of infected hematopoietic cells ("Trojan horses").[84,85]
2. By infecting peripheral sensory or motor nerves.

Following viral invasion in CNS, monocytes sneak into the infected CNS area and get transformed into required cell forms, for example, dendritic cell, macrophage, and microglial cells. Presence of Ly6C^{hi} monocyte in inflamed area of CNS is considered as pathognomonic finding of VE. These transformed cells aim at limitation and depopulation of viral components by assisting in antigen presentation and T cell stimulation. It also helps in producing numerous proinflammatory mediators and reactive oxygen species.[86] Pathogenic component that has reached CNS damages the nerve cells that results in disease and thus emergence of clinical symptoms. Apoptosis of nerve cells is causative factor of HSV-induced encephalitis.[25] ►**Fig. 1** illustrates pathogenesis of VE in brief.[87-90]

Clinical Signs and Symptoms of Viral Encephalitis

Emergence of clinical signs and symptoms mainly hinges upon type of viral infection, immune status, and age of the individual. As mentioned before, younger and elder people manifest more severe form of encephalitis compared with others.[21] Cardinal signs and symptoms are fever, headache, altered level of consciousness, changed mental status, nausea, and vomiting. When cortex is involved, seizures are one of the prominent findings.[39,91,92]

Findings associated with this disease can be grouped into following categories[21,93]:

1. Cognitive dysfunction: acute memory loss, speech, and orientation disturbance.
2. Behavioral changes: disorientation, hallucinations, psychosis, personality changes, and agitation.
3. Focal neurological abnormalities: ataxia, anomia, dysphasia, and hemiparesis.
4. Pyramidal signs: brisk tendon reflexes and extensor plantar responses.
5. Cranial nerve abnormalities: oculomotor and facial nerves are mainly involved.
6. Involuntary movements: myoclonus and tremors.
7. Seizures (may or may not be associated with the disease).

Diagnosis

Correct diagnosis guides into successful management of any disease. It starts with the observation of patient right from the moment when he walks into the clinic or hospital. Obtaining complete and precise patient's history is a key step toward unveiling hidden disease. In case of neuronal disorders, as patient is in a state of disturbed mental status, it is always better to approach patient's relative to seek his history. Following things should be asked for:

- Geographic and seasonal factors: certain viral diseases are more prevalent in certain season and in certain geographical area. For example, JE is endemic in Asian countries and spreads mainly in summer season.[21,94,95]
- Foreign travel or migration history. Any recent visit to area that is affected with VE should be considered into the account.
- Contact with animals (e.g., farm house) or insect bites.
- Immune status. Immunosuppressed individuals are more susceptible to certain specific encephalitis; for example, cytomegalovirus-induced encephalitis.[21]
- Occupation. People who work in farm, especially paddy fields, are more prone to JEV.

After proper case history, general examination has to be performed that must be followed by relevant investigations.

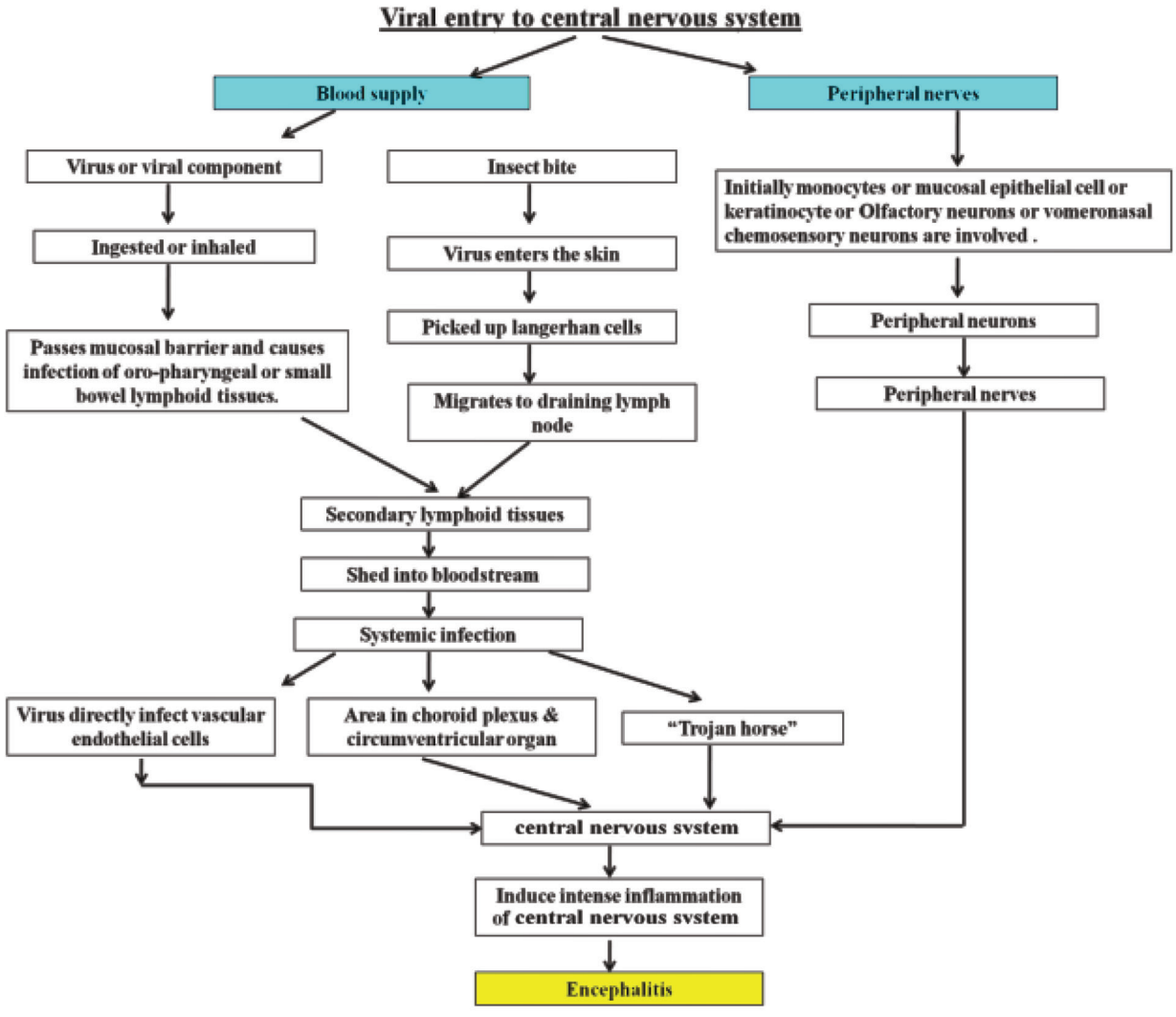

Fig. 1 Nutshell of pathogenesis of viral encephalitis.

General Examination

Most of the patients who are suffering from VE are bound to show up with mucosal or cutaneous lesions owing to viral infections. For example, herpes virus and varicella zoster infections often lead to skin rashes.[21] Therefore, thorough examination of patient's body is an important part of diagnosis.

Investigations

Once clinician suspects VE, various investigations are recommended to confirm the provisional diagnosis. Previously certain techniques such as viral cultures and immunological assays were commonly looked upon for carrying out investigations on suspected cases. But recently polymerase chain reaction (PCR) has dramatically restructured viral diagnostics by enhancing recognition sensitivity and specificity.[96] ►**Table 3** presents certain criteria proposed by International Encephalitis Consortium to define encephalitis case.[7,9,97,98]

Blood and Serological Tests

In VE, there is marked lymphocytosis that is evident on complete blood picture evaluation.[70] Serological investigations such as enzyme-linked immunosorbent assay (ELISA) to detect antibodies and antigenic components can also help in taking diagnosis to further level. But available literature indicates that for ELISA, cerebrospinal fluid (CSF) sample should be preferred over serum samples as specific activity (antigen binding per mole) of immunoglobulin M in CSF is believed to be greater than that of the serum. Thus, for diagnosis of VE by ELISA, CSF offers both superior sensitivity and specificity over that of serum.[79]

Direct Detection of Virus in CSF

Direct detection of virus by employing electron microscope has been mentioned in previous studies. Results obtained through electron microscopy were not much promising, hence resulted in its limited use in investigations.[99]

Table 3 Criteria to define encephalitis

Major criterion (required)	Minor criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis)
• Change in mental status of patient which lasts for more than 24 hours, for example, alteration in consciousness level or in personality	• Documented fever ≥38°C (100.4°F) within the 72 hour before or after presentation • Generalized or partial seizures not fully attributable to a pre-existing seizure disorder • New onset of focal neurologic findings • CSF WBC count ≥5/cubic mm • Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset • Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell.

Electroencephalography and Neuroimaging

Electroencephalography helps to mark epileptic seizures and it is helpful in differentiating encephalitis from generalized encephalopathy.[100] In case of herpes simplex encephalitis (HSE), periodic lateralized epileptiform discharges is a specific finding.

Neuroimaging also helps in detecting neuronal diseases as brain imaging is one of the important investigations. Magnetic resonance is preferred in case of acute encephalitis. Certain specific neuroimaging findings may assist to provide clue toward the etiology; for example, HSE causes frontotemporal changes along with small hemorrhagic lesions in the limbic system,[101] JE often presents with thalamic hemorrhage, and Eastern equine encephalitis results in disseminated lesions in the brainstem and basal ganglia.[21] Blood flow evaluation with the help of technetium-labeled hexamethylpropyleneamine oxime and single photon emission computed tomography provides critical information and hint of HSE.[102,103]

Cerebrospinal Fluid Analysis

CSF is checked for cell constituents including its morphology, protein, and glucose levels. CSF profiles of these elements often indicate basic character and severity of CNS infection. Out of 100 viral encephalitis patients, 90 exhibit abnormal CSF findings that consist of marked lymphocytic pleocytosis (>5 lymphocytes/mm^3), slight elevation in protein content (little above than 40 mg/dL),[7] whereas glucose level remains unchanged.[32,103,104] In enteroviral encephalitis and HSE, presence of neutrophils dominates the picture.[105,106] Unlike bacterial encephalitis, opening pressure of CSF remains normal in VE. Sometimes HSE exhibits increased level of erythrocytes in CSF (>500/mm^3) suggestive of intracerebral hemorrhage.[7] Sometimes abnormal lymphocytes have been encountered in CSF of Epstein–Barr virus (EBV) or cytomegalovirus-induced encephalitis.[107] In later stages of HSE, glucose level of CSF usually decreases.[108] A few recent researches have revealed that there is alteration in inflammatory cytokine levels in CSF. Interferon-γ and interleukin-6 (IL-6) levels are higher in initial stage of the disease but as the diseases progresses, tumor necrosis factor-α, IL-2, and soluble CD8 levels get elevated.[109]

Aforementioned data concludes that these CSF findings are not completely reliable for definite diagnosis, and thus various serological assays and genome analyses come into the picture.

Cerebrospinal Fluid Assays

It has been reported that in CNS infections intrathecal antiviral antibodies are been produced by choroid plexus. CSF assay proves its importance in diagnosing diseases where direct viral detection is not easy. This process involves demonstration of any of the following three antibodies, IgG, IgA, or IgM antibody, and it is considered as evidence of CNS infection even in the cases where blood–brain barrier is intact.[110] Government of India has set certain criteria to diagnose acute encephalitis, out of which, if IgM antibodies have been detected against a virus or its component in CSF, it is considered as causative factor of the disease.[111] The existence of a large number of constantly evolving viral serotypes can render antibody-based detection nearly impossible. Also, to present with detectable number of antibodies, CSF requires a period of minimum 1 week, which makes it less useful in early detection of disease.[108]

Brain Biopsy

It used to be a "gold standard" in diagnosis infectious encephalitis. It was advised frequently for detection of acute encephalitis in olden days with its sensitivity being 95% and specificity being above 99%. Histological findings reveal presence of inflammatory cells entrapping blood vessels, neuronal loss, and gliosis.[112] In case of HSE, temporal lobe region displays necrotic area. At microscopic level, certain viral inclusion bodies pertaining to specific viral infections can be observed, for example, intracytoplasmic eosinophilic Negri bodies in rabies, intranuclear Cowdry type A inclusions in herpes, and intranuclear inclusions in subacute sclerosing panencephalitis caused due to measles[112-115].

One of the main concerns associated with this investigation is invasive surgical approach that can lead to permanent neuronal damage.[4,45,69,97,116-118] After newer antiviral drugs came into the picture (e.g., Acyclovir), the trend of brain biopsy started to decline. In present scenario, it is contemplated when surgical decompression is a part of treatment for elevated intracranial pressure.[21] Brain biopsy may sometimes be necessary to confirm the diagnosis in cases where symptoms are worsening and treatment is not working.

Molecular Techniques

Before introduction of nucleic acid amplification technique, virus isolation through cell culture was considered as "gold standard" for isolation of viral component.[119,120] ►**Table 4** presents a list of trending molecular assay methods being employed to detect viral components.

Ligase Chain Reaction

It amplifies the nucleic acid instead of nucleotides. Ligase chain reaction (LCR) uses two enzymes: a deoxyribonucleic acid (DNA) polymerase (used for initial template amplification and then inactivated) and a thermostable DNA ligase. The concept of LCR relies on ligation of adjacent two synthetic oligonucleotide primers, which distinctively hybridize to one strand of the target DNA. This allows the differentiation of DNA sequences that are dissimilar even in a single base pair and thus this method is more specific than PCR.[121]

Polymerase Chain Reaction

PCR helps in detection of specific nucleic acid present in CSF by amplifying the target nucleotides. It is truly helpful in cases of HSV, VZV, cytomegalovirus, and EBV-induced encephalitis. If it is performed by experts, it delivers 100% specificity and >90% sensitivity.[108] CSF PCR withholds its sensitivity even after short courses of antiviral therapy.

Merits of PCR over other investigations are:

- Its high sensitivity.
- It can be accomplished in short duration of time (within 6–8 hours).
- It needs small quantity of sample (100–300 µL).[7]
- It is exclusively specific for particular set of genomes.

There are certain limitations of conventional PCR; for example, the maximum number of viruses detectable in a single assay is relatively small. To distinguish various viral subtypes or genera, supplementary steps, for example, restriction enzyme analysis, sequencing, or hybridization blotting of the PCR product, are needed. Although PCR gives promising results, its availability in every diagnostic laboratory is not obvious. Thus, initial serological assays screening is recommended before sending the samples to higher laboratories.[56,122]

Table 4 Nucleic acid amplification methods

Target-amplification techniques
• Polymerase chain reaction • Ligase-chain reaction • Isothermal transcription-based amplification methods: Transcription-mediated amplification Nucleic acid-based sequence amplification • Strand displacement amplification • Loop-mediated isothermal amplification
Signal-based amplification methods
• Branched deoxyribonucleic acid method • Hybrid capture assay

Reverse Transcription PCR

When ribonucleic acid (RNA) viruses have to be traced out, reverse transcription PCR comes into picture. It is similar to conventional PCR except for the first step where complimentary DNA (cDNA) is formulated out of RNA. It can be performed using two-step method or single-step method. In two-step procedure, reverse transcription of RNA occurs in the presence of reverse transcriptase enzyme that is followed by amplification of cDNA in the presence of different DNA polymerase enzyme. On the other hand, in single-step procedure, single thermostable enzyme that possesses both reverse transcriptase and DNA polymerase activity is used.[7]

Real-Time PCR

In real-time PCR, a fluorescent signal is released during each round of PCR amplification. It has produced good results in detecting WNV, Saint Louis encephalitis virus, and dengue virus) nucleic acid from different types of samples.[123,124] A comparative study to evaluate three diagnostic tests to detect JEV has been done. The study concluded that real-time PCR is more, sensitive, and specific method when compared with IgM antibody capture ELISA (MAC ELISA) and virus cultivation technique.[79] Ledermann et al in 2011 had conducted a study on horses and showed that real-time PCR can detect viral nucleic acid in samples that had very low viral load. Thus, it can help in detecting viral components in early stages of infection when viral load is less.[125] Real-time PCR has following merits over regular PCR technique[126]:

- Risk of contamination is reduced.
- Quantification of target is easy.
- Sensitivity is high.
- Reproducibility is high.
- Multiplexing can be considered.

Multiplex PCR

Main objective of multiplex PCR is to detect more than one target simultaneously. It is helpful in diagnosing diseases that have multiple etiologies.[127] Thus, it can assist in detection of etiology in case of VE. The challenge that is posed in this technique is the difficulty in designing compatible multiplex primer sets.

Other Nucleic Acid Amplification Methods

Transcription-Based Amplification Methods

There are two wildly known methods that follow this approach[128]:

I. Nucleic acid sequence-based amplification (NASBA) and
II. Transcription-mediated amplification.

Unlike conventional PCR, these procedures do not require wide range of temperature as these are isothermal reactions. When compared with conventional PCR, amount of amplified nucleic acid copies generated is more in these procedures. NASBA amplifies RNA thus it eliminates one step of cDNA synthesis that is needed in conventional PCR.[7]

Loop-Mediated Isothermal Amplification

It is also an isothermal reaction. It utilizes an enzyme with strand displacement property along with four primers out of which two are inner and two are outer primers. These primers recognize six different sites in the target nucleic acid and thus make it more specific reaction/assay.[7,129,130]

New Emerging Techniques

To overcome the constraints of available techniques, newer procedures such as microarray and multianalyte flow cytometry are being proposed.

Microarray

It is a genomic approach to assist viral detection. DNA microarray is capable of detecting around 100 viruses simultaneously.[96] A DNA microarray (also commonly known as DNA chip or biochip) is a collection of microscopic DNA spots attached to a solid surface. Generally nucleic acid (DNA, cDNA, or an oligonucleotide) microarrays are mottled onto a solid matrix at low density. The solid matrix is usually a glass slide.[131] A DNA microarray has been employed in investigations of VE with sensitivity being 93% and specificity being 100%.[132]

Multianalyte Flow Cytometry

This technique can systematically differentiate between equally sized particles on the basis of their internal properties. Therefore, it can be employed in designing immunoassays, Western blot-like antibody assays, and nucleic acid hybridization assays.[133] It is one of the new emerging approaches to detect multiple targets such as antibody, antigen, or nucleic acid.[7] There is not much data available on role of this technique in diagnosis of VE and thus further research in this area is recommended.

Specimens Other than CSF and Blood in the Investigation of Encephalitis

Specimens such as blood CSF have been routinely used in carrying out investigations of VE. Literature suggests that enteroviral infections have a replicative stage that occurs in throat and gastrointestinal tract. Thus, during this phase viruses can be obtained from specimens collected from these locations. Availability of viral component can be observed up to 4 to 8 weeks from throat samples and up to 11 weeks from stool samples. This extended duration of availability of viruses provides more time to conduct investigations.[7,134] In cases of viral infections that cause vesicle eruptions, the aspirate of vesicle can be used to carry out PCR.[100]

Management

Patients suffering from VE generally need intensive care.[135] Over the period of time, with advent of newer diagnostic techniques, drugs and clinical setups, management of VE has took a major leap.[100,136]

Essentially, while dealing with VE, following three parameters are to be addressed.

1. The need of antiviral or immune modifier drugs to arrest the infection.
2. To keep a check on symptoms and sufferings of patients; for example, to manage seizures, phenytoin and low dosage of benzodiazepines can be used.[100]
3. To prevent any late deleterious outcome of the disease; for example, certain drugs can result in nephrotoxicity and raise serum liver enzymes.[21]

The detailed available drugs have been mentioned in the ►**Table 5**, which are frequently used in VE therapy.[65,135-138]

Acyclovir is advised to combat HSE and VZE. It hinders viral DNA synthesis and thus halts virus replication.[21,65,139] This drug is more effective when administered in early stages of disease.[31,42,140] Lately, one more therapeutic strategy that has shown favorable results has emerged out. It implicates induction of histocompatible, virus-specific T cells into immunocompromised person suffering from infections such as cytomegalovirus and EBV.[141,142]

Table 5 Drugs used in treating viral encephalitis

Drugs	Dosage[a] and recommendations
Acyclovir	For adult, intravenous: 10 mg/kg every 8 hour For neonatal herpes simplex encephalitis is 60 mg/kg/d
Valacyclovir	1000 mg every 8 hour
Ganciclovir	Intravenous: 5 mg/kg every 12 hour. Recommended against cytomegalovirus infection
Valganciclovir	900 mg twice daily (induction) 900 mg once daily (maintenance/prophylaxis)
Foscarnet	Intravenous: 90 mg/kg every 12 hour or 60 mg/kg every 8 hour (induction). Recommended against cytomegalovirus infection
Cidofovir	Intravenous: 5 mg/kg weekly for 2 weeks (induction), then once every 2 week (maintenance)
Immunoglobulin	Intravenous: 400–500 mg/kg daily or every other day
Interferon-α	Assists in restriction of viral replication and is recommended against arbovirus infections. For example, West Nile virus or St. Louis encephalitis virus
Corticosteroids	To control raised intracranial pressure. It is also recommended when disease is accompanied by vasculitis. Prednisone equivalent dose of 1 mg/kg daily should be considered

[a]Dosage must be adjusted according to renal function.

Prognosis

There has been a marked improvement in prognosis of this disease in the past decades. Acyclovir intravenous therapy has decreased the mortality risk from 70 to 20%.[136,143,144] But still the satisfactory level of results has not been obtained. Approximately, up to 10% of the cases suffer from reactivation of the disease after completion of antiviral therapy.[100] A large section of patients, who manages to recover from VE, often complains of symptoms suggestive of permanent neurologic damage.[145-148] Prognosis of this infection also relies on age and immune status of the patient, etiology, and severity of the disease. Recovery from severe HSE often leaves the patient with symptoms such as seizures and anomia.[7] Patients of younger and older age groups are at greater risk to sustain permanent neuronal damage.

Vaccines and Other Preventive Measures

Prevention is always better than cure; thus, infections against which vaccines are available should be prevented by providing proper immunization to the suspected population. There has been an observable fall in number of new cases of JE after the development of JE vaccine.[149] Along with JE, vaccinations targeting polio, rabies, influenza, VZ, tick-borne encephalitis virus, mumps, measles, and rubella have also been introduced and have resulted in decline in incidences of related encephalitis cases.[135,150] Preventive vaccines against certain viruses such as WNV, dengue virus, and Zika virus are under investigations.[135] Along with immunization, measures to control vector population (e.g., mosquitoes) must be promoted.

Conclusion

Among all CNS infections, VE has always managed to keep itself in limelight. Recent past decades have certainly witnessed a marked improvement in diagnosis of VE but still a considerable number of patients go undiagnosed of exact etiology. VE is still one of the major threats to global health. Interestingly, molecular techniques have contributed in unveiling many hidden aspects of VE; hence, the upcoming techniques such as multianalyte flow cytometry and microarrays must be further researched to make them useful in diagnostic investigations. For a better management, it is recommended that upcoming investigations must have more inclination toward prevention of disease rather than treatment aspect.

Funding

The authors gratefully acknowledge the support provided by Department of Health Research under the Ministry of Health & Family Welfare (Government of India), New Delhi, India, and Indian Council of Medical Research (ICMR) in the form of establishment of state level Viral Research and Diagnostic Laboratory network under scheme 5066.

Conflict of Interest

None declared.

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Euthanasia: Ethical Challenges of Shift from "Right to Die" to "Objective Decision"

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Ann Natl Acad Med Sci (India) 2019;55:110–116

Abstract

Euthanasia is mercy killing to alleviate the pain and misery of moribund persons. The thought in this regard is "Right to Life" includes "Right to Die." This paper examines the issue of euthanasia in advanced stage of terminal cases with no possibility of reversal and it has been argued that there is a case for lifting euthanasia from the domain of human rights "Right to Die," bringing the issue as a matter for professional opinion, a kind of medical advice/prescription. Guidelines need to be framed and criteria are laid down and notified under which euthanasia can be recommended. The decision is taken whether or not the criteria laid down are fulfilled in an objective manner. Like for other medical interventions "informed consent" is essential. In consideration of safeguards the decision is entrusted to a medical board and is subject to a legal prescrutiny. Professionally prescribed decision will to a great extent reduce emotive response surrounding euthanasia. The family may not have to face a difficult dilemma in deciding about euthanasia. There may not be a necessity of "living will," although it may still be useful. The change to treat euthanasia as a professional decision/medical advice will require making legal and administrative provisions to empower medical establishment to discharge responsibility of euthanasia. It is essential to legalize euthanasia with corresponding modifications of medical ethics and code of conduct prescribed by Medical Council of India, State Medical Councils, and other regulatory bodies. It is essential to identify the procedure for carrying out euthanasia and the personnel assigned to actually carry out. Injection of lethal substance in lethal dose may be a favored choice. Once final decision after legal prescrutiny is arrived for euthanasia, differentiating passive and active euthanasia is unnecessary. In one perspective, active euthanasia is less disturbing for the patient, family, and friends as withdrawal of supporting tubes leading to dehydration, wasting, and struggling for breath associated with passive euthanasia, which nullifies the basic tenet of euthanasia, can be avoided. There is a possibility of spill over benefit of "active euthanasia" in the form of opportunity to promote cadaveric organ transplantation. Caution has to be exercised for effective safeguards to prevent misuse. There is a case for consideration for brining decision-making process regarding euthanasia within medical professional assessment and implementation.

Keywords
- euthanasia
- active euthanasia
- human rights
- mercy killing
- peaceful death
- chronic vegetative state

Introduction

In the context of the present paper, the term "euthanasia" refers to "mercy killing" with a view to alleviate the misery and suffering of patients, their families, and society at large in cases of terminal stages of incurable disease with no hope of reversal and living, socially unproductive vegetative existence, that is, termination is considered a better

DOI https://doi.org/10.1055/s-0039-1698362
ISSN 0379-038X.

option than continuation of life. The present paper attempts to explore the possibility of euthanasia to be a professional evaluation and decision, a kind of medical prescription.

There are two kinds of euthanasia, passive and active. Passive euthanasia is withholding interventions and active euthanasia involves taking specific steps. Both are intended to cause death. Euthanasia is administrated death which in common parlance is understood as murder and self-administrated as suicide. Both of these are criminal acts and any discussion on euthanasia has to address these concerns. Withdrawal of organ support system in "brain dead" or heart beating cadaver does not qualify as euthanasia as "brain dead" person is a dead person. This seemingly paradoxical situation is because of paradigm shift of definition of death from stoppage of heart beat and breathing to cessation of brain activity. Guidelines for declaration of brain death are included in the Act.[1] Functioning status of some organs may be preserved by use of technology but that should not be construed as life-support system or prolongation of life. The objective of provision of "brain death" is to determine end of life beyond which medical care of the patient is redundant. The opportunity thus offered for consideration of cadaveric organ transplantation program is incidental. Euthanasia is aimed to address issues of those who are living but the termination is considered a better option than continuation of life.

Current Focus

There are several issues surrounding the concept of euthanasia and are subject of public debate in many countries including India. The Honorable Supreme Court of India has opined that the High Courts may permit passive euthanasia on case–to-case basis till legal provision is enacted.[2] Law Ministry of Government of India has placed a draft of legislation on passive euthanasia in the pubic domain inviting public comments.[3] This draft bill deals only with passive euthanasia which in itself is a major short coming. A suggestion that the legislative exercise should include active euthanasia has been made.[4] Unfortunately, legislative process to enact a law on euthanasia has not been completed.

The Supreme Court has in a recent judgment legalized "passive euthanasia" and "living will" despite reservations by central government in recognizing living will on the ground that the patient may not be aware of the advancements in the treatment.[5] The concerns of the government are valid and hopefully the provision of medical board included in the judgment will address the issue. Major challenge is to identify and formulate practice guideline where termination is considered a better option than continuation of life. It is satisfying to note that euthanasia has been granted legal sanction though only passive euthanasia is covered. Differentiating passive and active euthanasia on the basis of mode of carrying out the decision does not appear to be logical or justifiable. Hopefully, legislation will address the issue of euthanasia in a comprehensive manner and include "passive" and "active" euthanasia on equal footing.

The current focus is to consider euthanasia under the doctrine of rights, such as "patient's right to die" as a follow-up of "patient's right to life." It has been argued to shift management of dying to the dying person as an expression of control including end–of-life decisions and euthanasia.[6] Exercising this right, a patient may opt for death instead of life of what he perceives life of misery, remorse, dependence on others for even tasks of daily living, and not worth living. The person may have expressed his desire/decision in favor of euthanasia to his family members, friends, well-wishers verbally, or in a written form, a kind of living will that is a statement of directions to be carried as per his/her wishes when he/she is not in a position to give directions directly but is still technically living, and the document has the same standing as a will and therefore is called living will ensuring wishes are performed.[7] As per court directive guidelines for living will are to be included in the proposed law on passive euthanasia.[8] There is a wide spread practice referred to as "Do Not Resuscitate" (DNR) followed when the process of natural death has started in a terminally ill patient so as not slow down or delay death.[9]

The situation may be complex in cases where the final event in the process of natural death has not started but the condition of patient is otherwise considered fit for euthanasia; termination is considered better option than continuation of life. The process of passive euthanasia consists of withholding food, water, medicines, and life-support system which may be a disturbing feature to witnessing the loved one in great misery slowly withering away, dehydrated, struggling for breath, particularly, so if it lingers on. Such a situation is against the spirit of euthanasia aimed at relieving miseries.

The patients, their family members, well-wishers, and caregivers may pray silently and hope for early death but still hesitate taking active steps for relief from miserable existence out of fear, training, cultivated mind set, social norms or behavior, and other reasons. In some cases, additional measures may be taken for the purpose of causing death. The relatives on request from the patient or otherwise provide information and substances to the patient thereby assisting and abetting suicide. Some persons wanting euthanasia may not be able to do final act for various reasons. Physician assisted suicide then assumes some important role in the context of euthanasia.[10] Involvement of medical persons is known to occur, though secretly. Some cases remain unreported.[11] Books offering practical suggestions are available to help persons desirous of euthanasia.[12] In absence of clearly defined law, it is not certain whether those involved in euthanasia are assured of protection against charges of wrong doing.

Taking an overall view when seen in context of human rights, euthanasia becomes an emotive issue with contradictory and irreconcilable ideological positions. Is there any alternative?

Alternate Approach

An alternate approach is to lift euthanasia from the domain of human rights and treat it as a professional decision. Euthanasia then becomes an objectively considered opinion and recommendation, a kind of medical prescription if one may like to call it, to terminate a life which has lost its purpose, is

meaningless and has no usefulness to the society. Like other professional decisions and recommendations/prescription/advice suggestion of euthanasia will be subject to informed consent by the concerned person or legally valid representatives. The concept of informed consent in medical interventions is well accepted.[13] A living will is of immense values in this context.

If such a proposal of treating euthanasia as objective medical decision is accepted, multiple operative steps are required to be decided.

Legalizing Euthanasia

As a first and foremost preliminary step of euthanasia, without creating distinction between passive and active euthanasia, will have to be legalized, so that option of euthanasia is put on proper and sound footing. Working out further details will be relevant and meaningful only if euthanasia is accepted legally in principle and otherwise permissible. Legislative initiative must be comprehensive and include not only the concept and social acceptability but also address various concerns and critical issues, such as under what circumstances termination is considered an option, who decides, what methods to be used and who should carry out, dangers and safeguards, required changes in medical ethics and code of conduct, and administrative and other provisions to accommodate the change. The authors attempt to address some of these concerns and provide suggestions.

Task Force

A committee or "Task Force' should be constituted to examine different issues arising from the suggestion that euthanasia be considered as a part of professional decision instead of its being an issue in the domain of rights, "patient's right to die." The task force must be broad based group consisting of physicians dealing with advance incurable diseases, givers of end-of-life care, medical ethicists, legal profession, medical sociologist/anthropologists, human rights activists, social worker, political and religious leaders.

Key Issues

Indications for Euthanasia

Guidelines have to be framed that under what conditions and situations euthanasia may be considered as an option and recommendation. A statement on the lines like euthanasia may be considered when a patient is in chronic vegetative state, has lost meaningful existence, is suffering with miseries, etc., can best be taken as general principle but is not sufficient or of practical value. The guidelines must clearly identify to the extent possible the diseases/conditions and points in the progression and clinical profile at which termination is considered a better option than continuation of life. It is essential to define and lay down the criteria for expression "chronic vegetative state." Though difficult, it is most essential part of the exercise. Involvement of clinical disciplines and end-of-life caregivers is very useful in formulating these points. Special investigation for confirmation and objective decision making process may also be included.

Authorized Agency: Medical Board

Next major issue is to identify the agency authorized to take decision in respect of euthanasia establishing whether or not a particular patient fulfills the criteria laid down. The medical establishment is expected to discharge this responsibility and evaluate the patient's status on the relevant parameters. Being a sensitive issue the decision regarding euthanasia may not be entrusted to a single physician or a single unit. A system of shared responsibility needs to be put in place.

A Medical Board may be entrusted with this responsibility. The Board must have representation of social scientist, family counselor, medicosocial worker, in addition to medical team. The aim is to reduce subjective element and to gain confidence and acceptability by the society. Such a Board may be linked to an already existing committee like institutional ethics committee or be a separate stand-alone entity. The jurisdiction of the Board may be limited to one particular institution or may cover a group of institutions for logistic consideration and economic reasons. This aspect also will have to be examined by the task force.

There may be a situation when a patient is not admitted to a hospital but is being taken care of at home or a hospice, nursing home, etc., and the patient may have reached a stage which merits evaluation for euthanasia. There must be a provision to address this situation. A system of referral to an area wise designated Medical Board may be introduced. The treating physician or caregiver refers the case to the relevant Board with all the clinical notes and other information as is required. A specially designed format will help in recording of essential information and minimizing chances of omission. The Board will go through these documents and may elect to examine the patient independently and interact with family or well-wishers. The referring physician or caregiver from outside should also be available for clarification, if any is needed.

Legal Prescrutiny

In an effort to reduce errors in the judgment of the authorized agency, a system of built-in mechanism of legal prescrutiny may be put in place. The recommendations and notes of the Medical Board along with all documents are to be sent for scrutiny to a court designated for the purpose. The aim is to ensure that the criteria as laid down have been fulfilled, and there has been no extraneous consideration in arriving at conclusion by the Medical Board. The finality of the recommendations is reached only on confirmation by the court. Subsequent action is initiated after confirmation.

Administering Euthanasia

Medical technology will have to devise a humane method to carry out euthanasia which is less painful and faster. It may be noted that the basic idea behind mercy killing, euthanasia, is to reduce misery and not enhance it by such techniques as withholding respiratory support, tube feeding, intravenous

fluids, and medications, followed in passive euthanasia which is perceived as "safe method," though actually is against the spirit of euthanasia. As such passive and active euthanasia are directed to the same goal of causing death. The distinction between passive and active euthanasia is unnecessary.

There is a need to define process to administer euthanasia identifying the procedure and personnel to carry out the decision. The treating physician or team is best suited as a nodal point for coordinating and preparing the necessary papers for the Medical Board. The patients from outside who are brought to the institution empowered to evaluate for euthanasia will have to be admitted to the institution where evaluation is under taken. The referring physician or caregiver from outside should also be available for clarification, if any is needed by the Board.

There is also a necessity to identify the team who will actually carry out the procedure. The treating unit has an advantage of continuity and good rapport with the family that will lessen emotional and sentimental strain on the well-wishers. Association of team of intensive care unit (ICU) where patient is likely to be located will be useful. Participation by ICU team and anesthesiologists will have an added advantage in case cadaveric organ donation is contemplated. Creation of a special team may not be appropriate.

Apprehensions and Reservations

There are certain apprehensions and reservations before medical establishment in getting involved in the issue of euthanasia, particularly in carrying out the procedure, and these must be addressed adequately and satisfactorily.

There is moral dilemma for a physician, directly or indirectly, to be responsible for death. The training and mind set of physicians are tuned to do everything to preserve and prolong life, and nothing is done to harm the patient. The concept of euthanasia is in complete contrast to this dictum. There is a perceived danger of charges of violating the medical ethics and code of conduct prescribed by the Medical Council of India and State Medical Councils. Therefore, if the suggestion, made in this paper, is to gain ground, necessary modifications have to be effected in the norms of regulatory bodies.

Strategies to modify mind set will also have to be evolved to accept euthanasia as part of legitimate and acceptable professional activities, and it should be possible. In this context, reference to a similar situation may be made as an example. Abortion was banned before Medical Termination of Pregnancy (MTP) Act came into existence and induced abortions were called criminal abortion. Now with MTP Act, termination of pregnancy under certain conditions is part of practice of the relevant discipline. Therefore, it may not be out of place to conclude that a change in the mind set and norms of regulatory bodies are possible. The medical profession is likely to accept euthanasia as part of professional work.

Collateral Issues

Some issues which are not central to the concept of euthanasia or to the suggestion being placed in this paper are important and need attention. There is an issue of death certificate. The committee assisting legislative process must determine whether there is a need of mentioning the fact of euthanasia on the death certificate. In any case, it must be ensured that the death certificates remain valid, without controversy, for all purposes including insurance and medical bill reimbursement.

Permission for autopsy from the family may be sought as per normal practice as an exercise for continuing medical education. However, extra care should be taken to avoid giving an impression that autopsy is a precondition. There should not be any interference in the medicolegal postmortem.

Efforts should be made to counsel the family for organ donation in suitable cases to promote cadaveric organ transplantation. In this situation, extra care must be taken to dispel an impression that organ donation is a prerequisite. Cadaveric organ transplantation may be collateral side benefit but the central issue is addressing terminal illness. In this context, it is prudent to approach the topic only after the finalty is reached on confirmation by the designated court. If organ donation is agreed, the organ retrieval team is informed and the euthanasia is scheduled accordingly. Otherwise the timing is adjusted according to the convenience of family.

Care must be taken to ensure dignity and respect for religious sensitivities in handing over dead bodies to the relatives.

Dangers and Safeguards

There is a danger of overuse and misuse of provisions. It must be ensured that euthanasia is the last and not an alternate option in the end-of-life program. Loss of autonomy, degree of dependency, and family and physicians' support are significant factors in the evaluation for euthanasia.[14-16] The dignified death is gaining importance in consideration of issue of aging,[17] although the concept of euthanasia is not confined to old age but is concerned with terminal incurable disease in all age groups. It is important to distinguish between suitable and unsuitable candidates. The dividing line is thin, and it is essential to avoid errors. The risk of making errors is reportedly small.[18]

These dangers are inherent in the concept of euthanasia per se and not connected with the suggestion contained in this paper. There is additional danger is this proposal. There may be a vested interest in being extra liberal to promote cadaveric organ transplantation. This danger may be real or only imaginary and a theoretical possibility. Hopefully safe guards outlined earlier of constituting Medical Board for decision, informed consent, and built-in legal prescrutiny will address the safety concerns adequately.

Sociocultural Dimensions

The discussion on death and dying in general and euthanasia in particular are emotive issues and are surrounded by controversies. Some aspects of social science perspective of euthanasia have been dealt with elsewhere.[19] The present

paper deals with decisions-making process with a plea to lift euthanasia from the domain of "human rights" to bring it under professional evaluation and decision or a prescription, subject to informed consent. The proposition has wider sociocultural ramifications. Even if legally permitted, the medical persons are reluctant and feel uncomfortable in associating with the activities to cause death.[20]

In the doctrine of euthanasia as a "right," the patient or family member or caregiver perceives the need and seeks euthanasia which is decided by legal process on case-to-case basis. The patient may have given advance authorization by way of living will which may facilitate consideration, even then appropriate assessment by the authorized personnel, the medical team is needed to establish whether the patient's status fulfills the conditions of the living will. The family and well-wishers and caregivers may face a serious moral dilemma in deciding even in presence of living will.

Under the proposed decision-making process, the treating team recommends euthanasia as per guidelines. The recommendation is subject to informed consent like any other intervention assuring participation by the patient or family. The shift from "right" to "professional opinion" has wider social implications.

Criteria under what conditions euthanasia is considered are determined and notified. The given patient is assessed whether or not these are fulfilled and a system of legal prescrutiny before finalty provides further safeguard. The proposed decision-making process by professional assessment strengthens the confidence and acceptability of euthanasia by the society.

The patients and their representatives feel relieved on the knowledge that the decision is arrived at on the basis of competent assessment. The dilemma faced by the family in the difficult situation is resolved. However, the suggestion is not to endorse paternalist approach with patient occupying a passive role. The point is that euthanasia needs to be demystified and may be treated at par with other medical interventions that require informed consent. It is essential to appreciate need for laws to reduce unnecessary procedures for prolongation of life[21] which are not serving any useful purpose and actually delaying death only. Though curtailing unnecessary interventions may result in substantial savings, economic consideration should not become determining factor.

In many societies including India, high premium is attached to "peaceful death" and the prescription of active euthanasia by medical personnel offers such an opportunity. When the end comes, it is possible to organize the family members and friends to be at bed side of the patient which is highly valued sentiment. In a study of interaction in medical setting, it was observed complex hospital rules may be the cause of dehumanizing experience of modern medicine[22] which may be the case when the patient is in hospital or ICU with restrictions of entrance.

Among other debates concerning euthanasia there is continuing discussion on choice between passive and active euthanasia. If euthanasia is accepted in a given case, distinction is unnecessary. The process of passive euthanasia is disturbing to witness and may be prolonged. It may be recalled in case of Teri Schavio in the United States, it took 13 days for death after feeding tubes were withdrawn.[23] In this perspective, active euthanasia is a better option.

Euthanasia and active euthanasia by medical opinion may come in direct conflict with medical ethics and standard teaching or doctors restraining them from killing person. This uneasy feeling is further increased by participating in active euthanasia. Need for legalizing euthanasia and corresponding modifications of medical ethics and code of conduct are essential component of consideration for euthanasia. There is a felt need for education of physicians in end-of life-care palliative care programs[24] and euthanasia as a last resort may be included.

Conclusion

There is a strong case for shifting euthanasia from the domain of 'right to die' and bringing the issue within the fold of professional evaluation, and decision as per prescribed guidelines subject to informed consent and clearance by legal pre-scrutiny. Active euthanasia is a better option than passive euthanasia for alleviation of miseries and ensuring 'peaceful death' which are the primary objectives of mercy killing: euthanasia.

Conflict of Interest
None declared.

Acknowledgment
Notes and draft of a paper presented by late Prof. Aneeta A. Minocha, Department of Sociology, Delhi School of onomics, University of Delhi, at a Seminar on Euthanasia organized by Vidyasagar Institute of Mental Health Sciences, New Delhi, in November, 2004 have been used to formulate this paper. Authors duly acknowledge the use of her work in the present paper.

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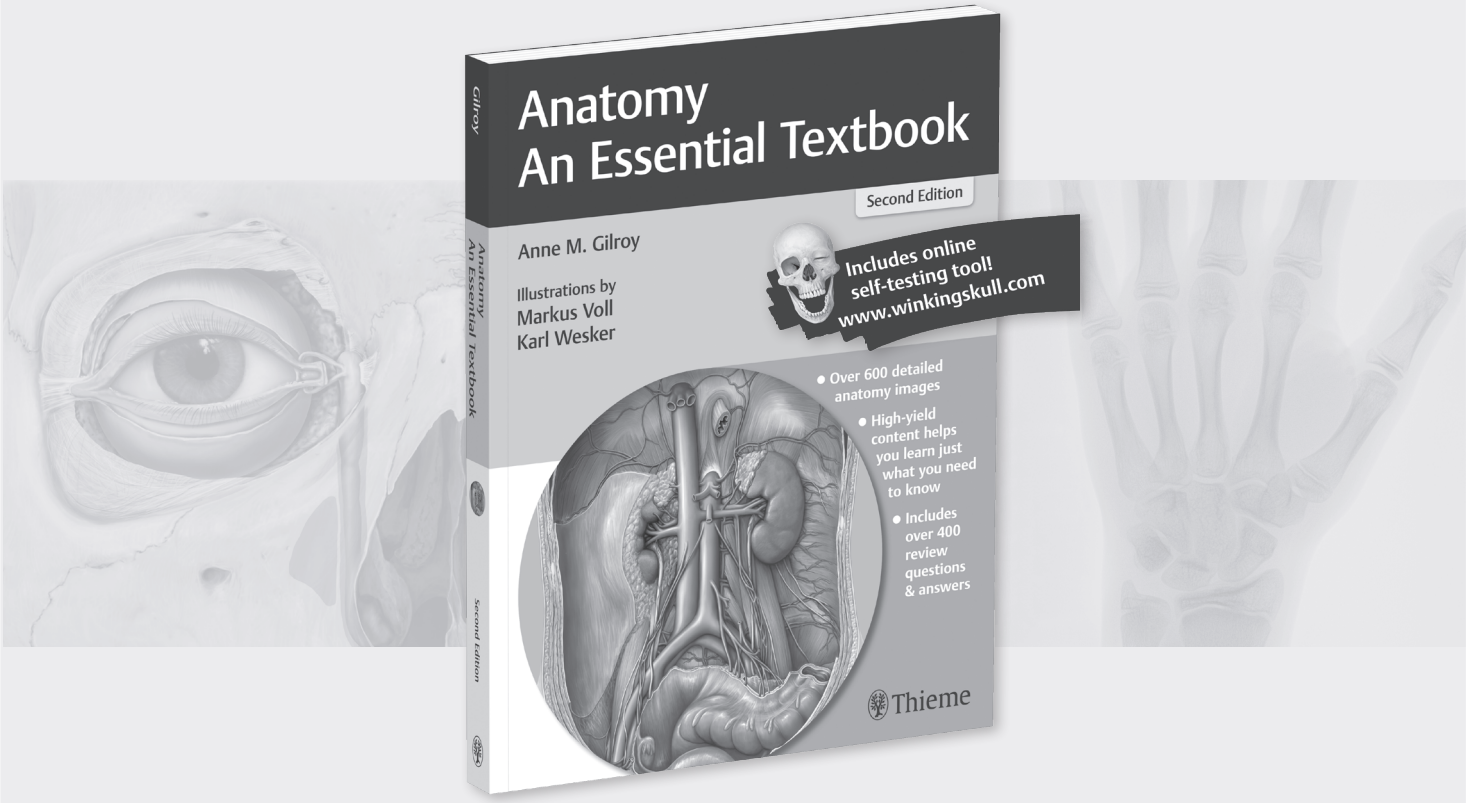

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