



REVIEW

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NUCLEAR MEDICINE & ITS APPLICATIONS

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ABSTRACT

Nuclear Medicine is involved in diagnosis of many clinical problems. Similarly therapeutic role involves treatment of diseases in many treatment of thyroid diseases like Grave's disease, toxic hot nodule toxic multinodular goiter (MNG) and ablation of differentiated carcinoma of thyroid with radioactive iodine organs (^{131}I) similarly ^{32}P is used for bone pain palliation in metastasis. Medical students have minimum exposure to Nuclear Medicine at undergraduate and even at postgraduate level. This review would briefly introduce the subject and would also be helpful for FCPS-II students.

Abbreviations: $^{99\text{m}}\text{Tc}$ (Technetium = isotope used for diagnostic purpose), ^{201}Tl (Thallium = isotope used mainly for cardiac scan), mrem/hr (unit of radiation exposure), ^{18}F (Flourine = isotope used in (PET) Positron Emission Tomography studies), SPECT (Single Photon Emission Computerized Tomography), PET (Positron Emission Tomography), FDG (Fluorodeoxyglucose), MIBI (6-Methoxy isobutylisonitrile), RIA (Radioimmuoassay), IRMA (Immuno radiometricassay), RIS (Radioimmuno scintigraphy).

INTRODUCTION

Nuclear medicine is the speciality, which utilizes radioisotopes for the purpose of diagnosis and treatment of different clinical problems. Diagnostic aspect being the major portion involves scintigraphic imaging while the therapeutic aspect is limited. Recent developments for new radioisotopes, radiopharmaceuticals and computerized equipments have markedly improved the outcome. This modality gives much more functional

status of an organ as compared to other diagnostic techniques like ultrasound, CT and MRI which provide better structural details. The basic principle involved in Nuclear Medicine is tagging of radioisotope to an organ specific pharmaceutical. The radiopharmaceutical approaches at cellular level of the target organ furnishing its physiological status. Many radioisotopes have been developed for diagnostic and therapeutic purposes but commonly and most widely used isotopes are technetium [$^{99\text{m}}\text{Tc}$], Thallium [^{201}Tl] and

radioactive iodine [^{131}I]. Technetium is the isotope having half-life of 6 hours and gamma energy of 140 Kev which is the near ideal isotope used worldwide for diagnostic purpose. Radioactive iodine [^{131}I] is mainly utilized for treatment of Grave's disease, toxic hot nodule, toxic MNG and ablative therapy of differentiated carcinoma of thyroid. ^{123}I is isotope used for thyroid scan in developed countries but due to its non-availability in Pakistan, ^{131}I is employed for this purpose.

Conventional planer imaging is now being augmented with computerized tomography. Single photon emission computerized tomography [SPECT] and positron emission tomography [PET] provide three dimensional picture of the target organ and furnishes much better functional information.

$^{99\text{m}}\text{Tc}$ is the isotope used in planer and SPECT imaging. PET utilizes the positron emitting isotopes [^{18}F , ^{11}C , ^{15}O , ^{13}N]¹. There are no side effects of the radiopharmaceuticals used in nuclear medicine; however, occasionally minimal skin rash or itching may be seen. Pregnancy being the absolute, while lactation is the relative contraindication for any radioisotopic investigation.

DIAGNOSTIC ASPECTS:

- Bone scan
- Liver scan
- HIDA scan
- Brain scan
- Renal scan
- Lung scan
- Meckel's scan
- Salivary gland scan
- Labeled RBC scan
- Radionuclide venography
- Radionuclide lymphangiography
- Cardiac scan
- Thyroid related investigations

BONE SCAN

Commonly this investigation is advised to see metastatic spread of carcinomas, however, there is a long list of indications as this test is quite simple, noninvasive and cost effective. An injection of $^{99\text{m}}\text{Tc}$ labeled MDP

[Methylene diphosphonate] is given IV followed by an interval of 3 hours. The radiopharmaceutical localizes in bony tissue with more avidity for sites having increased osteoblastic activity while less affinity for osteolytic lesions. Planer imaging is usually performed which shows area of increased osteoblastic activity as "HOT" and vice versa. SPECT scanning is also performed for doubtful lesions, not clearly visible on performed for image. Bone scan has the capability to localize the area of metastatic spread much earlier as compared with conventional radiology^{2,3,4}. Primary bone tumours as osteogenic sarcoma, Ewing's sarcoma and osteoid osteoma are also picked up by this technique. Bone scan appearances of osteoid osteoma are usually characteristic having high sensitivity for lesion detection compared with X-ray^{5,6}. "3-phase bone scan" is carried out in order to see blood flow to any localized area of the body followed by static "3-hour bone scan" to differentiate bony pathology from soft tissue infection. This technique is helpful in suspected cases of osteomyelitis, stress fractures, shin splint and avascular necrosis. Many army recruits, athletes, weight lifters and cricket fast bowlers are prone to develop stress fractures and shin splint which are difficult to pick up on x-ray in the initial stage while "3-phase bone scan" has the capability to diagnose these lesions quite early. Patients of avascular necrosis of head of femur, osteomalacia, rickets and renal osteodystrophy also benefit from this test.

LIVER SCAN

Liver scan is done 15 min after IV injection of $^{99\text{m}}\text{Tc}$ labeled tin colloid. Radiotracer localizes in the reticuloendothelial cells of liver and spleen. As the distribution of these cells is altered at the site of any focal liver pathology, the specified area appears as a focal defect. Similarly in cases of cirrhosis and hepatic parenchymal disease, the ratio of distribution of tracer in liver, spleen and bone marrow is deranged resulting in specific findings on scan. Indications include cirrhosis, hepatitis, hepatoma, proliferative disorders and assessment of splenic function. Equivocal lesions seen on ultrasound like focal area of fatty infiltration, focal area of fatty sparing and suspected hemangiomas need further work up on colloid liver scan.

HIDA SCAN

Dimethyl-iminodiacetic acid [HIDA] is a pharmaceutical labeled with radiotracer [^{99m}Tc] and given IV to a patient with 6 hour NPO. Liver, gall bladder, biliary tract and the passage of the tracer into the gut are normally seen within 30 minutes of the injection. This investigation is commonly called HIDA scan because of the common name of the pharmaceutical. However, now-a-days DISIDA [Diisopropyle iminodiacetic acid] is employed routinely because of its better characteristics. Common indications include acute cholecystitis, chronic cholecystitis, assessment of patency of biliary tract, biliary leaks, biliary enteric anastomosis, biliary atresia and work up of patients to differentiate pre and post hepatic cause of jaundice.

When clinical symptomatology is typical of acute cholecystitis, including Murphy's sign, fever and leucocytosis, no additional work up is necessary. Most of the acutely ill patients, however, do not present so typically⁷. Demonstration of gallstones in gall bladder on USG does not confirm the diagnosis of acute cholecystitis. Identification of cystic duct obstruction with a stone is the major criteria but the ability of sonography to diagnose cystic duct obstruction especially with impacted cystic scan, the gall bladder is not visualized within 1 hour of the tracer injection confirming cystic duct obstruction in case of acute cholecystitis. Cases of "acalculous cholecystitis" are also diagnosed by this investigation. The sensitivity and specificity approaches 95%, if the test is performed properly¹. After the gall bladder is visualized, fatty meal is given to the patient to see its contraction response. Normally tracer is seen in gut within 30 min, however, different pathologies of biliary to enteric pathway prolong the passage time.

BRAIN SCAN

Radioisotope brain scan is advised for the assessment of conditions like CVA, tumors, metastases, abscess and infection. Conventional planer scan is performed with the tracers that do not cross the blood brain barrier. ^{99m}Tc -DTPA is commonly employed for static imaging which is performed after 1 hour of IV injection and pathologies like CVA, primary or secondary brain tumors appear as a hot area. Intracerebral hemorrhage leads to positive brain scan after several hours of onset while cerebral embolism leads to positive findings

within 1-7 days of insult. In cerebral infarction, the scan remains silent in the initial 7-10 days with maximum tracer uptake between 6-8 weeks of the start of symptoms. Similarly cerebral contusion leads to silent brain scan in the initial 7-10 days, becoming increasingly abnormal afterwards, stabilizing by 2nd to 3rd week and disappears in 8-10 weeks. In chronic subdural hematoma, scan is usually positive after 2 weeks as it has the tendency to encapsulate with a membrane beginning to form about 72 hours after venous rupture¹.

^{133}Xe , ^{123}I -IMP, ^{99m}Tc -HMPAO are radiotracers used in SPECT studies, which demonstrate changes in blood flow in neoplasia, metastases, stroke and epilepsy⁹. Position emission tomography [PET] has further helped in evaluation of metabolic pathways and functional status of different regions of brain.

RENAL SCAN

Kidneys are better assessed by DTPA/MAG3 scan from functional point of view while the anatomical details are better visible on DMSA scan.

DTPA [Diethylenetriamine pentascetic acid] is the pharmaceutical filtered by glomeruli. This agent is labeled with ^{99m}Tc and injected IV, followed by sequential images of the urinary tract. Different computer soft wares are used to display static pictures, graphic representation of the study (renography), relative renal function and glomerular filtration rate. No patient preparation is required except for good hydration. This investigation is simple, cost effective, very informative, carrying no risk of anaphylaxis and completed within 30 minutes. Giving IV frusemide during the study can also assess response of kidneys to diuretic stress. Patients suffering from hypertension are evaluated for renal artery stenosis and hypertensive nephropathy. Renal transplant assessment is another hallmark of this investigation. There are situations when patients present with markedly impaired renal function in CRF. As DTPA is mainly glomerular filtration agent, the kidneys are not properly visualized, making it difficult to assess their function. MAG3 [Mercaptoacetyl, triglycine] is another pharmaceutical which is tubularly secreted agent having extraction efficiency three times greater than DTPA⁹. This agent gives better results in cases of CRF and also evaluates

ERPF [Effective Renal Plasma Flow]. Filtration fraction is defined as the ratio of GFR and ERPF and is 0.2 in normal adult human reflecting that 20% of plasma reaching the kidneys ends up as a glomerular filtrate¹.

DMSA (dimercaptosuccinic acid) is another pharmaceutical, which is temporarily fixed, in proximal convoluted tubules. This scan is performed to see the structural details like size, shape, symmetry, space occupying lesions and cortical scarring secondary to infection or vesicoureteric reflux. Ectopic kidney, if not visualized on USG can easily be located with DMSA scan.

LUNG SCAN

Lung perfusion scan reflects the relative distribution of pulmonary arterial blood flow throughout the lungs. In case of pulmonary embolism, typical segmental or subsegmental perfusion defects are noticed indicating interruption of regional blood flow to that localized area.

Lung ventilation scan provides a visual display of the regional ventilation. In pulmonary embolism, perfusion to a specified area is interrupted which appears as a defect while the ventilation is still intact. This mismatch is the major diagnostic criteria for PE. This investigation is critically important in pulmonary embolism but has got minimum role in cases of COPD, lung parenchymal disease, effusion and bronchogenic carcinoma.

MECKEL'S SCAN

^{99m}Tc pertechnetate is the radiotracer having affinity to localize in gastric mucosa. Children presenting with rectal bleeding can be screened for the possibility of Meckel's diverticulum containing gastric mucosa. A period of 6 hours NPO is the prerequisite. Intravenous injection of the tracer localizes the problem within a few minutes. This test is simple, noninvasive, and easily acceptable to children and their parents.

SALIVARY GLAND SCAN

Salivary glands especially parotids can be imaged with ^{99m}Tc pertechnetate. Tumors and parotid duct obstruction can be demonstrated with simple

intravenous injection within a few minutes. No specific patient preparation is required. Response of salivary glands to lemon is also ascertained easily.

LABELED RBC SCAN

There are patients presenting with bleeding per rectum, the cause of which cannot be established even on sigmoidoscopy and colonoscopy. Labeled RBC scan is simple, non-invasive test for detecting the site of bleed.

This investigation is also very sensitive and specific in "liver haemangioma". Frequently, an echogenic area is seen on ultrasonography. However, differentiation between a metastatic deposit and hemangioma is difficult. Radioisotope labeled RBCs show pooling at the site of lesion to confirm the diagnosis. No patient preparation is required for this simple, highly sensitive and specific test.

RADIONUCLIDE VENOGRAPHY

Bed ridden patients, cases of IHD and females during postpartum period are prone to develop DVT, which can easily be confirmed by this study, which is quite simple and completed within a few minutes.

RADIONUCLIDE LYMPHANGIOGRAPHY

Venous or lymphatic origin of lower limb edema is sometimes difficult to diagnose clinically. Radionuclide lymphoscintigraphy needs subcutaneous injections in first web space in both feet followed by serial pictures to see the upward flow. Any obstruction to flow can be demonstrated in addition to visualization of lymph nodes and lymphatics.

CARDIAC SCAN

Nuclear Medicine techniques provide more functional information of any organ relative to the structural details. Anatomical information of the heart is better obtained on echocardiography but physiological assessment of the organ is best done with Nuclear Medicine techniques. First pass cardiac studies are conducted for determination of ventricular ejection fractions. Labeled RBC (stress & rest) gated studies are also done for assessment of ejection fraction, wall motion abnormalities and cardiomyopathies. Coronary

artery disease is assessed by non-invasive myocardial perfusion scan. Thallium-201 is the isotope used for this purpose; therefore this test is commonly called as “Thallium Scan”. Recently, many other tracers [MIBI, Tetrofosmin, Teborexime] have been developed which provide better quality of image especially with computerized tomography. Common indications for myocardial perfusion scan are;

[1] Suspected coronary artery disease

- Atypical chest pain
- Abnormal resting ECG
- Asymptomatic patient with positive ETT

[2] Suspected myocardial infarction

[3] Evaluation of an equivocal angiogram

[4] evaluation of myocardial viability for bypass surgery or angioplasty

[5] Follow up after coronary bypass grafting or angioplasty¹⁰.

TECHNETIUM [99m] THYROID SCAN

^{99m}Tc-pertechnetate is the isotope trapped by thyroid follicles but is not organified unlike iodine. Tracer is given intravenously and no patient preparation is required. Nodules accumulating more tracer as compared to the normal tissue are termed “HOT” while those capturing less tracer are called ‘COLD’. ‘WARM’ is the terminology used when almost equal tracer distribution is noticed in the nodule and the surrounding normal thyroid tissue. In neonates, where ectopic thyroid or congenital atresia is being suspected, ‘^{99m}Tc-thyroid scan’ is the investigation of choice.

RADIOIODINE UPTAKE AND THYROID SCAN

Radioactive iodine [¹³¹I] has the half-life of 8 days with the principle gamma energy of 364 Kev. Due to longer half-life and higher gamma energy it is not considered an ideal isotope for thyroid scanning. Iodine [¹²³I] having half-life of 13.3 hrs and gamma energy of 159 Kev is superior to ¹³¹I and still used for this purpose. Thyroid iodine uptake pattern is quite informative in cases of hyperthyroidism, iodine deficiency state, thyroiditis and hypothyroidism but is subject to variation by various factors. Iodine is given orally and empty stomach is the prerequisite. This test is of prime importance in suspected cases of thyroiditis where only thyroid profile is not sufficient. Proper diagnosis of

different phases of thyroiditis depends upon correlation between thyroid profile and thyroid ¹³¹I-uptake pattern.

“¹³¹I-whole body scan” is another hallmark of Nuclear Medicine, which is an important investigation in cases of differentiated carcinoma of thyroid. After total or near total thyroidectomy, a gap of 4-6 weeks is required without thyroxin therapy followed by “¹³¹I-whole body scan”, to localize the residual thyroid tissue in neck and metastases in rest of the body. The patient is scanned from head to toe after 48-72 hr of an oral tracer dose.

RIA & IRMA

Radioimmunoassay and immunoradiometric assay are best techniques to determine minute concentrations of hormones in serum. Regarding sensitivity, specificity, precision, reproducibility and cost, these methods are far better than biochemical and enzyme immunoassays. Many hormones including those of thyroid [T₃, T₄, TSH], reproductive hormones [FSH, LH, Oesrogen, Progesterone, Prolactin, testosterone], Growth hormone [GH], and PTH are estimated with these methods.

In addition to the above mentioned common applications of Nuclear Medicine, there are many other tests available including “infection & inflammatory imaging”, “adrenal imagin”, “parathyroid scan”, and “tumor imaging” etc.

THERAPEUTIC ASPECT

Nuclear Medicine has relatively limited therapeutic portion. However, role of this specialty in treatment of thyroid disorders has been well established. Radioactive iodine (¹³¹I) is also employed for ablative therapy of differentiated carcinoma of thyroid. Previously, there was concern that this form of therapy might also produce thyroid carcinoma, leukemia and transmissible genetic damage. However, during the years in which radio-iodine has been in use, no increased prevalence of thyroid carcinoma in patients so treated has been noticed^{11,12,13}. Cancers in other organs are no more common in patients treated with ¹³¹I^{14,15}. The prevalence of leukemia is also no greater in patients treated with radio-iodine¹⁶. Finally, the frequency of genetic damage in the offspring of patients treated earlier with radio-iodine does not appear to be increased. Indeed, the conventional dose of radio-iodine employed in

treatment of thyrotoxicosis delivers to the gonads a radiation dose approximately equivalent to that delivered by a barium enema examination or intravenous urogram. In view of the lack of evidence for significant carcinogenic, leukemogenic or teratogenic effects of radio-iodine in doses generally employed for treating hyperthyroidism, the age limit for use of radio-iodine has been lowered progressively from the initial limit of 40, so that in some clinics it is now employed in children and adolescents¹⁷.

Patients getting ablative ¹³¹I therapy for differentiated carcinoma of thyroid are admitted in special isolation rooms until the radiation exposure is <8 mrem/hr at one-meter distance¹⁸. P³² is another isotope employed for pain palliation in cases of bony metastatic lesions.

RECENT DEVELOPMENTS

Conventional planer imaging has been augmented with SPECT (Single Photon Emission Computerized Tomography) in which gamma camera detector is mounted on an arm capable of 360° rotation around the patient. The rotating camera acquires the data, which is subject to a mathematical filter prior to reconstruct three-dimensional imaging of the target organ. This technical improvement has increased the diagnostic efficiency for many minute pathologies. Application of SPECT in brain helps in diagnosis of stroke, epilepsy and dementia. Similarly, SPECT cardiac perfusion scan provides minute perfusion details of different regions of heart. PET technique relies on the coincidence counting, in opposite detectors, of the 511 Kev gamma photons arising from positron annihilation. The resolution and quantification capabilities of PET are thus markedly superior to those of SPECT system⁹. ¹⁸F labeled deoxyglucose (FDG) has been employed to observe glucose metabolism in brain during normal resting condition, different working conditions and diseased states like stroke, epilepsy, Huntington's disease and dementia.

Regarding recent developments in pharmaceuticals, MIBI [6-methoxyisobutyl isonitrile], tetrofosmin and teboroxime have been developed as these are labeled with ^{99m}Tc. The need for these pharmaceuticals was felt as commonly used isotope of ²⁰¹Tl for myocardial perfusion scan has the disadvantage of low energy and long half-life. ^{99m}Tc labeled MIBI and tetrofosmin give

higher spatial resolution and higher count density allowing gated perfusion tomograms and assessment of region wall tomograms and assessment of regional wall motion and wall thickening¹⁹.

Continuous research and development in methodology has lead to many improvements in scintigraphy. Patients with renovascular hypertension [Renal artery stenosis], now get benefit from "captopril test". This ACE inhibitor relaxes the efferent arterioles of juxtamedullary nephrons resulting in fall in GFR. This parameter has been assessed by baseline study first followed by captopril test after 1-2 days or vice versa. Doses of 25-50 mg captopril have been used⁹.

Development of monoclonal antibodies and their labeling with radioisotopes have opened up a new chapter for diagnosis and treatment fo many tumors. Tumor markers like carcinoembryonic antigen [CEA] and alpha fetoprotein [AFP] are circulating tumor markers, which are not cancer specific. However, many antigens for ovarian cancer, colorectal cancer, melanoma and neuroblastoma have been separated, monoclonal antibodies developed against them, and labeled with isotope to image the tumor.

FUTURE TRENDS

As mentioned earlier, circulating tumor markers like CEA and AFP are not tumor specific. Main goal is the separation of specific antigen from tumor, so that monoclonal antibody may be prepared. This would lead to tumor localization and radioimmunotherapy. Prostate cancer is an obvious candidate for radioimmunoscintigraphy (RIS) and antibodies against, for example, prostatic specific antigen are likely to be better than those presently available²⁰.

The assessment of cerebral perfusion with SPECT is being increasingly used in routine clinical evaluation of neurological and psychiatric disorders. Alzheimer's disease is being investigated with ^{99m}Tc-HMPAO-SPECT and PET. Both techniques detect characteristic temporoparietal abnormalities. However, the presence of abnormalities in other associated areas is better seen with PET. The pharmaceutical MIBI commonly used for myocardial perfusion scan has been found informative in localizing many other diseases like CA breast, actinomycosis, CA lung and parathyroid adenoma.

Further research on its applications is still underway.


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