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Editorial

Fifty-third Annual Conference of the National Academy of Medical Sciences held at Jodhpur was a milestone in the progress of National Academy of Medical Sciences towards achieving its objectives. The Inaugural Address delivered by Dr. R. Chidambaram, DAE-Homi Bhabha Professor, BARC, Chairman, Scientific Advisory Committee to the Cabinet, Principal Scientific Advisor, Government of India lauded the role of National Academy of Medical Sciences during the last five decades since its inauguration by Sh. Jawaharlal Nehru in 1961, and the first Convocation Address delivered by Dr. S. Radhakrishnan in 1963. He felicitated the Academy for recognizing the outstanding research by awarding Fellowships of the Academy to biomedical, clinical, public health scientists and medical educationists as well as health administrators. He referred to the role of the Academy in organizing continuing medical education programmes and scientific symposia relevant to the health needs of the country.

He observed that such academic activity can be further enhanced by strengthening and reinforcing continuing professional development through its connectivity with National Knowledge Network (NKN).

Dr. Chidambaram stated ***"After enormous work spread over 4 years, the second Working Group has compiled the SOPs (Scientific Operating Procedures) as a Report, which, I believe, would be of immense use to practicing medical professionals, the nursing staff and the hospital administrators. My Office will be happy to work with NAMS to run a web-cast Workshop (through NKN) on this subject, which can also be archived and made available on request."*** The inaugural lecture reflects his concerns in 'Health Care and Medical Research'.

The President of the National Academy of Medical Sciences, Dr. C.S. Bhaskaran awarded scrolls to the newly elected Fellows and Members. He conferred Lifetime Achievement Award on Dr. S. Padmavati, a past President of the Academy. Dr. Padmavati at the age of 94 years not only attended the Convocation but also participated in all scientific sessions including the Orations and Scientific Symposium on Regenerative Medicine. The present issue of the Annals include some of these Orations which reflect scientific excellence in basic sciences including development of new drugs, reappraisal of drug resistance in epilepsies through the study of molecular genetics, new imaging modalities, innovative technology such as cochlear implantation, and life-style interventions in the prevention of cardio-metabolic

disorders. The quality of the scientific research exhibited in these Orations delivered by the Fellows of the Academy not only reflects the life time dedication and devotion of these researchers but also inspires younger Fellows and Members of the Academy (elected directly or after obtaining DNB). Keeping this in view the President-in-Council decided that the copies of each issue of the Annals should also be distributed amongst the Members to serve as the source of new current developments in medicine.

Jodhpur conference also showed the valuable contribution of NAMS-AIIMS Collegium which was established in February, 2013. The new AIIMS have been established by the Ministry of Health, Government of India during the Eleventh Five-Year Plan with objectives similar to that of AIIMS, New Delhi. These institutions have initiated programmes contributing not only to under-graduate and post-graduate education but also strengthening continuing professional development. NAMS has provided both academic and financial support to some of these institutions.

For the first time, both the scientific proceedings and the NAMS Convocation were web-cast and are now available on NAMS website : nams-india.in.

Recognising the leadership of Dr. Sanjeev Misra, Director, AIIMS, Jodhpur and the organizing capability of Dr. Kuldeep Singh, it was decided that Annals of the National Academy of Medical Sciences will be printed at Jodhpur. The editorial responsibility will continue to remain at the office of the NAMS, New Delhi. Accordingly, the January-June issue of 2013 'Golden Jubilee Lectures' and July-December issue of 2013 on 'Sleep Medicine' were published at Jodhpur and the copies have been sent to all Fellows of the Academy. In addition, the contents of these two issues are also available on the NAMS website (free of charge).

In these efforts, I shall like to compliment Dr. Sanjay Wadhwa, Chief Editor & his associates and thank the Members of the Editorial Board, Editorial Associates & Members of the Advisory Editorial Board for their continuing guidance.

I acknowledge the assistance of the staff of the NAMS in accelerating the progress of the Academy in its academic activity.

(Prof. J.S. Bajaj)
Emeritus Editor

Ann Natl Acad Med Sci (India), **50(1&2):**01-05, 2014

Address by Dr. R. Chidambaram in the Convocation Ceremony of the National Academy of Medical Sciences, Jodhpur, October 26, 2013

"Health Care and Medical Research"

It is a privilege to be with the Fellows and Members of the National Academy of Medical Sciences (NAMS) and with so many distinguished doctors and bio-medical scientists. I am very grateful to Prof. J.S. Bajaj, Chairman of your Academic Council, for inviting me to the Convocation Function, which is a part of the Annual Conference of the National Academy of Medical Sciences. I congratulate the award winners and the newly elected Fellows and Members. It was so pleasant to hear about their research achievements in a variety of medical fields

2. Jodhpur has now a special position in the medical scenario of India because AIIMS Jodhpur is one of the six new AIIMS established by the Ministry of Health and Family Welfare. Personally, it has also a special place in my heart because, during the preparations of the nuclear tests in 1974 and 1998, we always went to Pokhran via Jodhpur.

3. The quality of health care in a hospital depends on the quality of the doctors and of other staff. On the other hand, a good hospital must provide excellent and *affordable* health care to the patients. The late pioneer neurosurgeon, Dr. B. Ramamurthi once told me a few decades back that, when he headed the Madras Medical College, he used to tell his doctors that when they ordered pathology tests, nine out of ten should show an abnormality. This would be the best way of utilizing our limited pathology resources. More so then, compared to now. At the same time, a leading hospital must be quick enough to adopt the latest technologies.

4. We must also remember that most of our high-end diagnostic and therapeutic medical instruments are now imported. There are, of course, outstanding exceptions like the Co-60 radiation therapy unit BHABHATRON, designed by the Bhabha Atomic Research Centre. Doctors and engineers in the country must get together to indigenise more and more such advanced instruments. Doctors should not go by branding alone.

5. If we are to become a Knowledge Economy, India must have a judicious mix of basic research, applied research, technology development, innovation and manufacturing skills. Indigenisation of high-technology hardware and software products is essential. This is particularly true of electronics hardware, where we have lagged behind, except in the mission-oriented agencies. As I said, in the different context of advanced defence equipment, if you want to be a global leader *in the long term*, you must be willing to often live in the short term with

equipment with lower specifications, as long as it satisfies your critical requirements. This also holds for the 'Medical Devices' field.

6. I understand that, of the approximately 3200 types of medical devices available globally, India manufactures only around 100. Here again we have some excellent initiatives. Starting with the mechanical heart valve of Dr. M.S. Valiathan, designed in the Sree Chitra Tirunal Institute for Medical Sciences and Technology, many other devices and bioproducts have been made in their Bio-Medical Technology Wing. The Institute has continued to strengthen its partnership with industry. Good groups are coming up in IIT Madras and some other institutions in the medical devices field, with links to industry. Incidentally, I have been associated with the Sree Chitra Tirunal Institute as the President of its Governing Body and its Institute Body.

7. A Hospital should also be a Research Centre. Encouragement should be given to both clinical and basic research. Due to the high patient load in India, high quality medical research in India is limited. NAMS should play a pivotal role in enhancing this substantially. Internationalization of science is growing, as also collaboration among scientific institutions within India. Electronic connectivity is an important facilitator of this collaboration.

8. The National Knowledge Network(NKN), a project being implemented by the National Informatics Centre, is a multi -10 gigabits per sec optical fibre network, which will eventually connect 1500 knowledge institutions in India—1100 are already connected'

9. In order to demonstrate the capabilities of NKN – high bandwidth and low latency – NKN launched a series of Model Projects to showcase its potential across a spectrum of applications, many of them focusing on medical education and health care. Each project is carefully handcrafted to address a specific challenge. In the area of medical education, NKN launched a model project with AIIMS as the Principal Investigator. Eight institutions joined AIIMS in this experiment and have come up with solutions after mutual consultations and actual field trials. It is interesting that they use high-end graphics coupled with animation for “routine” skills' transfer (Blood and urine Sample, Blood Pressure monitoring, etc.) transfer and direct video for classroom interaction, and a combination to share knowledge about surgical skills that are cardiac-oriented.

10. The basic idea in another model project is to use engineering design solutions to solve medical requirements. Collab CAD platform - originally designed as software capable of three-dimensional structural simulation with all the engineering nuances – was retargeted to solve a personalized dental imaging problem in 3-D. Three leading organizations - NIC, CSIO, and AIIMS Delhi- were brought together. While NIC

took care of the ICT part, CSIO concentrated on the imaging part, and AIIMS articulated the end-user requirements, so that multiple 2-D images were used to create a 3-D virtual reality.

10. My Office is funded for what I called 'Synergy Projects', which tries to bring together scientists in different institutions with different competencies to work in synergy on a project. One such was the development of a total knee prosthesis for use in orthopaedic oncology. The institutions involved were IIT Bombay, NFTDC Hyderabad and TMH Mumbai. The 'Total Knee Prosthesis' is now ready for clinical trials. This kind of megaprostheses implants, made essentially from titanium alloys, need to be customized through what is called 'additive manufacturing', an important component of the current 'Third Industrial Revolution' , which is driven by the Internet.

11. When I was in McGill University three years back, one of the projects presented to me was what they called C-Brain or Canada Brain, to bring together all scientists working in Alzheimer's to share MRI images through their network CANARIE. We have had their collaboration in developing what I call I-Brain or India-Brain, to bring together all scientists working in Alzheimer's or Dementia or maybe Stroke, to share clinical data like MRI Images. This Model Project, established as a research infrastructure layer over NKN, is led by the National Centre for Brain Research, Manesar, near Delhi. ICMR is planning to use it as a general purpose infrastructure for several brain - related research projects that are multi-institutional.

12. Each one of these Model Projects has a theme and a purpose. But these are only for demonstration and I am sure that many more projects will be conceptualized and realized through the NKN by the scientific community, including the medical community.

13. The availability of drugs in a pure and unadulterated form to the patients still remains an issue. This is not only true in developing economies like India, but also in developed economies in the western world. The other issue that has become a major cause of concern is the mushrooming of the so-called diagnostic centres across India, without adequate checks and balances. Given the importance of the problem, and its ramifications in the public health domain, my Office decided, in November, 2008, to constitute a Working Group on possible Scientific and Technological Measures to counter Spurious & Sub-standard Drugs and Diagnostic Centres, primarily in the Indian context. Dr. P.N. Tandon, famed neurosurgeon, very kindly accepted my invitation to be the Chairman of that Group. While the Secretariat remained my Office, the members were carefully chosen, in consultation with Dr. Tandon, to include medical scientists and professionals of high repute, as well as senior representatives of the Ministry of Health and Family Welfare, Government of India. This Group has brought out an

excellent report, in which various scientific and technological measures already available, or those in the pipeline have been collated. An attempt has been made to evaluate their advantages and disadvantages. It may be pointed out that no single technology has yet been approved anywhere in the world to provide a fail-proof measure for this purpose. The Working Group, likewise, had no personal choice of any particular technology included in its Report. It has only provided a comprehensive list of various alternatives, gathered from diverse sources, for the pharmaceutical industry to choose from, according to its own requirements.

14. In early 2004, the attention of my Office was drawn, by some medical professionals, to medical consumables and devices being sometimes not in a sterile form, despite being stamped as sterile. This applies, of course, in varying degrees, to all countries in the world. As a consequence, in October 2004, my Office had, through a working group of medical professionals, a radiation expert and a microbiologist, prepared a report on the "Scientific Evaluation of Sterilization Practices in India". This report has been well received by the medical fraternity in the country. Later we felt the need for having what we now call the Scientific Operating Procedures (SOPs) of medical sterilization—all three forms, autoclaving, use of ethylene oxide gas and use of gamma radiation. My Office, therefore constituted another Working Group for that task in October 2008, with largely the same composition as the earlier one, but with the addition of a representative from the Directorate General of Health Services. After enormous work spread over 4 years, the second Working Group has compiled the SOPs as a Report, which, I believe, would be of immense use to practicing medical professionals, the nursing staff and the hospital administrators. My Office will be happy to work with NAMS to run a web-cast Workshop (through NKN) on this subject, which can also be archived and made available on request.

15. Living organisms, including humans, are so wonderfully put together that a great deal of research outside medicine goes to mimicking their compositions and functions. Bones are extraordinary composites. Robotic scientists now have an area called 'soft robotics'; they are trying to build robots that can jump like a hare or slither like a snake! One of the optimization techniques in the solution of physical problems is called "neural networks" which tries to mimic the brain in a somewhat elementary way. On the other hand, in the brain, the network of circuits formed with neurons, each circuit carrying out a specific function but which is able to operate in spite of destruction up to a point and the interchanging functions of these neural circuits, is the envy of computer designers who are able to build in redundancy and fault tolerance in computers only up to a point.

16. Conversely, among the many major branches of neuroscience, there is also computational neuroscience, which

studies the information processing properties of these circuits, borrowing from the concepts of computer science, and is now making some initial attempts to construct such functional neural circuits using electronic chips. There is a 'Gifted Children' programme of our Office - how to identify and nurture gifted children, gifted in science and mathematics. The groups includes an applied psychologist and experts in cognitive science. The question is : are the brains of gifted children recognisably different? If so, in what way?

17. Genotyping an individual may in the future lead to a totally individualised treatment. Interestingly Ayurveda, on the other hand, goes for holistic treatment - phenotyping an individual rather than genotyping him/her. Our Office has supported a very successful project on "A Science Initiative in Ayurveda" under the leadership of Dr. Valiathan. He calls this field 'Ayurvedic Biology'.

18. Let me thank you all and particularly Prof. J.S. Bajaj once again for this wonderful opportunity to be with you. I wish you in the medical fraternity all the best and, selfishly speaking, what is good for the doctors is good for all of us also!

Thank you.

Dr. R. Chidambaram

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Molecular Genetics of Drug-resistance in Epilepsies

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SUMMARY

Nearly one-third of newly diagnosed patients with epilepsy remain unresponsive to antiepileptic drugs (AEDs), etiopathogenesis of which is poorly understood. The genes encoding the proteins that regulate the pharmacokinetics such as P-glycoprotein *[ABCBI]*, major vault protein *[MVP gene]* and drug metabolizing enzymes *[ABCB1, ABCG2, MVP, CYP2C9, CYP2C19, CYP3A4, CYP3A5, EPHX1, UGT1A1, UGT2B7],* and pharmacodynamics such as sodium channels *[SCN1A, SCN2A]* and GABA receptors *[GABRA1, GABRA6, GABRB2, GABRG2]* of AEDs are under intense investigation to unravel the mysteries of AED-resistance. However, till today, a consistent and reliable result that could help the clinician either to predict drug-resistance or to overcome it has not been forthcoming. The discrepant results may be related to variations in the definition of drug-resistance, heterogeneous patient populations, ethnic variations in the frequency distribution of single nucleotide polymorphisms (SNPs) and the selection of SNPs. Understanding of these limitations of existing studies, hopefully, will help in designing better studies.

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DR. BALDEV SINGH ORATION delivered during NAMSCON 2013 at the All-India Institute of Medical Sciences, Jodhpur

Introduction

Epilepsy is a common neurological disorder and is a major public health concern, directly affecting an estimated 50 million people worldwide and involving an additional 500 million people as family members and caregivers of patients (1). It constitutes a heterogeneous group of disorders characterized by recurrent unprovoked epileptic seizures due to widely different etiologies with a prevalence rate of about 5 per 1,000 and an annual incidence rate of about 50 per 100,000 (2). Although, a majority of patients with epilepsy are responsive to presently available antiepileptic drugs (AEDs), 20% to 30% of them continue to exhibit recurrent seizures, despite optimal AED therapy (3). Based on a conservative estimate, there will be more than five million people with active epilepsy in India, and of them, at least one million will be drug-resistant. Resource-poor countries are ill-equipped to tackle the enormous medical, social and economic challenges posed by drug-resistant epilepsies (4)

Definition of drug-resistance

It is generally agreed that an adequate trial of appropriate AEDs should be given before labeling the epilepsy as drug-resistant. However, the concept of adequate trial of AEDs is highly arbitrary. To overcome some of the ambiguity involved in defining drug-resistant epilepsy, International League Against Epilepsy (ILAE) has proposed a consensus definition of drug-resistant epilepsy (5). According to this definition, drug-resistant epilepsy is defined as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom". Sustained seizure freedom is defined as seizure freedom for a minimum of 12 months or for a period three times the previous longest seizure-free period, whichever is longer. The ILAE definition places a greater emphasis on seizure freedom, as this is the only meaningful outcome which can lead to improved quality of life of persons with epilepsy. This definition equally emphasizes the importance of appropriate and tolerated treatment schedules as treatment failures due to inappropriately chosen or non-tolerated drugs, non-compliance to drugs or due to the unknown drug schedules cannot be classified as drug-resistant. Failure of two AEDs has been included in the definition with the recognition of the fact that once the patient fails two AED trials, subsequent chances of sustained seizure freedom from further AED trials are very unlikely (3).

Patients with drug-resistant epilepsy have considerable impairments in activities of daily living, education, employment and social interaction due to continuing seizures and AED side effects. These patients are at higher risk of developing various psychological problems like depression, anxiety and psychosis (6). Additional morbidity and mortality of continued seizures include accidental injury, cognitive decline and sudden death (7). Rates for employment,

marriage and fertility are considerably lower in patients with poorly controlled seizures (8,9). Patients with drug-resistant epilepsies account for nearly 80 percent of the annual cost attributable to epilepsy (10). A select group of patients with drug-resistant epilepsy has a chance of becoming seizure-free with epilepsy surgery. However, a majority of them are not candidates for epilepsy surgery and will have to be continued on AED therapy with the hope of achieving seizure control.

Causes of drug-resistance

Several clinical factors have been found to be associated with the drug-resistance in patients with epilepsy, which include early seizure onset, number of seizures before the initiation of AED, high seizure burden within first few months of starting AED, seizure clustering, family history of epilepsy, febrile seizures, electroencephalographic abnormalities, history of status epilepticus, demonstrable brain lesion on magnetic resonance imaging, remote symptomatic etiology, abnormal neurological status, traumatic brain injury, and psychiatric comorbidity (11,12). However, a significant proportion of patients may not have any one of the above attributes to associate with drug-resistance. Perhaps, the most important determinant of AED response/resistance is the epilepsy syndromic diagnosis. While an idiopathic epilepsy syndrome like juvenile myoclonic epilepsy responds very well to AED therapy, the syndrome of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is very resistant to AED. Moreover, the pattern of the drug-resistance observed also varies; *de novo*, where patients might be resistant right from the starting of AED therapy, progressive drug resistance, where patients become resistant in due course of disease progression and a third type, waxing and waning resistance, where active epilepsy is interrupted by periods of remission (13). Conceptually, the variable response to AEDs can be attributed to factors related to altered pharmacokinetic factors and pharmacodynamic factors influencing their efficacy and tolerability.

Putative mechanisms of drug-resistance

The clinical efficacy of an AED depends on its absorption, distribution and elimination, which in turn is influenced by the physicochemical properties of the drug **(Figure 1).** Most of the AEDs are lipophilic and penetrate the biomembranes by passive diffusion. The activity of the efflux transporters in the gastrointestinal tract and blood-brain-barrier influence the absorption and brain uptake of AEDs, respectively. Furthermore, the altered targets of AEDs may affect the clinical efficacy. In addition, the differential activity of the drug metabolizing enzymes, which are substrates for AEDs, influences drug efficacy and tolerability. To understand the genetics of drug-resistance, three major hypotheses have been proposed **(Figure 1).**These mechanisms are not mutually exclusive; they can occur together in an individual patient and can collectively contribute to drug-resistance.

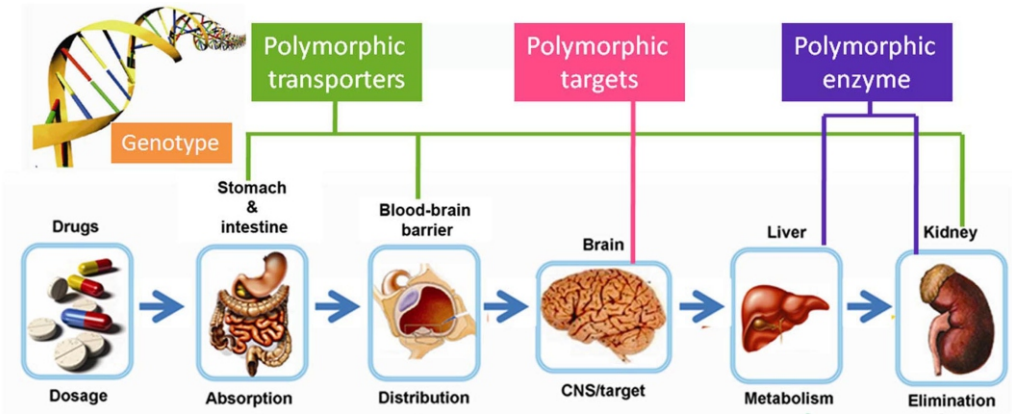

Figure 1: A schematic illustration of the mechanisms involved in inter-individual variability in drug-response.

Transporter hypothesis

According to transporter hypothesis, drug-resistance is a consequence of increased expression or function of multidrug transporter proteins, so that sufficient intraparenchymal AED concentrations are not attained at their targets, even in the presence of adequate serum AED levels. This notion has been supported by the characterization of different efflux transporter proteins that function as drug efflux pumps at the blood-brain-barrier, gastrointestinal tract and other privileged environments (14,15). The genes that encode efflux transporters are highly conserved and the vast majority of them belong to the super family of adenosine triphosphate-binding cassette (ABC) proteins. Single nucleotide polymorphisms (SNPs) of the encoding genes of efflux transporters, including P-glycoprotein (p-gp) (*ABCB1*), and other members of the multidrug resistance-associated protein family (ABCC/MRP family) and breast cancer resistance protein (BCRP) (*ABCG2/BCRP*) can theoretically affect the function of the blood–brain barrier and for this reason been widely studied in context of AED-resistance (14,15).

Target hypothesis

To exert its pharmacological effect, AED after successfully crossing the blood-brain-barrier, should reach its target. Currently available AEDs act on a relatively smaller number of targets. The major targets of the AEDs are voltage-gated sodium channels, calcium channels and neurotransmitter systems (GABA and glutamate). Voltage-gated sodium channels form the targets for a majority of first-line AEDs. According to target hypothesis, drug-resistance can be caused by the modification of one or more AED target molecules resulting in reduced efficacy of a given AED (16).

Role of drug metabolizing enzymes and other factors in drug-resistance

An array of enzymes is involved in the biotransformation of AEDs. Drug

metabolism is accomplished by two phases, where the most common reaction involving phase I enzymes (cytochrome P450 family of mixed function oxidases) is hydroxylation. Phase 2 metabolism involves various conjugation reactions that increase hydrophilicity and facilitate renal excretion of drug. A genetic variation with a very high enzymatic activity may be associated with poor drug response in conventional dosages (13,16).

Molecular Genetics of Drug-resistance

The molecular targets with respect to above described three hypotheses are depicted in **Figure 2.** Although several of these targets have come under intense investigations, it should be admitted that, till today, a consistent and reliable result that could help the clinician either to predict drug-resistance or to overcome it has not been forthcoming. What follows is a critical appraisal of the molecular genetic studies on AED-resistance, including my own. These studies can be broadly grouped into those inquiring genetic variations in the pharmacokinetic and pharmacodynamic aspects of AEDs **(Table 1).**

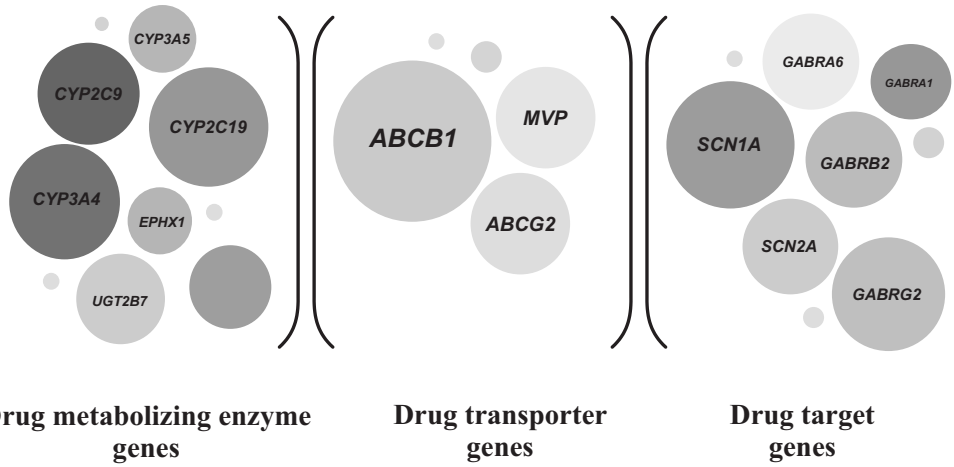

Figure 2 : A schematic illustration of the candidate genes for studies on drug-resistance.

Over the last five years, the author and his colleagues at the R. Madhavan Nayar Center for Comprehensive Epilepsy Care, in collaboration with the Rajiv Gandhi Center for Biotechnology, Trivandrum, has undertaken a series of molecular genetic studies with respect to AED-responsiveness/resistance. We studied several genes related to AED pharmacokinetics and pharmacodynamics among three homogeneous groups of subjects: 200 drug-resistant epilepsy (MTLE-HS), 200 drug-responsive epilepsy (juvenile myoclonic epilepsy) and 200 non-epilepsy controls from south Indian population of Kerala. We screened 29 SNPs from 10 genes involved in AED

pharmacokinetics (*ABCB1, ABCG2, MVP, CYP2C9, CYP2C19, CYP3A4, CYP3A5, EPHX1, UGT1A1, UGT2B7*) and 13 SNPs from 6 genes involved in pharmacodynamics of AED (*SCN1A, SCN2A, GABRA1, GABRA6, GABRB2, GABRG2*), totaling 42 SNPs from 16 genes. We selected these SNPs based on their functional significance or by the tagging status to uncover maximum

Table 1 : Classification of phamacogenetics of drug-body interaction with regard to antiepileptic drug-resistance

Protein / Receptor	Gene
Pharmacokinetic Interaction	
P-glycoprotein	ABCB1
Breast cancer resistance protein	ABCG2
Major vault protein	MVP
Metabolizing enzymes	
Phase I	CYP2C9, CYP2C19, CYP3A4, CYP3A5, EPHX1
Phase II	UGT1A1, UGT2B7
Pharmacodynamic interaction	
Voltage gated sodium channel	SCN1A, SCN2A
GABA receptor	GABRA1, GABRA6, GABRB2, GABRG2

Genes involved in AED pharmacokinetics P-glycoprotein *(ABCB1)*

The gene encoding p-gp, *ABCB1,* is the maximally investigated gene with respect to AED-resistance (Aronica, 2012). An initial study in 2003 showed a significant association of a synonymous variant (C3435T) of *ABCB1* with multidrug resistant epilepsy (17). However, a series of studies that followed, including ours, failed to consistently replicate such an association. We found that subjects carrying ABCB1 rs1922242 polymorphism had five times higher risk of developing corpora amylacea accumulation in the hippocampus, compared to those MTLE-HS patients without this polymorphism (18). In addition to its function as an efflux transporter, the role of CoA in sequestration of toxic cellular metabolites is being increasingly recognized (19). Therefore, upregulation of p-gp function in patients with uncontrolled seizures might be a consequence rather than the cause of seizures (20). Two recent meta-analyses on AED-resistance and *ABCB1* genotype, both having over 3000 drug-resistant epilepsy patients and controls across multiple populations, revealed no

significant association between the *ABCB1* C3435T genotype and resistance to AEDs (21,22).

Breast cancer resistance protein *(ABCG2)*

A limited number of studies have investigated genetic variations in *ABCG2,* which codes for the BCRP. The non-synonymous polymorphisms, rs2231142 (C421A) and rs2231137 (G34A) have been associated with decreased BCRP expression and decreased BCRP transporter activity, respectively (23,24). In our study, three functional variants of *ABCG2* were screened and the data did not identify any significant association between these polymorphisms and response to AED treatment. Similarly, a Korean study and a Chinese study on multidrug-resistant epilepsy patients revealed no association of drug-resistance with *ABCG2* gene (23,24).

Major vault protein *(MVP gene)*

Recent studies have associated an intracellular organelle called vaults (named so because of their resemblance to vaulted ceilings in cathedrals) with multidrug resistance in cancer cells (25,26). Vaults are localized mainly in the cytoplasm, but a small fraction also resides at the nuclear membrane and the nuclear pore complex. Although the exact function of vaults remains unknown, several lines of evidence indicate that they are involved in intracellular vesicular and bidirectional nucleo-cytoplasmic transports (25,26). Over expression of MVP has been reported in brain tissue samples from rat model of drug-resistant temporal lobe epilepsy, AED-resistant human MTLE-HS, frontal lobe epilepsy, and focal epilepsies due to benign neoplasm (27,28). We compared the distribution of three SNPs of the *MVP gene,* rs4788187, rs3815824 and rs3815823, among cohorts of AED-resistant and responsive patients and non-epileptic controls (29). To our knowledge, ours is the first study that inquired the association of genetic variants of *MVP* gene with AED resistance. However, the results revealed that rs4788187, rs3815824, rs3815823 variants of *MVP gene* were associated neither with predisposition for epilepsy nor with AED-resistance in the population we studied (29).

Drug metabolizing enzymes

The Phase I and Phase II drug metabolizing enzymes are major players in determining AED pharmacokinetics. The author studied the functional polymorphisms in Phase I drug metabolizing enzymes (*CYP2C9, CYP2C19, CYP3A4, CYP3A5, EPHX1*) and Phase II (*UGT1A1, UGT2B7*) drug metabolizing enzymes. Studies have reported the association of genetic variations in drug metabolizing enzymes with dosage requirement of commonly prescribed AEDs (30). It can be hypothesized that patients with over-expression of metabolizing enzymes are more likely to become drug-resistant during the course of AED treatment than

with slow metabolizer phenotype, which require lesser drug doses to control seizures. However, we could not observe any significant association of functional variants pertaining to AED response/resistance. The frequency distribution of the variants among the MTLE-HS and juvenile myoclonic epilepsy cohorts was similar to that of the normal Kerala population. In a study from North India, the frequency of a variant genotype (*CYP2C9*1/*3*), which is known to result in slow metabolizer phenotype, was found significantly lower in drug-resistant group as compared to drug-responsive group (31). With respect to *EPHX1*, involved in the biotransformation of carbamazepine, we did not find a significant difference in the frequency of the alleles among the AED-resistant and responsive epilepsy patients. The distribution of the SNP frequencies in the present study differed from those reported in other Indian studies, which can be attributed to the differences in the phenotypic classification of the drug-resistant and responsive epilepsies. The frequency of the extensive metabolizer (EM) TT genotype, intermediate metabolizer (IM) CT genotype and poor metabolizer (PM) CC genotype of rs1051740 in epilepsy patient groups pooled together in our study were 41%, 42.2% and 16.8%, respectively, which is different from the frequency distribution of North Indian epilepsy patients of 43.5% TT, 41.6% CT and 14.9% CC genotypes (32). However, the distribution of EM and IM genotypes, when pooled together, were similar in both populations. The frequency of EM, IM and PM of rs1051740, in AED-resistant group were 41.1%, 44.7% and 14.2% and in AED-responsive group, the distribution was 40.9%, 39.4% and 19.7%, respectively. In case of rs2234922, frequency of EM GG genotype is higher (8.8%) in the pooled epilepsy samples, AED resistant (7.3%) and AED responsive (10.5%), when compared to the data from the North Indian epilepsy samples (32).

Genes involved in AED pharmacodynamics

Studies that have investigated the role of target genes have concentrated on genes encoding voltage-gated sodium channels and $GABA_A$ receptors.

Voltage-gated sodium channel genes

Voltage-gated sodium channels are primarily involved in the generation of action potentials and also the high frequency firing in epileptic discharges. With the notion that nucleotide variations in the genomic region coding AED binding domains, DIIIS6 and DIVS6 segments of the NaV1.1 channel, can affect the drug binding and thereby drug response, we selected SNPs from *SCN1A*. Additionally, we genotyped three SNPs of SCN2A that were found to be associated with AED-resistance in the Chinese population (33). The results showed that there was no association of the studied SNPs with drug-resistance. Our results were contradictory to the initial report and were aligning with other studies (33,36), with the exception of a study from Japan which demonstrated a significant

association between the rs3812718 AA genotype and carbamazepine-resistant epilepsy (34). Additionally our study also showed, the variant rs3812718 increases the susceptibility to MTLE-HS, independently without increasing the susceptibility to the febrile seizures (35).

GABA receptor genes

In a rodent model of drug-resistant temporal lobe epilepsy, altered GABA receptor subunit expression and differential drug response has been observed (36**).** We probed the role of functional variants in *GABRA1, GABRA6, GABRB2, GABRG2* receptor subtype genes for its contribution to the AED-resistance in Kerala population. Although we found no association of these variants with respect to AED-resistance, the variant rs211037 in *GABRG2* showed an association with the increased predisposition to develop epilepsy. Previous reports from North Indian epilepsy patients (37) and in Caucasians epilepsy patients (38,39) did not show any involvement of *GABRG2* rs211037 synonymous variant with epilepsy.

Putative causes for the discrepant results

Despite the large volume research undertaken during last one decade in epilepsy pharmcogenetics, translation to clinical utility has been very limited, to date, with the exception of a strong association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese people (40). The discrepant results can be accounted for a variety of factors such as variations in the definition of the drug resistance, heterogeneous patient populations, ethnic variations in the distribution of the SNPs and the selection of SNPs.

Variation in the definition of AED-resistant epilepsies

The lack of consensus among the different study groups in defining the drug-resistance might have resulted in the inclusion of the patients defined as drug-resistant in one study as drug-responsive in another, and thereby influencing the results of the genetic association. Generally, in clinical practice, AED-resistance is defined as seizure recurrence despite the trial of two to three AEDs or surgical intervention for seizure control, and drug responsiveness as seizure freedom on AEDs for a certain period of time. In studies reviewed here, the number of seizures and duration have varied widely from no seizures for one year, one seizure in 6 months, ≥1 seizure in a month, ≥1 seizure in a year, ≥4 seizures in 6 months to one year, >10 seizures in a year, > 2 seizures in 2years, and 50% reduction of seizures in a year. The AED-responsive cohort has been defined more or less uniform throughout the studies mainly as seizure freedom for >1 years, although certain studies have defined >6 months to 2 years of seizure freedom. Hopefully, future studies are likely to adhere to the recent ILAE definition of AED-resistant epilepsy (5).

Heterogeneity of epilepsy phenotype

A majority of the pharmacogenetic studies in epilepsies conducted till now have included a variety of epilepsy syndromes together by ignoring the underlying disease pathobiology (41). Since epilepsy syndromes are highly heterogeneous with respect to age at onset, seizure type, pathogenesis and AED responsiveness, comparison of molecular genetic results from heterogeneous samples becomes difficult (42).

Population stratification

Population stratification can results in the non-replicability of genetic association studies, which can be defined as occurrence of subpopulations for the studied populations that have different allele frequencies for the candidate gene studied. This disparity in frequencies arises because each population has a unique genetic and social history, and thus ancestral patterns of geographical migration, mating practices, reproductive expansions and bottlenecks, and stochastic variation all yield differences in allele frequencies between individuals (43). Thus the differential risk of a trait for the subpopulation and its inclusion in a study population can confound the association between the candidate gene and the disease. The issue of the population stratification and admixture effects can be addressed by matching geographical region (at study design stage) and by ancestry information markers (at analysis stage).

Biased selection of functional variants

The lack of association can also be attributed to the biased selection of functional variants, which may not be tagging the true causal variants. Since the selection of tagged SNPs to uncover maximum variation are based on the HapMap database with reference to Caucasian and Gujarati Indians, subtle difference may occur in the linkage disequilibrium pattern with respect to studied population of Kerala, which affects the tagging status and information content of the selected SNPs. Further, the small effect size of the common variants in explaining a small fraction of variability and heritability of the complex traits makes then clinically negligible.

Future perspectives

Future studies should attempt to rectify the problems of existing literature by assembling uniform patient populations, especially with respect to drug-resistance and epilepsy syndromic diagnosis. With the slashing of the cost of genotyping technologies, studies should undertake high density genotyping to identify the common variants and whole genome sequencing to identify the rare variants with high effect size (44). Further, better statistical analysis methods, which accounts for all potential confounding factors, have to be developed to enhance the accuracy of the results. With the rapid progress being made in the field of pharmacogenetics, hopefully, we will in the near future be able to identify patients with drug-resistant epilepsy early and

consider alternate treatment options. Further, genomic information will enable the clinician to prescribe syndrome specific AED therapy with optimum dosage for efficacy and with minimum adverse drug reaction, thereby paving way to individualized management of persons with epilepsy.

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Experimental and Clinical Evaluation of Nootropic Activity of Bacopa monniera Linn. (Brahmi)

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SUMMARY

Bacopa monniera Linn. (Brahmi) is an annual creeper belonging to family Scrophulariaceae and growing all over the Indian sub-continent in marshy areas. It is a major *Medhya Rasayana* used in *Ayurveda* for treatment of memory disorders. Large number of saponins and glycosides has been isolated from the plant. Most of the experimental and clinical studies have been done with crude extracts or standardized preparation of the two active saponins Bacosides A and B.

Extracts or saponin mixture facilitate learning, improve consolidation of learned behavior and delay extinction in several models of learnt behavior in normal rats and mice as well as in chemically induced or transgenic models of Alzheimer's disease. They also prevent or reverse amnesia produced by drugs, stress or ischemic hypoxia. Other CNS effects include anti-anxiety, anti-convulsant and analgesic activity. Several mechanisms have been proposed to explain the mechanism of these CNS effects.

Extracts as well as the bacoside preparation have been found safe and well tolerated in healthy volunteers in single dose or chronic administration for several weeks in a number of double blind placebo controlled studies in India and abroad. Chronic administration significantly improved information processing, learning and memory consolidation. It was found more effective than caffeine in a comparative study.

Double blind placebo controlled studies with bacoside preparation have demonstrated beneficial effects and safety in elderly patients with Age Related Memory Impairment and in children with Attention Deficit Memory Disorder. It has also been found useful in anxiety neurosis, epilepsy and sleep disturbances in post menopausal women.

The standardized preparation is marketed as a prescription drug after having obtained the necessary regulatory approval in India, Australia, New Zealand and South Africa and as an OTC product in several other south east Asian and African countries.

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Introduction

Bacopa monniera Linn. (Syn. *Herpestis monniera* Linn H.B. & K, *Brahmi)* is an annual creeper belonging to family Scrophulariaceae and found all over the Indian sub-continent in damp and marshy areas. It is an important plant in *Ayurvedic* materia medica. It is classified in *Charak Samhita* as a *Medhya rasayana* for improvement of memory and described in *Sushruta Samhita* as being efficacious in loss of intellect and memory(1). It has been as a single herb and also in formulations with other ingredients. *Centella asiatica* (*Hydrocotyle asiatica)* is also used in Ayurveda for similar indications and thee is often confusion between these 2 plants. Singh and Sinha (2) have clarified that *Bacopa* is *Brahmi* and *Centella* is *mandookparni.* They have also stated that the former is more potent and used as drug while the later is recommended as a dietary constituent (*Saka dravya* or vegetable).

Chemical studies on the plant were initiated in 1931 by Bose and Bose (3) with isolation of the alkaloid Brahmine followed by isolation of a saponin, hersaponin by Sastri *et al* in 1969 (4). Detailed chemical analysis was undertaken at Central Drug Research Institute Lucknow (CDRI), leading to isolation of the major saponins, Bacosides A and B (5-7). Bacoside A was subsequently shown to be a mixture of 4 aglycones, Bacogenins A_{1-4} (8-10). Other minor constituents isolated at CDRI were Bacoside A_1 (11) and A_3 (12). Several minor constituents have been isolated subsequently by investigators elsewhere. These include: 4 dammarane type triterpinoid Bacosaponins A-D (13, 14); 2 pseudojujubogenin glycosides Bacoposides I and II (15) and saponins Bacopasides III-V (16) and Bacosaponin G (17). Most of the experimental studies have been done with crude extracts or standardized mixture of Bacosides A and B (Bacoside mixture) developed at CDRI

Experimental Studies

Major emphasis in experimental studies has been on analyzing its effect on learning and memory but some other CNS effects have also been reported. The major findings have been summarized below under effects on learning and memory, anti-amnesic activity and other CNS effects.

Effects on Learning and Memory

Prakash and Sirsi (18) published the first report in 1962 on improvement of performance of rats in motor learning with alcoholic extract. Sinha (19) reported facilitation of acquisition, consolidation and retention with the glycoside, hersaponin, in a brightness discrimination test. Improvement in maze learning by rats with a decoction was observed by Dey *et al* (20).

A more detailed study has been at CDRI, initially with the alcoholic extract in rats (21). Animals treated with 40 mg/kg extract per oral for 3 or more days showed better acquisition, improved

retention and delayed extinction in a shock motivated brightness discrimination test. It also reduced reaction time significantly in an active conditioned flight test and improved performance in Sidman's continuous response test. Similar effect was obtained in the first 2 tests with a much lower dose (2.5-7.5 mg/kg) of Bacoside mixture. It also significantly reduced lithium chloride intake in conditioned taste aversion test (22). It abolished the 'Kamin's deficit' (23) in the re-learning schedule of Y-maze test (24). Improvement in learning has been confirmed in rat (25) and mouse (26, 27) from other laboratories.

Bhattacharya *et al* (28) and Uabundit *et al* (29) have shown its beneficial effect in a rat model of Alzheimer disease. Rastogi *et al* (30) have found that long term (3 months) treatment with bacosides prevented age-associated neuronal degeneration in female Wistar rats. Charles *et al* (31) have reported similar reversal of galactose induced attenuation of contextual associated learning in ageing rats. A reduction in β-amyloid level in brain associated with improvement in Y-maze performance and open field hyper-locomotion has been obtained in doubly transgenic PSAPP mice (32). Protection against β-amyloid induced cell death has been observed in primary cortical cell culture also (33). These results are suggestive of its potential utility in patients of Alzheimer's disease.

Anti-amnesic Activity

Bacosides reverse retrograde amnesia in rats produced by immobilization stress, electroconvulsive shock or scopolamine (1).Reversal of scopolamine amnesia has also been reported by Manjarekar (34) and Das *et al* (35). Studies in mice have shown their ability to reverse amnesia induced by diazepam (36), NOS inhibitor L-NNA (37), phenytoin (38), 1-(m-chlorophenyl) biguanide (39) hypobaric hypoxia (40) and ischemia (41).

Other CNS Effects

Extracts and pure compounds isolated from *Bacopa* have been shown to have tranquilizing (42), anti-anxiety (43-45), anti-depressant (45-47), anti-convulsant (48) and analgesic (49) activities. Antagonism of haloperidol induced catalepsy also has been reported (50).

Studies on Mechanism of Action

Bacosides enhanced protein kinase activity in hippocampus, hypothalamus and cerebral cortex (1). They also prevent decrease in SOD, intra-neuronal lipofuschin accumulation and necrotic changes induced by aluminum trichlorate in CA-1 region of hippocampus (51) and cerebral cortex (52). Bhattacharya *et al* (53) have reported anti-oxidant, free radical scavenging and anti-lipid peroxidation effect of *Bacopa* extract. Rasso *et al* (54) have found protection against NOS inhibition

evidenced by altered NO synthesis, reduction in intracellular oxidants and prevention of DNA damage in cultured astrocytes. The studies of Saraf *et al* (36) in mice suggest that anti-amnesic activity may be partly due to restoration of NO release by reducing NOS inhibition. The protection from oxidative damage is achieved by maintaining functional integrity of mitochondria (55) and membrane ionic balance (56). Dhanasekeran *et al* (57) observed reduced concentration of divalent metals in addition to reduction in lipid peroxides and lipoxygenase activity. They suggest a role of the metals in reduction of β-amyloid in brain of Alzheimer's disease animal models.

Kar Choudhury *et al* (58) have conducted studies in stressed rats. The decrease in Hsp_{70} expression and SOD release was blocked. Similar results have been obtained by Annbarasi *et al* (59) in animals exposed to cigarette smoke.

Several neurotransmitters may be involved in nootropic activity of *Bacopa* preparations. An increase in 5-HT and lowering of norepinephrine has been found in hippocampus, hypothalamus and cerebral cortex of adult rats treated with bacosides without any effect on their receptors (1). Charles *et al* (60) treated young rats with *Bacopa* extract on post-natal days 15-29. Their results suggest that nootropic activity may be mediated through regulation of expression of tryptophan hydroxylase (TPH_2) leading to raised 5-HT level. Dopamine levels decreased significantly but no changes were obtained in levels of glutamate or acetylcholine. Das *et al* (35), however, found inhibition of acetyl cholinesterase in mice brain and suggested involvement of a cholinergic mechanism. Limpeanchob *et al* (33) also found a reduction of β-amyloid induced increase in acetyl cholinesterase activity in cultured cortical neurons with a *Bacopa* extract. Bacoside-A pre-treatment could revert fall in GABA receptors in hippocampus of rat model of temporal epilepsy (61). The authors suggest possibility of modulation by a cholinergic mechanism

Kamkaew *et al* (62) studied the effect of alcoholic extract of *Bacopa monniera* on cerebra blood flow in rats. There was 25% increase in cerebral blood flow without any effect on systemic blood pressure. They suggest a role of improved blood supply in the nootropic effect.

Preethi *et al* (63) have demonstrated down-regulation of micro RNA-24 by *Bacopa* extract in young rats. It has been postulated that this would result in up-regulation of CREB which regulates activation of immediate early genes facilitating synaptic plasticity (64). *p*.$CREB_1$ is involved in regulation of synthesis of synaptic proteins necessary for consolidation of long term memory (65).

Clinical Studies

Normal Volunteers

The first Phase I study under GCP

norms was undertaken at CDRI with standardized Bacoside preparation (CDRI formulation) after generating the required pre-clinical efficacy and safety (acute and chronic toxicity, teratogenicity and mutagenicity) data and obtaining approval from the Drugs' Controller General of India. The double blind placebo controlled study was conducted in male volunteers after obtaining informed consent. It was well tolerated and devoid of untoward effect in single (200-300mg) or multiple (100 and 200 mg daily for 4 weeks) dose schedules (1, 66). Pravina *et al* (67) found similar results in an open study in 23 volunteers given 300mg daily for 15 days followed by 450 mg for next 15 days.

Nathan *et al* (68) studied effect of single 300 mg dose of CDRI formulation in a placebo controlled double blind study in 38 volunteers. It was found safe but had no effect on cognitive functioning. Administration of same dose for 3 months led to significant improvement in information processing, learning and memory consolidation judged by storage and retention of new information (69, 70).

Mandal *et al* (71) gave 750 mg whole plant powder daily for 16 weeks in a placebo controlled double blind study. Significant facilitation was observed in verbal span test, verbal memory task and text comprehension tests. Raina *et al* (72) compared the effect of 500 mg plant powder with 200 mg caffeine daily for 16 weeks in 40 volunteers. *Bacopa* powder was better than caffeine in improving reaction time in a battery of cognitive tests with fewer side effects.

Senior Citizens with Memory Impairment

Most of the studies have been done with CDRI formulation. Raghav *et al* (73) evaluated the effect of 12 weeks treatment in 40 subjects having Age-associated Memory Impairment without any evidence of dementia or psychiatric disorder. The study was double blind randomized. It significantly improved mental control, logical memory and paired associated learning without any drug related abnormality in clinical, hematological or biochemical parameters. Significant improvement in logical memory, digit forward, paired associated learning and total score was obtained in a study at another centre also (74). Similar results regarding efficacy and safety has been obtained in several other placebo controlled double blind studies in India (75, 76) and abroad (77, 78).

Morgan and Stevens (77) observed more gastrointestinal side effects than in the placebo treated group and suggest that these may be due to its cholinergic effects. Agrawal (79) has reported that treatment with *Brahmi* powder prevented depletion of blood acetylcholine in patients of psychosomatic disorders.

Children with Impaired Learning

A double blind placebo controlled study has been done with CDRI formulation in 40 children with Attention Deficit Memory Disorder (80). The drug

or placebo was given for 12 weeks. Significant improvement was observed in tests for mental control, sentence repetition, logical memory, word or picture recall and paired associated learning. Sharma *et al* (81) reported improvement in perpetual motor function in a placebo controlled trial in 40 school going children. Abhang (82) carried out a double blind study for one month in 100 male students (10-13 years age) with subnormal IQ. There was improvement in direct memory, some verbal factors and arithmetic skill.

Other CNS Disorders

Mukherjee and Day (83) published the first clinical with Brahmi in 1966. They compared the effect of defatted alcoholic extract (2-4 mg/kg) with aqueous extract (2 oz/day) for 5 months in patients of epilepsy and found the former more effective. In a follow up study Dey (84) showed a close parallelism in clinical improvement and EEG changes in 2 of these patients

Singh and Singh (85) treated 30 cases of anxiety neurosis with 30 ml extract (prepared from 12g of crude drug) in two divided doses for one month. There was significant relief in symptoms associated with a reduction in urinary excretion of vinyl mandellic acid and corticoids. Subsequently they gave dried extract of 2.5g crude drug in capsule thrice daily for 4 weeks to 18 normal subjects and same number of patients of anxiety neurosis (86). There was significant improvement in symptoms of anxiety and depression, mental fatigue and memory span.

Kumar *et al* (87) found significant improvement in anxiety and stress level with the CDRI formulation given to 94 adult volunteers for 6 months in a double blind placebo controlled cross-over study. Other recent studies have reported improvement in quantity and quality of sleep in post-menopausal women (88) and in the range of movement and joint pain etc. in patients of sciatica (89).

Concluding Remarks

The CDRI formulation has been available as a prescription drug for memory disorders in India since 1994 under several trade names. It has been subsequently being marketed as a prescription drug for same indications in Australia, New Zealand since 2009 and South Africa since 2011. It was made available as an OTC product in Sri Lanka in 1996 followed by Philippines (largest selling natural product), Malaysia (among top 5 selling herbal drugs), Singapore, Thailand and several African countries.

Bacopa preparations show a wide spectrum of CNS effects in experimental studies. Initial clinical studies (reviewed above) indicate beneficial effect in anxiety neurosis and epilepsy. This data along with animal and clinical safety data suggest the need of more extensive clinical trials in these and other relevant CNS disorders to assess its potential as primary treatment or adjunct to other drugs. They may also be useful in

ameliorating detrimental effects of drugs like benzodiazepines or anticonvulsant drugs on cognitive function in patients using these drugs for long periods. Experimental studies also suggest their potential utility in management of stressful conditions (90) and morphine abstinence syndrome (91).

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Recent trends in Molecular Imaging : PET/CT in Neurology

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SUMMARY

PET/CT is an important molecular imaging technique for the assessment of neurological disorders. The most widely used radiopharmaceutical for both clinical and research purposes is [18F] 2-fluoro-2-deoxy-D-glucose (FDG). It is extensively used owing to its favourable physical characteristics. It enables depiction of cerebral glucose metabolism, and has thus been used to study various pathological states. Despite this, FDG has its own limitations. This is owing to its limited specificity and high cortical uptake. This has paved the way for the development of several non-FDG PET radiopharmaceuticals. We present the insights gained at our institution, using these radiotracers in the assessment of neurological disease. Our study shows that the use of FDG and non-FDG novel PET radiopharmaceuticals facilitates the early diagnosis, delineation of extent, prognostication and monitoring of therapeutic response in several neuropathological states.

Key Words : Molecular imaging, PET/CT, Neurological disorders

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Introduction

The first oncological application of PET was in the assessment of brain tumors (1). In general, PET/CT using FDG has gained widespread acceptance in tumor evaluation owing to its ability to detect tumors and define their extent, provide information that aids planning of radiotherapy and operative interventions, show response to treatment, and detect tumor recurrence. FDG has been aptly called the molecule of the millennium owing to its profound impact on oncological imaging. However, FDG may not be an ideal imaging agent for brain tumors as there is a high physiological glucose uptake in normal brain parenchyma, glucose being an obligatory energy substrate for brain. This leads to intense radiotracer uptake in normal brain tissue (2), and, as a result, low grade tumors, small tumors, and tumors with early recurrence may go undetected. Moreover, FDG uptake is relatively nonspecific and is seen to occur in inflammatory and granulomatous tissues also (3).

A host of non-FDG PET radiotracers with oncological applications have been developed. These include radiotracers for amino acid synthesis, Deoxyribonucleic acid (DNA) synthesis, lipid synthesis, hypoxia, angiogenesis, and peptide receptors.

Each of these has their inherent strengths and limitations, a detailed understanding of which is a pre-requisite to their optimal utilization.

One of the most important neurological application of PET imaging is in the work-up of the dementia patient (4). It serves as a useful aid to enable an accurate diagnosis as early in the course of the disease as possible. It also aids in differentiating the different forms of dementia on the basis of pattern of FDG uptake in different parts of the brain parenchyma. Further, it facilitates the determination of the course and severity of the disease. FDG PET/CT is also proving useful in the detection of cases with MCI (mild cognitive impairment). The early diagnosis and response to therapeutic intervention is an area of intense research today.

Movement disorders, namely Parkinson's Disease and Parkinsonian Syndromes can be assessed using PET/CT. Based on the differential pattern of uptake of FDG in various disorders, the various subgroups of movement disorders can be distinguished. Further, PET imaging with 18F-fluorodopa has been performed to evaluate the presynaptic dopaminergic function, and has shown abnormalities in the nigro-striatal projection (5). 18F-fluorodopa studies have been used in early diagnosis, investigation of clinical course and the effects of therapy in patients with movement disorder. Imaging with postsynaptic dopamine receptor tracers has also been undertaken, to assess the pathogenesis and course of the disease.

Other important areas where PET/CT plays an important role is cerebrovascular disease (haemorrhafic or

ischemic), seizures, brain trauma etc.

Material and Methods

The study comprised of 286 patients with neurological disease. Of these, there were 117 subjects with dementia 104 subjects with movement disorders and 65 subjects with brain tumors. All patients underwent an FDG PET scan. Of the 286 patients, 153 number of cases further underwent scanning using non-FDG novel radiotracers. All participants provided written informed consent.

For the FDG PET study, all subjects were fasting for at least 4 hours prior to the study. The study was performed in a resting state with eyes closed. It was performed on a Discovery STE 16(GE) camera. A dose of 370 MBq of FDG was injected intravenously and a brain scan was obtained after an interval of 60 minutes, with patient in supine position and head immobilized in a head rest. An initial scout was followed by a low dose CT acquisition. This was followed by a static 20 minute single bed position 3-dimensional emission scan. Reconstructed data was viewed on a Xeleris work-station. Data acquisition was performed along similar lines for other non-FDG PET tracers, with modification of dose and post-injection waiting period depending on the individual radiopharmaceutical, eg. 550-740 MBq of 11C-methionine with 20 minute delay post-injection.

Data analysis was performed by visual image interpretation using plain PET, CT and fused PET/CT images. Semiquantitative assessment using SUVmax was also performed in those cases where a lesion was localizable. SUV (standardized uptake value) is a semiquantitative numerical value which normalizes the lesion uptake to injected dose per unit body weight. The same procedure was performed for both FDG and non-FDG PET procedures.

Results

The patients evaluated on PET/CT could be broadly categorized into 3 large subsets : brain tumor, cases of dementia and movement disorder.

Brain Tumors :

A total of 97 patients with intraparenchymal brain tumor was assessed. Of these, histological confirmation was possible in 65 cases. Of these 65 subjects with brain tumor, there were 18 newly diagnosed cases and 47 previously treated cases. FDG PET/CT was performed in all cases, while 11C-methionine scan was performed in 45 cases, F-DOPA (3,4-dihydroxy-6-18F-fluoro-L-phenylalanine) scan was performed in 20 cases, FLT (18-fluorothymidine) in 19 cases, FMISO (18F-misonidazole) scan in 3 cases and FET (O-(2-[18F]fluoroethyl)-l-tyrosine) in 2 cases.

11C-methionine was found to be more efficacious than FDG PET/CT both for the primary detection of tumor and

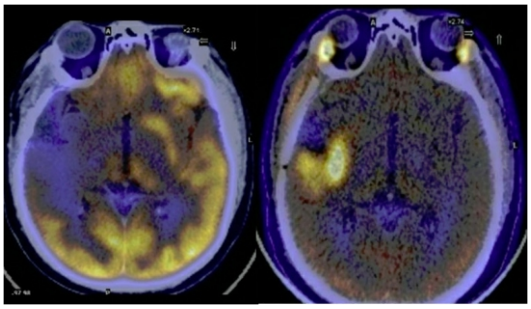

Fig.1 : A post-operative case of grade II glioma. FDG PET/CT image (A) shows no area of increased uptake at the operative site s/o negative study. However, 11C-methionine scan (B) clearly shows recurrence in the right temporal region (arrow).

delineation of its extent (fig.1). It was useful in distinguishing tumorous from non-tumorous lesions. It showed selective uptake in neoplastic tissue, and was thus useful in assessing the size and margins of the lesion. This was applicable both for primary tumors and post-treatment cases as well. Low grade gliomas were also better depicted on 11C-methionine PET/CT. In case of recurrent brain tumors, it was superior to FDG not just in the delineation of the area of recurrence, but also in the detection of secondary deposits. Also, interobserver variability in interpretation was less on 11C-methionine compared to FDG.

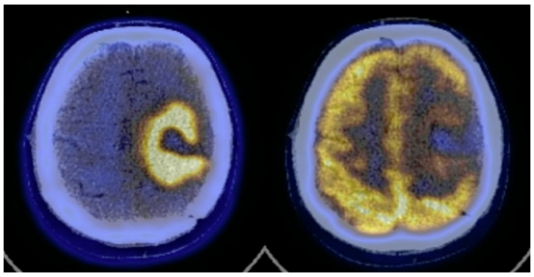

Fig.2 : A post-operative case of recurrent glioma. Lesion delineation is superior on F-DOPA PET/CT image (A) compared to the FDG PET/CT image (B).

F-DOPA was extremely sensitive in picking up both primary and recurrent lesions (fig.2). It scored over FDG in the evaluation of all types of brain tumors, but most significantly in the case of low-grade gliomas. It was positive in all cases of primary and recurrent low grade gliomas and negative in patients with remission.

FLT exhibited high sensitivity and specificity in case of high grade gliomas. However, it faired suboptimally in case of low grade gliomas – both in case of primary and recurrent tumors. FMISO was sensitive in picking up areas of recurrence, and showed areas of tumor hypoxia. The limited study performed using FET also showed it to be superior to FDG in delineation of tumor extent.

Mild cognitive impairment (MCI) and Dementia:

Of the 117 subjects included with neurocognitive deficits, there were 39 patients with MCI, 40 with Alzheimer's Disease (AD), 14 with Fronto-temporal Dementia (FTD), 13 with Diffuse Lewy Body Dementia (DLBD) and 11 with dementia due to miscellaneous causes. FDG PET/CT was performed in all patients. All patients were followed up clinically for a period of at least one year. MCI patients showed reduced tracer uptake primarily in the mesiotemporal cortex, AD patients in the temporoparietal lobes with advanced cases showing frontal lobe involvement as well (fig.3), FTD cases in the frontotemporal lobes (fig.4), while DLBD showed global reduction in tracer uptake including the

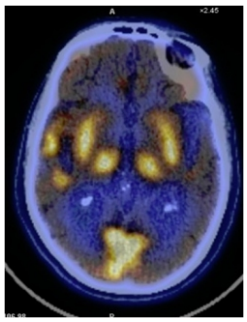

Fig.3 : An advanced case of Alzheimer's disease : FDG PET/CT scan shows bilateral temporo-parietal and frontal hypometabolism with sparing of occipital cortices.

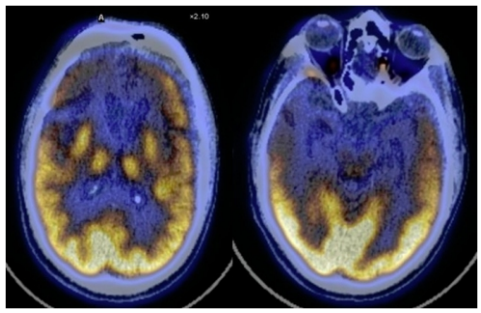

Fig.4 : A classical case of fronto-temporal dementia : FDG PET/CT scan shows bilateral fronto-temporal hypometabolism.

occipital cortices.

Movement disorders:

A total of 104 patients with Parkinsonism were evaluated on FDG PET/CT. Of these, F-DOPA studies were performed on 87 cases. Only patients who could be clinically followed up for at least one year were included in the study. Differentiation of various types of Parkinsonian syndromes was possible on FDG PET/CT studies. Early untreated PD showed pallidothalamic hypermetabolism (fig.5,6). Several patients also showed cortical hypometabolism, predominantly in the parieto-occipital and dorsolateral prefrontal cortices. Patients with progressive supranuclear palsy (PSP) showed hypometabolism predominantly in the mid-brain, basal ganglia and anterior cingulate cortices. Patients with multisystem atrophy (MSA) showed hypometabolism in the pons and dorsolateral putamen, with or without hypometabolism in bilateral cerebellar hemisphere. Patients with

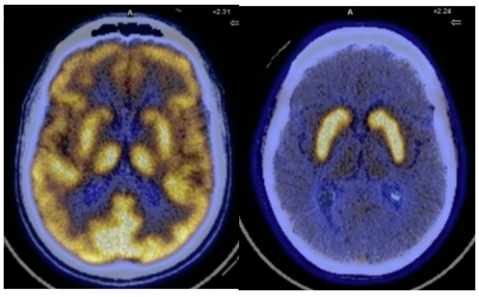

Fig.5 : FDG-PET/CT scan in a normal control (A). Note uniform metabolic activity in cerebral cortices and deep grey matter. The F-DOPA scan (B) in this healthy patient shows intense uptake in the basal ganglia with minimal activity in the cortices.

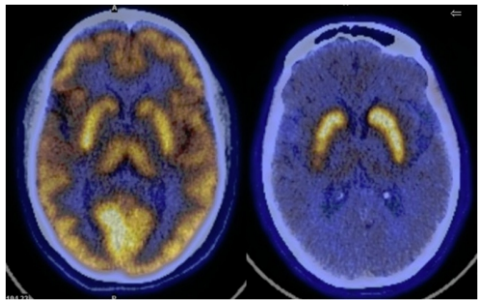

Fig.6 : FDG-PET/CT scan in a patient with Parkinson's disease (A). Note the relative hypermetabolism in the basal ganglia compared to the metabolic activity in cerebral cortices. The F-DOPA scan (B) in this patient shows reduced uptake in bilateral putamen with preserved uptake in the cerebral cortices.

corticobasalganglionic degeneration (CBGD) showed asymmetrical hypometabolism in parietal cortices and basal ganglia contralateral to the clinically more affected side. F-DOPA studies showed high sensitivity towards the detection of PD and Parkinsonian syndromes. Reduced uptake in the putamen with relatively normal uptake in the caudate nucleus was seen in cases of PD (fig.5,6). Uniformly reduced F-DOPA uptake was noted in both caudate and putamen in case of Parkinsonian syndromes, although DOPA could not help distinguish between the various categories of Parkinsonian syndromes.

Discussion

PET/CT has been widely used in the study of various central nervous system disorders. A number of different radiopharmaceuticals labelled with positron emitting radioisotopes, such as carbon-11 (^{11}C), fluorine 18(^{18}F) and nitrogen -13 (^{13}N) have been developed for measuring blood flow, neurotransmitter systems and cerebral metabolism (6). The radiopharmaceutical which is most popularly used at present is FDG. Owing to certain inherent limitations of this radiotracer, newer agents are being used to study the pathological states in the brain.

Brain tumors:

The novel PET radiotracers used for oncological applications include tracers for amino-acid synthesis, DNA synthesis, lipid synthesis, hypoxia and angiogenesis. Malignant transformation increases the use of aminoacids for energy, protein synthesis and cell division. Among the radiotracers for protein synthesis, 11C-methionine, 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine (F-DOPA) and O-(2-[18F]fluoroethyl)-l-tyrosine (FET) have been widely studied. These radiotracers have proven superior to FDG in the evaluation of brain tumors as their reduced uptake in healthy brain tissue results in enhanced contrast between the brain tumor and the surrounding normal parenchyma (7). 11C-methionine has proven more efficacious than FDG PET/CT both for the primary detection of tumor and for delineation of its extent. Additionally, it can differentiate tumorous from nontumorous lesions with a high degree of sensitivity and specificity (8). Owing to its selective uptake in brain tumors, 11C methionine PET/CT has also been found to be a useful modality for assessing the size and margins of gliomas that may not enhance on contrast-enhanced Magnetic resonance imaging (MRI) imaging. It also plays an important role as a marker for cell proliferation and angiogenesis (9) and can be used to evaluate tumor grade in gliomas, thus allowing better tumor prognosis (10). The results of our study corroborate with those of previous studies, with clear evidence of better tumor delineation and improved diagnostic efficacy in both primary and recurrent tumors . Additionally, our study shows that interobserver variability in interpretation is less on 11C-methionine compared to FDG.

Owing to the short half life of 20

minutes that 11C methionine has, its use has been limited to institutions with an on-site cyclotron. Aminoacids labeled with a radiotracer having a longer half-life would be preferred in the routine clinical setting. Of these, F-DOPA and FET have been widely studied. These amino acids are retained in tumor cells, which exhibit higher metabolic activities than most normal cells. Our study shows that F-DOPA has proven superior to FDG in the evaluation of low grade tumors, which are frequently FDG negative. Owing to its affinity for low grade tumors as well, F-DOPA may not be useful for assessing tumor grade. FET PET when combined with MRI significantly improves the identification of cellular glioma tissue (11). In addition, high- and low-grade brain tumors can be differentiated on the basis of the different uptake kinetics of FET. It would be worthwhile to conduct a comparative analysis of these 3 major amino-acid radiotracers, namely 11C methionine, F-DOPA and FET. However, logistical considerations and radiation dose to the patient need to be taken into account, before undertaking such studies.

DNA synthesis is an important prerequisite for cellular proliferation. The most widely used radiotracer for assessing DNA synthesis is 3-deoxy-3-[18F] flurothymidine (FLT). The imaging of cellular proliferation has a potential advantage over glucose imaging because FLT is specific to tumors, while high levels of energy metabolism are also seen with other processes including inflammation(12). Thus, unlike FDG it does not show uptake into inflammatory cells and has been widely used to distinguish benign from malignant pulmonary lesions. Like 11C methionine, the background uptake in normal brain parenchyma is low, thus enhancing tumor detection. It has been found useful for the differentiation of low-grade from high-grade gliomas, but not for distinguishing low-grade gliomas from nonmalignant lesions(13). Our study shows that although FLT performed well in case of high grade gliomas, it faired suboptimally in case of low grade gliomas – both in case of primary and recurrent tumors. Adequate tumor vascularization is an important precondition to tumor growth. Inadequate vascularization would culminate in tumor hypoxia and eventual necrosis. Hypoxic tissue is inherently more resistant to chemotherapy or radiotherapy and this is often responsible for failure of chemo-radiotherapy and an overall poor response. Several *in vivo* PET tracers have been developed to assess tumor hypoxia, e.g.,[18] F fluoromisonidazole (FMISO) and 64/60Cu(II)-diacetylbis (N-4-methylthiosemicarbazone) (64/60Cu-ATSM), which have a propensity to accumulate in hypoxic rather than normoxic cells. The most extensively used radiotracer for hypoxia is FMISO(14). Inclusion of FMISO imaging data provides information that is complementary to FDG PET data by correlating metabolic activity to tumor hypoxia.

The next generation of PET tracers includes those that will bind to specific cancer-related receptors or antigens (2).

These agents would offer tremendous opportunities for selective imaging, thus increasing the sensitivity and specificity for a particular tumor. There would also be enormous potential for directing molecular therapies targeted at these neoplasms. The development of targeted radiolabeled drugs to explore the efficacy of anticancer regimens holds promise for the future.

Dementia

With the introduction of several novel drugs to treat patients with Alzheimer's disease, accurate and early diagnosis is paramount to assess the type of therapeutic intervention. Because the disease is initiated at the molecular and cellular level early in its course, metabolic imaging appears to be the modality of choice for screening patients with memory loss (15). The present study shows that FDG PET/CT is useful in early diagnosis of MCI, which is often a diagnostic dilemma clinically. At the early stages of the disease, functional imaging with flow tracers (using PET or SPECT), or MR perfusion studies may not be sensitive enough to detect evidence of the disease. In advanced cases of course, structural changes would accompany the functional derangements. FDG PET/CT enables the evaluation of glucose metabolism of the brain parenchyma, which is usually done qualitatively or semiquantitatively, although absolute quantification is also possible. In the healthy brain, cerebral blood flow is tightly coupled with local metabolic needs, thus both blood flow and glucose metabolic rate co-vary linearly. Thus, the pattern of distribution of the blood flow tracer oxygen-15-labelled water closely parallels that of the metabolic tracer FDG throughout the cortical surface (15). Dissociations may occur in certain pathological circumstances.

PET/CT studies using FDG in the dementia patient, have enabled early detection and differentiation of the various forms of dementia. Our study, which was the first of its kind performed on the Indian population, showed clear distinction in the patterns of glucose metabolism in the various subtypes, with hypometabolism in the mesiotemporal cortex in MCI, temporoparietal cortex in AD, frontotemporal cortex in FTD and diffuse involvement in DLBD. Further, a significantly higher proportion of frontal lobe involvement was noted in AD in the Indian population. Regional cerebral metabolic changes associated with early AD can be detected with PET/CT even before the symptomatic manifestations of the disease become obvious. FDG PET/CT can also serve explicitly as a prognostic tool, to determine likelihood of deterioration of mental status in the period following the time of scanning. PET thus has an incremental value beyond conventional clinical assessment.

Movement Disorders

PD is caused by the loss of the pigmented neurons in the substantia nigra and the locus coeruleus. It is believed that initially there is an upregulation of dopamine receptors, followed by a down-

regulation that occurs as the disease progresses (16). Conventional imaging techniques such as CT and MRI are not useful for detecting early disease or monitoring subtle changes in disease activity. There have been previous reports of FDG hypermetabolism in the basal ganglia in early PD (17). PD patients have been shown to have mild diffuse cortical hypometabolism compared to controls. In cases of dementia in association with PD, uniform cortical hypometabolism is noted. FDG PET studies enables differentiation of the various Parkinsonian syndromes based on the differential pattern of uptake. In MSA, FDG uptake is reduced in the striatum, frontal cortex and cerebellum (18). As with MSA, FDG PET has identified hypometabolism in striatum, frontal cortex, thalamus and cerebellum in PSP (19). The results of our study, performed on a large scale for the first time on the Indian population, also show differential uptake pattern in the various movement disorders, with pallidothalamic hypermetabolism in PD, hypometabolism predominantly in the mid-brain, basal ganglia and anterior cingulate cortices in PSP, hypometabolism in the pons and dorsolateral putamen in MSA and asymmetrical hypometabolism in parietal cortices and basal ganglia in CBGD.

F-DOPA plays an important role in the diagnosis, evaluation of disease progression and therapeutic monitoring of patients with movement disorders attributed to PD or Parkinsonian syndromes. Patients with PD demonstrate bilaterally reduced FD uptake in the putamen, with normal uptake in the caudate nucleus. Striatal uptake of F-DOPA decreases in proportion to disease severity. Striatal uptake of F-DOPA is markedly reduced both in caudate and putamen in CBGD, PSP and MSA. The findings in our study, which were performed for the first time in the Indian population, corroborated well with that described previously.

Conclusion

PET/CT is a powerful molecular imaging tool in the assessment of neurological disease. The use of FDG and non-FDG novel PET radiopharmaceuticals facilitates the early diagnosis, delineation of extent, prognostication and monitoring of therapeutic response in several neuropathological states, thus strengthening the diagnostic armamentarium of the clinician in his quest to alleviate suffering and conquer disease.

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Life Style Interventions in the Prevention of Coronary Artery Disease

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SUMMARY

Lifestyle diseases particularly coronary artery disease (CAD) has been noted to be the most important cause of the morbidity and mortality all over the world. India is currently passing through this epidemic so much so that it would be taking a heavy toll of Indian youth and economy to the tune of some 1.6 trillion $ during 2015-2030 . The main causative factors for CAD identified as coronary risk factors are: smoking / tobacco, physical inactivity, faulty diet, hypertension, diabetes, high level of cholesterol and stress. As most of these risk factors are lifestyle related attempt to modify them by appropriate interventions form the cornerstone of prevention of CAD epidemic. Studies done by Dean Ornish and several others prompted us to plan an interventional case control study in 640 patients of established CAD. These cases were given power point presentation regarding healthy lifestyle on one to one basis and followed up at three and six months. Primary outcomes variable were change in smoking /tobacco habits, physical activity, obesity, dietary habits, control of hypertension, diabetes and lipid profile. At the end of intervention it was possible to bring down the tobacco consumption, improve physical activity, better control of hypertension ($p< 0.03$) , reduction in obesity ($p= 0. 0005$) and raising HDL cholesterol (p 0.05) significantly in test group. Taking cue from above study a five step innovative strategy was developed for effective implementation of healthy life style in coronary patients attending Cardiac Clinic at HAH Centenary Hospital, Jamia Hamdard. This strategy included sensitizing patients to locally developed visuals , posters and pamphlets at registration desk , concurrent counseling by attending doctor at the end of clinical examination and showing patients and their family the features of atherosclerosis during carotid ultrasound assessment. These points were again reinforced at follow up visits. Initial results of current intervention model is very encouraging in the sense that > 60% of subjects have quit smoking and close to 50% have started regular walking and taking appropriate diet following our intensive counseling. It is thus possible to modify the risk prone behavior and making such people shun smoking / tobacco consumption, resume regular physical activity and eat appropriate diet. The above interventional model merits further evaluation and extensive application.

Key Words: Lifestyle, coronary artery disease, tobacco use, physical inactivity, faulty diet, intervention.

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GENERAL AMIR CHAND ORATION delivered during NAMSCON 2013 at the All-India Institute of Medical Sciences, Jodhpur

Introduction:

Coronary artery disease (CAD) has been established to be the foremost cause of the morbidity and mortality globally (1-3). India is currently passing through this epidemic in a subtle and silent way so much so that only its tip is visible in government hospitals or at private health care centers while the major portion of this morbid disease is submerged in the society. According to a modest estimate about five years back it was predicted that India would require an amount of Rs 3178.1 billion to treat various cardiovascular diseases while a sum of Rs 615.7 billion will be adequate enough to prevent it by lifestyle measures (4). However, in a most recent WHO report it has been calculated that a colossal amount of some 1.6 trillion $ would be needed during 2015-2030 for tackling cardiovascular ailments in India (5). The very fact that it would be taking a heavy toll of Indian youth and economy is a compelling reason to take all steps to prevent this malady adopting evidence based medicine (6).

It is interesting to note that Sushruta - the master clinician and surgeon knew very well some 500 BC that physical inactivity and rich fatty diet were twin causes for 'medoroga ' , known as current day atherosclerosis, and 'madhumeh' , popularly known as diabetes (7) . The type of exercise advocated by Sushruta like long walk, digging a well, wrestling, horse riding is akin to that of current day treadmill exercise. Interestingly Madhvacharya 7th AD period ancient physician too described vividly causative and diagnostic features of obesity (8). However, credit for firmly establishing coronary risk factors such as smoking , physical inactivity, faulty diet , hypertension, diabetes, high level of cholesterol and stress as the principal reasons for CAD cases goes to Framingham Heart Studies initiated in late 1950s and the landmark INTERHEART study (9-10). As most of these risk factors are life style related attempt to modify them by appropriate interventions formed the logical hypothesis to stem the tide of the CAD epidemic (11-12).

The present communication briefly gives a brief account of our work about the causes behind CAD particularly among poor and young and the effective ways for lifestyle interventions under following headings : 1. Current scenario of lifestyle diseases in India; 2. Early observations on coronary risk factors; 3. Lifestyle interventions and CAD reversal; 4. Our initial experience about effect of lifestyle interventions on coronary risk factors ; 5. Current model : Five steps for effective implementation of healthy lifestyle; 6. Conclusion

Current scenario of lifestyle diseases in India

Concurrent with rapid urbanization and development there has been a remarkable change in the lifestyle of most Indians. People tend to smoke or

Table 1: Current burden of lifestyle related disorders in India

Disease	Estimated number of people affected	Major risk factors
Obesity	155 million	Physical inactivity , faulty diet, exercise
Hypertension	140 million	Faulty diet, lot of salt, physical inactivity, tobacco, alcohol, stress.
Diabetes	64 million	Physical inactivity, faulty diet, stress
CAD	31.8 million	Smoking / tobacco, physical inactivity, faulty diet, stress.
Cancer	12.7 million	Smoking / tobacco, faulty diet, physical inactivity
Stroke & COPD	1.2 million	Hypertension, smoking / tobacco, Physical inactivity
Chronic respiratory diseases	30 million	Smoking

chew tobacco as a mark of social status, tend to ignore physical activity , eat more junk or fatty food , consume more salt, and prone to more psychosocial stress. The resultant effect of this change is epidemic like increase in life style related disorders (Table 1). According to a very modest calculation India is a home to 155 million obese, 140 million hypertensive, 31.8 million CAD, 64 million diabetes including pre-diabetes and 1-2 million stroke patients. (12)

Early observations on coronary risk factors

My early interest in role of life style in CAD stems from MD thesis on coronary risk factors some forty years ago (13-14) . It was observed that most important risk factors were smoking/ tobacco, hypertension, hypercholesterolemia hyperglycemia and obesity (Table 2). Out of these smoking and obesity have been a consistent risk factor in subsequent studies at Manipal and two regions of Delhi – one at north east , UCMS-GTB Hospital and another at south east , HIMSR, Jamia Hamdard (15-18) . The recent surge of CAD among youth that too in low to lower middle

Table 2: Risk factors in ischemic heart disease (IHD)

	N= 308 / (118 IHD : 90 healthy control)
Smoking	57.6%
Hypertension	68.3%
Raised cholesterol	47.1%
Hyperglycemia	37.2%
Obesity	26.6%
Diet	7%
Occupation	Businessmen, passive agriculture workers, retd. people.

Table 3: Risk factors in young CAD patients and control

Parameters	CAD group (n=292)	Control Group (n=92)	p value	OR (95% CI)
Age (years± SD)	36.3±4.11	35.6±3.26	0.1737	-
Smokers*	217 (74.3)	13 (14.1)	<0.0001	17.6 (9.2-33.4)
Hypertension	73 (25.0)	12 (13.0)	0.0235	2.2 (1.14-4.31)
Diabetes mellitus	43 (14.7)	7 (7.6)	0.1115	2.10 (0.91-4.84)
Dyslipidaemia	172/189 (91.0)	73/83 (87.9)	0.5787	1.39 (0.61-3.17)
High total Cholesterol	36/189 (91.0)	17/83 (20.5)	0.9134	0.91 (0.48-1.74)
Low HDL-C	122/177 (68.9)	47/79 (59.5)	0.1838	1.51 (0.97-2.62)
Figures in parentheses denote percentages *P<0.05				

*Aggarwal, Aggarwal,Goel, Sharma, Dwivedi (2012)

segment of the society observed at Banaras, Delhi, Jaipur and down south Delhi during last four decades has made a startling revelation that with every passage of decade the prevalence of CAD is not only increasing but the age of onset for first CAD episode is getting preponed by five to ten year in each decade (Table 3) (18-19) . One common trait all over India is the dominant presence of smoking and/or tobacco habit in younger people suffering from CAD (10, 18,20). This fact has been further corroborated by an autopsy study carried out in 100 cases dying due to road traffic accident in north east Delhi. It was noted that 92% cases had evidence of coronary/aortic atherosclerosis as early as $2^{nd} – 3^{rd}$ decade. The mean age of these cases was 31.64 years and many of them were smokers and/or tobacco users (21-22). Above observations further strengthened our earlier hypothesis that faulty lifestyle like smoking /tobacco habit along with physical inactivity is the dominant factor behind the CAD among younger people (16)

Lifestyle interventions and CAD reversal

It was Dean Ornish in 1990 who convincingly reported that CAD can be reversed and /or halted by appropriate dietary and stress management technique like yoga (11) . It was a revolutionary concept in the sense that till then curative measures like antiplatelets, beta-blockers, statins , angiotensin converting enzyme - inhibitors (ACE -- inhibitors) - , coronary care unit care (CCU care) , angioplasty and or other aggressive mode of therapy was the only evidence based therapy for tackling coronary problems. Nobody could dare talk of focusing on alternative methods like yoga, strict emphasis on smoking cessation and appropriate dietary regimen perhaps because of lack of strong evidence about their efficacy in reversing CAD process once started. Although there were several leads mainly from Finland and United States that strict avoidance of tobacco, emphasis on vegetarian diet with plenty of fruits and vegetables and daily exercise or walking for > 30 minutes every day would

result in better control of diabetes and prevention of cardiovascular diseases or stroke. The results in elderly and women were more convincing (23-28). Even in our own country Udupa (1975) and Datey (1976)had published authentic evidence on beneficial role of yoga in hypertension and ischemic heart disease (29 -30).

Soon after Dean Ornish work several Indian studies demonstrated beneficial role of yoga in retarding coronary atherosclerosis (30-33). These studies had small number of cases that too without a long term follow up. Further, these could not be replicated in other cities of India because they required aggressive and costly procedures like coronary angiography which may not be available at all cities in first instance and even if available may be beyond the reach of common people who happen to be the major victim of CAD in their prime of youth. Therefore we badly needed a strategy which could be easily executed and monitored at all city hospitals and be effective in preventing CAD.

Initial experience about effect of lifestyle interventions on coronary risk factors

Taking cue from Dean Ornish work and Finnish studies about the beneficial effects of lifestyle interventions in CAD we carried out a randomized controlled trial study in 640 eligible CAD subjects randomly divided into two groups at our centre (34). The study group was given interventional package in the form of power point presentation on one to one basis at baseline giving basic outlines of healthy lifestyle. They were also handed over a booklet in Hindi giving necessary details of healthy life style for maintaining healthy heart (Fig 1). Control

Table 4: Effect of lifestyle intervention on risk factors in subjects in study and control groups*

Risk factors	Study group							Control group						
	Baseline (Ref)	Three months			Six months			Baseline (Ref)	Three months			Six months		
		OR	95% CI of OR		OR	95% CI of OR			OR	95% CI of OR		OR	95% CI of OR	
Hypertension	1	0.41	0.289	0.586	0.30	0.193	0.467	1	1.08	0.805	1.445	1.05	0.775	1.408
Obesity	1	0.77	0.655	0.910	0.58	0.452	0.736	1	0.87	0.741	1.026	0.98	0.796	1.214
Tobacco	1	0.14	0.100	0.194	0.08	0.057	0.123	1	0.24	0.180	0.327	0.18	0.128	0.245
Lipid profile disorders	1	------	------	------	0.67	0.448	1.088	1	------	------	------	1.21	0.781	1.842
Lack of physical activity	1	0.97	0.790	1.186	0.63	0.515	0.763	1	1.27	1.024	1.570	1.20	0.964	1.535
Diabetes	1	------	------	------	0.52	0.383	0.701	1	------	------	------	0.71	0.537	0.939

CI – confidence interval, OR – Odds ratio

- Source - Ali Dehghani , PhD thesis 2012

Table 5 : Comparison of lipid profile before and after intervention in the study and the control group in CAD subjects*

	Group	Pre Mean	Post Mean	Change	p value
Cholesterol	Study	160.85+/-43.55	147.63+/-45.01	-11.843	0.74
	Control	163.31+/-45.56	153.01+/-45.64	-2.74	
HDL	Study	35.23+/-7.82	37.15+/-7.61	-1.68	0.05
	Control	36.84+/-8.32	36.86+/-8.41	0.78	
LDL	Study	94.208+/-34.96	78.24+/-39.58	-8.06	0.96
	Control	98.38+/-40.39	78.24+/-39.58	-8.32	
Triglyceride	Study	134.32+/-72.5	118.90+/-56.83	-9.25	0.883
	control	132.53+/-70.28	120.67+/-63.73	-10.59	

- Source - Ali Dehghani , PhD thesis 2012

group was not given such a package, though they were also told about harms of smoking, physical inactivity and faulty diet during routine management. The subjects were then followed at three and six months and risk factors were evaluated to find out reduction, if any in risk factors amongst them. There was a statistically significant difference in reduction in tobacco, improvement in physical activity and reduction in blood pressure at three and at six months ($p<0.03$) (Table 4) . Further there was statistically significant difference in obesity after 6 months of adherence to lifestyle measures in study group as against control group ($p=0.0005$). There was also significant improvement in HDL cholesterol after six months (Table 5). However , there was no significant difference in reduction in diabetes at six months in the study group as compared to control group ($p=0.419$).

This study is remarkable in the sense that it is the first kind of a statistically robust long term study emanating from India wherein health education plus clinical service based intervention has produces reduction in coronary risk factors in established CAD patients. The preventive significance of above observations becomes important in view of the fact that merely by modifying four major risk factors one may achieve 90% reduction in sudden death in women (35) . Further , it is also known that increased fruit and vegetable consumption is associated with decreased type 2 diabetes risk –a conclusion based on studying 3704 middle aged adults for a period spanning about 11 years (36). On individual levels we do come across several examples where such life style intervention has brought reduction in coronary and other life style related

Fig.1 : Booklet 'अपनाइये अच्छी जीवन शैली, कभी न होगी दिल की सेहत मैली'

Current model : Five step for effective implementation of healthy lifestyle

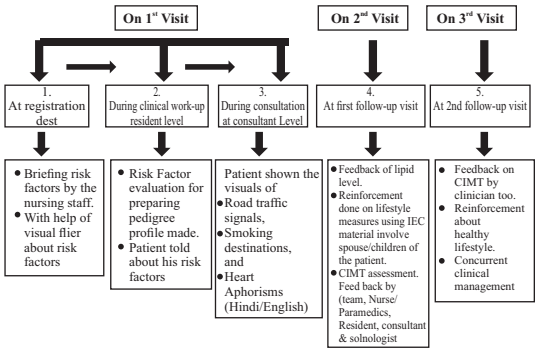

Fig. 2 : Current model

diseases (37). There is also a strong possibility that individually focused intervention as this may usher in such modifications in siblings and children because most of the time such habits are passed down to generations by elders in family (38).

Current model: Five steps for effective implementation of healthy lifestyle

1. Lessons learnt from above study prompted us to develop a model of intensive counseling concentrating on quitting smoking / tobacco habit, physical inactivity, diet, correcting central obesity and managing stress at HAH Centenary Hospital, Jamia Hamdard starting Jan., 2012 (Fig 2). The core features of this model is intensive health education comprising visuals, posters, aphorisms both in Hindi and English and comprehensive pedigree profiling of four major risk factors like tobacco, hypertension, CAD and diabetes in family and assessment of carotid intima media thickness (39) . Such a health intervention starts from registration desk at cardiac clinic and continues till final point of consultation under same roof. All subjects are given a colored visual depicting the harm inflicted by smoking/tobacco, inappropriate diet, central obesity, stress and physical inactivity at the entry point (Fig 3).

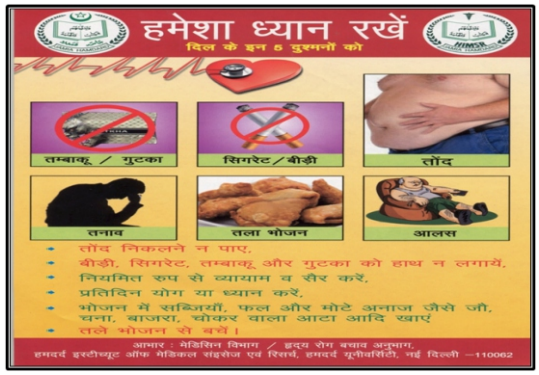

Fig. 3: Visual explained and given to each subject at registration desk

They are also shown posters showing the hidden health message behind traffic light signals at the end of the clinical work up same day (Fig.4).

Fig. 4 : Each patient explained the applied health message behind traffic light signals at the end of the consultation.

Beside these patient and his spouse / sibs / attendant are encouraged to read various posters displayed immediately outside the clinic (Fig 5). Notwithstanding these measures at 1st visit, patients are counseled again and again in the subsequent visits. In case of any default particularly smoking they are shown visual containing consequences of continued smoking (Fig. 6).

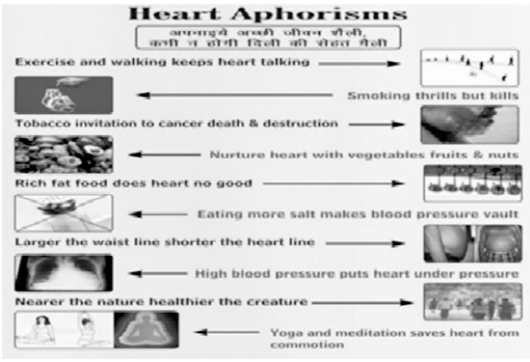

Fig 5 : Heart aphorisms explained to each patient by attending clinician after the clinical work up

We have been able to counsel some 200 cases suffering from CAD through such intervention. It was noted

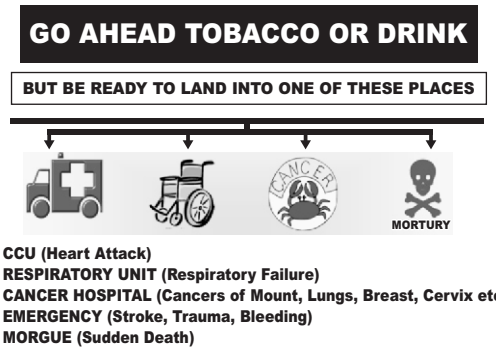

Fig. 6: Reinforcing not to smoke in follow up visit

that > 60% of subjects quit smoking and /or tobacco habit and close to 50% started regular walking and eating appropriate diet following above intervention . This is a remarkable achievement in our model compared to western findings of low success rate in smoking cessation. One of our 60-year-old patient who was known to be having hypertension , diabetes , psoriasis and had stroke about 6 months back continued to smoke and drink alcohol more than moderate amount till he visited our clinic; he left smoking after our 1st counseling (Fig.7).

Fig 7 : A-60-year-old painter, known hypertensive, diabetic who had two episodes of stroke continued heavy smoking and alcohol habit; left smoking and alcohol after our intensive counseling.

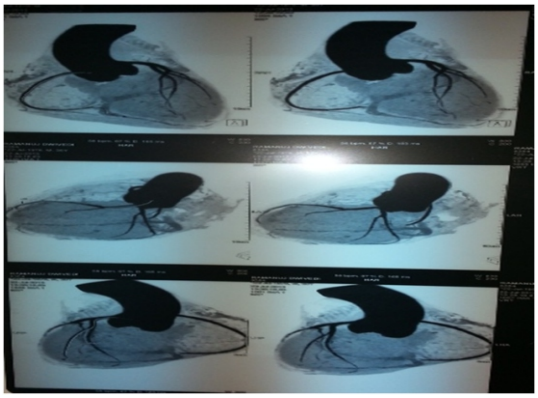

Fig. 8: A -56 –yr-old – male, non tobacco user with manifest central obesity developed hypertension, diabetes and finally detected to have TMT + ECG changes. He followed life style measures as per our counseling. His blood sugar improved and 64 slice MDCT revealed a normal coronary profile following three months of life style intervention.

This success is not limited to smoking subjects only but in non smoking people also. As we are well aware that diabetes is the most important cause of CAD next to smoking, our model takes care of this factor too. Another case who was 56-year-old- male , non tobacco user and obese , detected to be hypertensive , later on developing diabetes finally diagnosed to have positive tread mill test (TMT) and ECG ; he was suggested life style measures and given conventional antihypertensive drugs . After three months of above regimen his blood sugar improved and 64 slice computed tomography (CT) revealed a normal coronary profile (Fig.8).

Encouraged by this favorable response to our intensive health education we have now decided to take this campaign to some of the neighboring schools and sensitize the young minds about the healthy life style for ensuring good cardiovascular health.

Conclusion :

Coronary risk factors particularly tobacco use, physical inactivity and dietary modification can be modified appropriately if pursued aggressively by treating physicians and paramedical team using appropriate health education materials in hospital setting . A case for spreading healthy life style among youth is strongly advocated for preventing CAD epidemic.

Acknowledgements :

The author is grateful to 'Preventive Cardiology Group' UCMS-GTB Hospital and HAH Centenary Hospital, Jamia Hamdard for helping me in implementing life style measures among CAD patients in CCU as well as in 'Preventive Cardiology Clinics ' and particularly to Dr. Ali Dehghani, who carried out the earlier part of this work as his PhD thesis at UCMS , University of Delhi under our supervision.

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Auditory Neural Prostheses – A Window to the Future

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SUMMARY

Hearing loss is one of the commonest congenital anomalies to affect children world-over. The incidence of congenital hearing loss is more pronounced in developing countries like the Indian sub-continent, especially with the problems of consanguinity. Hearing loss is a double tragedy, as it leads to not only deafness but also language deprivation. However, hearing loss is the only truly remediable handicap, due to remarkable advances in biomedical engineering and surgical techniques. Auditory neural prostheses help to augment or restore hearing by integration of an external circuitry with the peripheral hearing apparatus and the central circuitry of the brain. A cochlear implant (CI) is a surgically implantable device that helps restore hearing in patients with severe-profound hearing loss, unresponsive to amplification by conventional hearing aids. CIs are electronic devices designed to detect mechanical sound energy and convert it into electrical signals that can be delivered to the cochlear nerve, bypassing the damaged hair cells of the cochlea. The only true prerequisite is an intact auditory nerve. The emphasis is on implantation as early as possible to maximize speech understanding and perception. Bilateral CI has significant benefits which include improved speech perception in noisy environments and improved sound localization. Presently, the indications for CI have widened and these expanded indications for implantation are related to age, additional handicaps, residual hearing, and special etiologies of deafness. Combined electric and acoustic stimulation (EAS / hybrid device) is designed for individuals with binaural low-frequency hearing and severe-to-profound high-frequency hearing loss. Auditory brainstem implantation (ABI) is a safe and effective means of hearing rehabilitation in patients with retrocochlear disorders, such as neurofibromatosis type 2 (NF2) or congenital cochlear nerve aplasia, wherein the cochlear nerve is damaged or absent on both sides and hence, a cochlear implant (CI) would be ineffective. In such patients, the brainstem implant bypasses the damaged / absent cochlear nerves and directly stimulates the cochlear nucleus in the brainstem. The auditory midbrain implant (AMI) has been designed for stimulation of the auditory midbrain, particularly the central nucleus of inferior colliculus (ICC). It is used especially in patients with large neurofibromatosis type 2 (NF2) wherein tumor induced damage to the brainstem/cochlear nucleus often co-exists. The efficacy and safety of auditory neural prostheses is well proven. Advancements in technology will enhance the benefit provided by these prostheses.

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ACHANTA LAKSHMIPATI ORATION delivered during NAMSCON 2013 at the All-India Institute of Medical Sciences, Jodhpur

Introduction:

Hearing loss is one of the commonest congenital anomalies to affect children world-over. WHO reports that nearly 2 - 3 per 1000 live births are found to have severe to profound hearing loss, making it the most common congenital abnormality to affect newborns world over. This scenario is even more pronounced in developing countries like the Indian sub-continent, especially with the problems of consanguinity. Hearing loss at birth is considered a social stigma even in present day society and ends as a double tragedy, as it leads to not only deafness but also language deprivation. However, hearing loss today, both congenital and acquired is the only truly remediable handicap, due to remarkable advances in biomedical engineering and surgical techniques. The advent of auditory neural prostheses, which are indicated for varying types and extent of hearing losses, has successfully broken the acoustic barrier, thus integrating people with hearing loss into normal society and providing them with a highly productive quality of life.

Auditory neural prostheses help to augment or restore hearing by integration of an external circuitry with the peripheral hearing apparatus and the central circuitry of the brain. They are safe and extremely effective in restoring hearing to both children and adults with severe - profound hearing loss, who do not receive benefit from conventional hearing aids. These implantable devices electronically stimulate the cochlea / auditory nerve or the higher hearing centers in the brain. The auditory system is unique in its organization because of the phenomenon of tonotopicity (place-pitch organization) which gives it the opportunity to receive and integrate external electronic circuits. This is possible because of the low potential for rejection of the device by the ear and nervous system. Thus, hearing restoration is the first successful path-breaking attempt in medical science to integrate an electronic device with the central nervous system, in order to fully restore a lost special sense organ.

COCHLEAR IMPLANTS

A cochlear implant (CI) is a surgically implantable device that helps restore hearing in patients with severe-profound hearing loss, unresponsive to amplification by conventional hearing aids. CIs are electronic devices designed to detect mechanical sound energy and convert it into electrical signals that can be delivered to the cochlear nerve, bypassing the damaged hair cells of the cochlea. These electrical signals are processed by an external speech processor and sent via a radiofrequency interface into an array of electrodes implanted surgically within the cochlea. The implant system preserves the tonotopic map of the cochlea and the auditory brain perceives these electrical impulses as sound(1).

Djourno and Eyries published the first description of cochlear implants in 1957. In 1961, House used a single channel CI and in 1984, Clark developed

the popular multichannel implant. FDA approval for CI was obtained in 1985. The first pediatric cochlear implantation was done in the US in 1987. Presently, a spectrum of implants is available along with improved speech processing strategies. Rapid technological advancements in bioengineering and implant manufacturing methods have led to miniaturization of the device, with refinement in sound signals, providing better "hearing in noise" and music appreciation among cochlear implantees.

Components of a Cochlear Implant System

The implant has external components, consisting of a microphone which receives and transduces sound into an electrical waveform, a speech processor which divides the signals into components for each of the electrodes, and a transmitting coil which sends the signals across the scalp to the internal components. The internal components include a receiver-stimulator, which receives the signals from the transmitting coil and sends it to the electrode array which is implanted in the scala tympani of the cochlea. (Fig.1)

Fig. 1 : Cochlear implant-internal and external components

Speech processors are currently available as body worn and ear level speech processors. All components play an important part in converting sound to an electrical stimulus. The microphone receives and transduces sound into an electrical representation. This is done in an analog (continuous) fashion. The external speech processor and signal-transfer hardware shapes the electrical signal. This requires amplifying, compressing, filtering, and shaping. Amplification is necessary to increase some signal levels to the point that they can be used in the electrical circuits. Compression is a necessary second step of signal modulation. The normal human ear can hear gradations of sound intensity in a range of 120 dB. Persons with severe to profound hearing loss do not have this same range. In the high frequencies, their dynamic range (the difference between their absolute threshold and painful sound) can sometimes be only 5 dB. The range in the lower frequencies is often 10–25 dB. This means that significant compression of the sound energy must take place in order to render it useful. Thus, all cochlear implants employ gain control of one kind or another. These systems monitor the output voltage and adjust the ratio of compression to keep the output in a range where it provides useful, but not painful stimuli.

Filtering of the input signal is the next step. Frequencies between 100 Hz and 4000 Hz are generally those most important for understanding speech. Sound energy is analyzed using several different types of filters. This allows the

unimportant frequencies to be removed and the frequencies of interest to be separately modified. Useful sound information is filtered into frequency bands. This information can then be analyzed for speech patterns and channeled to the appropriate portion of the electrode array. The transmitter, or outer coil, is placed on the mastoid (usually held in place by magnets) and sends the processed signal to the receiver via radiofrequency. The receiver, surgically placed in a well over the mastoid, receives the signal and sends electrical energy to one or many electrodes in the array. The electrode array, which lies within the cochlea, delivers the electric signal to electrodes along its length. The electrical field generated at these locations serves to discharge the neural components of the auditory system. The eighth nerve then conveys the signal. Just as important as any of the man-made components is the individual's ability to adjust to, interpret and respond to the electrical stimulus. Length of time spent without sound stimulation of the auditory system, presence or absence of previous experience with sound, personal motivation, community or family support, and opportunities for rehabilitation have been shown to be important factors in achieving a good outcome(2). These factors likely are important in understanding significant differences in patient outcomes despite similar preoperative auditory deficits, surgical course, and CI hardware.

Types of Cochlear Implants

Cochlear implants differ in the way that they process sound and how they present electricity to the hearing nerve. Other than the speech processing strategies discussed below, there are two different ways of encoding sound information. The first form, analog coding, involves continuous coding of the sound signal with subsequent transfer to the receiver in multiple radiofrequency channels. Electrodes are continuously stimulated. The second form, digital coding, requires sampling of the sound waveform and assigning a number to these “bits” of information. These bits of information are then transferred to the receiver where they are decoded. Electrodes are stimulated in a pulse fashion. Interestingly, neither approach is 100% effective for all implant users. Recently, combining the two schemes has seen some success. Cochlear implants can also be distinguished by their use of single versus multiple channels, the number of electrodes, and their use of either monopolar or bipolar stimulation. The number of electrodes stimulated with different electrical stimuli determines the “channels” used. In other words, an implant may have multiple electrodes but if the same information is presented to all the electrodes at one time, they are essentially functioning as a single channel system. In contrast, multichannel devices provide different information to several electrodes or groups of electrodes. Early implants had only one electrode (and one channel); recent advances have led to the

development of implants with multiple electrodes (22) and multiple channels (usually 4 to 8). Having more electrodes means that multiple channels can be localized to areas of the cochlea that are most responsive, and stray current that is stimulating adjacent structures (facial nerve, vestibular nerve) can be rerouted.

Cochlear implants can employ monopolar or bipolar stimulation. In a monopolar system, there is only one ground electrode for all the others. The ground is usually located at or outside the round window. Thus, an electrical field is created from the stimulated electrode to the ground. A bipolar arrangement is such that the ground for each electrode is much closer (adjacent to, or a few electrodes away). In the highly conductive environment of the inner ear, monopolar stimulation results in some limitations. As additional electrodes are stimulated with different streams (channels) of information, the electrical fields created by stimulated electrodes may interfere with fields at other sites. This makes it difficult to stimulate more than one electrode at a time, or electrodes that are close together. The bipolar configuration was an attempt to limit this interaction by placing a ground near each electrode, such that a smaller field would be created with less interference and more discrete stimulation. Once again, one approach does not achieve satisfaction with all patients. As a result, many implants offer both grounding methods.

Indications for Cochlear Implantation

Bilateral profound cochlear hearing loss, unresponsive to amplification by the most powerful hearing aids, is the prime indication for a CI. All children below the age of 6 years who have congenital or acquired profound hearing loss and who will not benefit from conventional hearing aids and all adults who have lost hearing after acquisition of language are ideal candidates. The only true prerequisite is an intact auditory nerve. Postlingual candidates do extremely well with an implant and in prelingual and perilingual candidates, an important factor influencing candidacy is neural plasticity, and the emphasis is now on implantation as early as possible to maximize speech understanding and perception. In very young children, language acquisition is easier, hence the need for early implantation. Owing to the loss of neural plasticity in older prelingually deaf people, the response to implantation may not be optimal and extensive preoperative counseling regarding realistic expectations is crucial. Presently, the indications have expanded to include candidates with low frequency residual hearing and those with severe hearing loss. These expanded indications for implantation are related to age, additional handicaps, residual hearing, and special etiologies of deafness. The minimum age for implantation in children has come down and children as young as 6 months of age have been implanted. Because the cochlea is full-size at birth, there is no anatomic difficulty with

electrode insertion in very young children. Medical and radiological criteria have expanded to include significant cochlear abnormalities including additional handicaps, as in syndromic deafness. The recent trend is towards bilateral simultaneous or sequential implantation, which provides immense benefits of binaural hearing.

Contraindications for Cochlear Implantation

Not all patients with sensorineural hearing loss are good candidates for cochlear implantation. For example, patients with pure tone thresholds greater than 90 dB with residual hearing through 2000 Hz often do better with hearing aids than with implantation. The absence of the cochlea (Michel deformity) and a small internal auditory canal (associated with cochlear nerve aplasia) are contraindications to implantation on that side. Other forms of dysplasia are not necessarily contraindications. However, when implantation of a dysplastic cochlea is to be undertaken, informed consent is especially important. Cochlear implants in these patients are associated with increased risk of poor outcomes, cerebrospinal fluid (CSF) leak, and meningitis. A diagnosis of neurofibromatosis II (history of progressive hearing loss and suggestive MRI findings), mental retardation, psychosis, organic brain dysfunction, and unrealistic expectations may also be contraindications.

The presence of active middle ear disease is a contraindication to surgery. This should be treated and resolved before implantation. Patients with a history of canal wall down mastoidectomy may need surgery to reconstruct the posterior canal wall or close off the canal.

Meningitis may lead to hearing loss and ossification of the cochlea. Labyrinthitis ossificans is usually identifiable on CT scan and Magnetic resonance imaging. Adults and children with acute meningitis should be treated with steroids to avoid hearing loss. In patients with profound hearing loss, implantation must be advocated as early as possible.

Advanced otosclerosis can also cause ossification of the basal turn of the cochlea. This finding is most often noted on CT scan. This is not a contraindication as long as the surgeon is prepared to perform a drill out or pursue implantation into the scala vestibuli. Patients with otosclerosis can achieve excellent results from implantation.

Preoperative Assessment

Prior to implantation, a basic workup including hematological, chest X-ray, ECG, TORCH screen need to be performed. An audiologic assessment is the primary means of determining implant candidacy. Audiological and electrophysiologic investigations include puretone or behavioral audiometry and impedance audiometry, otoacoustic emissions (OAE), brainstem evoked

response audiometry (BERA), auditory steady state response (ASSR), aided audiometry and a hearing aid benefit evaluation. Promontory stimulation testing can be done in older children and adults to assess the response of the cochlea to electrical stimulation.

High resolution CT scans of the temporal bones are done to plan the surgical route for implantation, identify the vital structures like the facial nerve and promontory, and also to rule out any evidence of middle ear disease/ mastoiditis. MRI is the gold standard investigation for the assessment of cochlear anatomy and the vestibulocochlear bundle(3). (Fig.2 &3) CT/MRI reveal anomalies like Mondini's and Michel's aplasia, labyrinthitis ossificans, or absent eighth nerve. Rapid advances in genetics and molecular biology are revolutionizing our understanding of congenital deafness, and genetic counseling should play an important part in prevention. Hence, a genetic specialist's opinion is sought in patients with syndromic etiology of deafness. Children need to get evaluated by a child psychologist for assessment of mental functions and IQ, prior to implantation and an ophthalmologist needs to perform a fundus examination to rule out associated visual impairment as seen in Usher's syndrome. In children, pre-implant meningococcal vaccination is carried out.[4] Preoperative habilitation is important before surgery. Counseling patients and parents prior to implantation to develop realistic expectations of the likely outcome is vital. Hence, candidates and parents need to meet and interact with other cochlear implantees, to have a perspective on the procedure and its outcome.

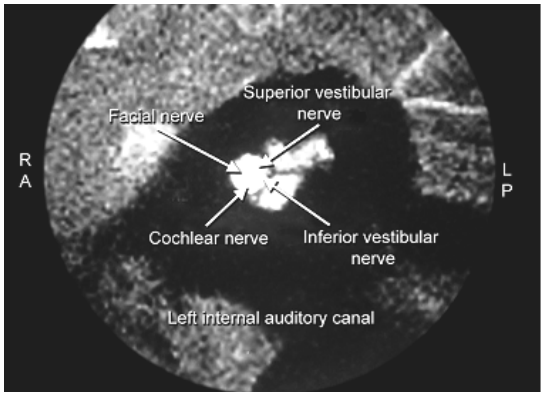

Fig. 2: MRI of the internal auditory meatus showing intact cochlear nerve

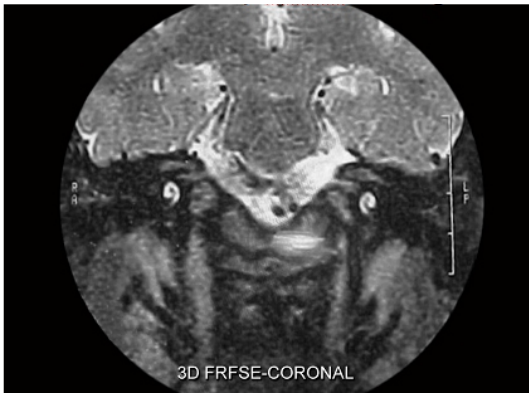

Fig. 3: MRI showing bilateral normal fluid-filled cochlea—the “Comma” sign

Cochlear Implantation Surgery

The goal of CI surgery is to insert the entire electrode array into the scala tympani with as little damage as possible to the structure of the inner ear. The success of cochlear implantation depends on scrupulous attention to technique at all

the various steps of the procedure. Implantation is performed with strict aseptic precautions and is done under general anesthesia. Surgery is essentially the same in children and adults because the anatomic structures are of adult configuration at birth. However, in very young children, there is a slightly increased risk of facial palsy and blood loss may be an issue.

The steps of surgery are as follows: usually an extended postauricular incision is made to expose the mastoid cortex. The incision should be made more than 1 cm away from the location of the coil of the implant. The mastoid is drilled out to expose the mastoid antrum. Saucerization of the cavity is not done. Posterior tympanotomy is performed, the promontory and round window niche are exposed, without exposing the facial nerve. A well for receiver-stimulator is fashioned in the skull behind the mastoid cavity using a template as a guide, and a groove is made to connect it to the mastoid cavity. Tie-down holes are made on either side of the well for securing the implant. Cochleostomy is done at the basal turn of the cochlea which is opened anterior to the round window to make the axis of introduction of the electrode array straight. The electrode array is inserted atraumatically into the scala tympani using a claw. Alternatively, a round window insertion may be performed after drilling out the anterior lip of the RW niche and adequately exposing the secondary tympanic membrane (Fig.4). Once the

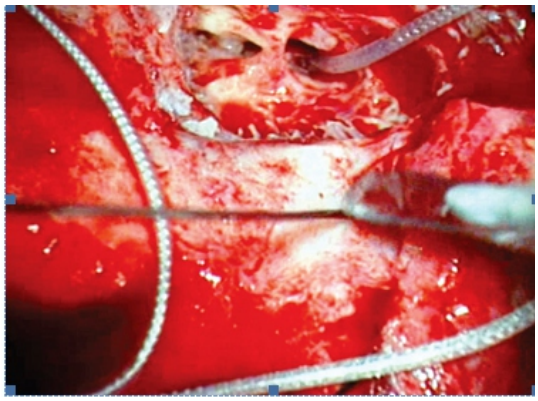

Fig. 4: Cochlear implantation electrode array in situ

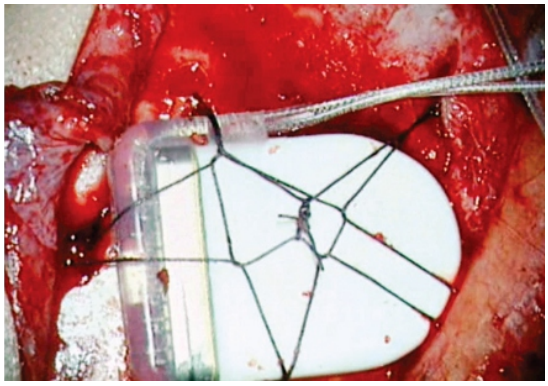

Fig. 5: Cochlear implantation receiver-stimulator coil in situ

electrodes are inserted, diathermy should not be used. Fixation of the device and electrode array (Fig. 5) and wound closure is done.

Electrophysiological testing (impedance telemetry), neural response telemetry and electrically evoked stapedial reflex thresholds are performed intraoperatively to confirm the optimal performance of the implant in situ. This assures the implant team that the device is functioning and that the patient is receiving an auditory stimulus and responding appropriately.

Switch-on and Mapping of Cochlear Implant

The switch on and speech processor tuning is done 3 weeks after surgery. Mapping is done at periodic intervals till a stable map is achieved. Frequent mapping sessions are required, and prolonged and intensive (re)habilitation after implantation is essential. Habilitation aims at improving receptive language skills and expressive skills. The habilitation program is started out based on baseline skills of the patient; periodical assessments of outcome need to be done in terms of environmental sound, open set, closed set speech, speech discrimination and telephonic conversation. The recommended period for auditory verbal habilitation is 1 year.

Outcomes of Cochlear Implantation

The success of a CI program is directly dependent on its ability to address the issue of patient expectations and balance it with the outcomes. A multidisciplinary approach is required involving the ENT surgeon, audiologist, speech therapist, auditory verbal habilitationist, child psychologist, and pediatrician. The patients and their family must also be highly motivated for the implant. Variables affecting the outcome of CI in children are the duration and etiology of deafness, age at onset of deafness, preimplant amplification history, communication mode, age at implantation, type of speech processor used, and duration of implant usage. In very young children, language acquisition is easier and hence the need for early implantation. Owing to the loss of neural plasticity in older prelingual deaf people, the response to implantation may not be optimal and extensive preoperative counseling regarding realistic expectations is vital. Factors influencing the overall outcomes are the transparency of the program, expertise of the team, patient motivation, family support, and facilities for habilitation.

Complications

The surgical complication rate after cochlear implantation is estimated to be less than 5%. The most common problems are wound infection, biofilms and wound breakdown. Rarely, extrusion of the device, facial nerve injury, bleeding, CSF leaks and meningitis, vertigo, tinnitus, facial nerve stimulation, numbness of scalp, loss of taste can occur. Device-related complications include intracochlear damage, slippage of the array, breakage of the implant, and improper or inadequate insertion and device failure.

Centers for Disease Control and Prevention (CDC) recommend vaccination of implanted or soon to be implanted patients. Children less than 2 years of age who have implants should receive pneumococcal conjugate vaccine. Children with implants 2 years and older who have completed the conjugate series should receive one dose of the pneumococcal polysaccharide vaccine.

Children with implants between 24 months and 59 months who have never received vaccination should receive two doses of pneumococcal conjugate vaccine 2 months apart, and then one dose of pneumococcal polysaccharide vaccine at least 2 months later. Finally, persons aged 5 years and older with cochlear implants should receive one dose of pneumococcal polysaccharide vaccine.

Difficult Scenarios in Cochlear Implantation

With increasing experience in cochlear implantation, the indications for implant surgery have widened to include cochlear anomalies, syndromic associations, and multiple handicapped individuals. Implantation is beneficial in such situations. However, the surgeon must anticipate challenges during implantation and also, the subsequent habilitation may be challenging.

Cochlear Implantation in Labyrinthitis Ossificans

A common abnormality encountered is the ossified cochlea, mostly occurring as postmeningitic sequelae, although other pathologies may predispose to ossification including otosclerosis, chronic otitis media, ototoxicity, autoimmunity, trauma and others. This remains one of the significant surgical challenges for the otologist. It is diagnosed with a CT/MRI scan. On confirmation of an obstructed basal turn, the proximal turn is drilled with a microdrill to a depth of 6–8 mm until an open lumen is discovered, and the electrode array is inserted. In total ossification, a complete drill-out of the basal turn is required and the implanted array is seated in a trough that surrounds the modiolus. A double-array implant may be used with some electrodes into the basal turn and others into the second turn.

Cochlear Implantation in Mondini's Deformity/Large Vestibular Aqueduct Syndrome

Cerebrospinal fluid leak during cochleostomy has to be sealed. A variety of techniques may be used to help control the flow of CSF including firm plugging of the cochleostomy using soft tissue coupled with reducing the flow of CSF by lumbar drainage and intravenous mannitol drip, if necessary. Such leaks may also be encountered in cases of enlarged vestibular aqueduct (LVAS)**.** The 'pulsatile stapes sign' has been described by the author to diagnose LVAS intra-operatively.

Auditory Neuropathy/Auditory Dys-synchrony Spectrum Disorder

Normal outer hair cell (OHC) function and dys-synchronous neural responses characterize this disorder. Patients will show a normal OAE with absent BERA waveforms, which is pathognomonic of this condition. Cochlear implants are a viable management option for patients with auditory neuropathy/auditory dys-synchrony spectrum disorder (AN/ADSD) and are beneficial in

bypassing the desynchronous neural network, but the outcomes may be suboptimal or guarded, and the family needs to be counseled regarding the same.

Cochlear Implantation in Multihandicapped Individuals

Early diagnosis and rehabilitation of deafness and additional handicaps are crucial. An implant helps in the habilitation of deafness and other handicaps as well. However, patient selection criteria must be stringent. Evaluation, surgical intervention, and postimplantation management of these patients can be challenging.

Minimally Invasive Cochlear Implantation

Due to improvements in CI technology, smaller and more powerful implantable cochlear implants have evolved which has enabled smaller external incisions, smaller skin flaps, shortened surgical time, and faster healing. Current techniques in cochleostomy (Peep-hole cochleostomy) and round window electrode insertion (soft insertion) have resulted in preservation of residual hearing.

Bilateral Cochlear Implantation

Bilateral CI has significant benefits which include improved speech perception in noisy environments and improved sound localization.(5) The advantages include elimination of head-shadow effect, significant benefits from summation effects (improvement in hearing threshold from redundant information presented to each ear) and squelch effects (improvement in hearing threshold from brainstem processing of inter-aural time and intensity differences).

Cochlear Endoscopy

Cochlear endoscopy was first described by Balkany and colleagues in 1990 who used flexible fiberoptic microendoscopes (0.7–1 mm diameter)(6). Currently, the indications for cochlear endoscopy are limited and it is not recommended routinely during CI. The present indications are visualization of obstructed segments of the cochlea in labyrinthitis ossificans and the interior of the cochlea in cochlear dysplasia. Visualization of the interior of the cochlea will help in preinsertion assessment as well as to verify proper insertion of the implant.

Perimodiolar and Midscalar Cochlear Implantation

These implants are assumed to have a slightly enhanced speech perception. After the electrodes are inserted into the cochlea, the stylet is withdrawn and the electrodes come into a perimodiolar/midscalar position. The electrode-neural interface seems to be minimal in this position, and hence clarity of auditory inputs are much better.

Future Directions In Cochlear Implantation

CI surgery and technology continue to evolve. In the future, fully implanted devices (like the TIKI prototype), improved speech coding strategies, cochlear hair cell, and nerve growth factors used in conjunction with an implant may be available.

MERF Experience

Nine hundred cochlear implantations were performed over 15 years. Majority of candidates were pre-lingual, 10% candidates were postlingual and 20% were peri-lingual. Outcomes were dependent on age at implantation and duration of deafness, the best outcomes were observed when implantation was performed before 3 years of age. Children responded better with very good outcomes if implanted early. Children in 1-5 yrs age group achieved category 7 (use telephone) on CAP score and category 5 (connected speech intelligible to all listeners) on SIR score earlier than children in 6 -10 years age group.

Electroacoustic Stimulation

One of the latest applications of implantable hearing technology combines electric and acoustic stimulation (EAS) into a hybrid device designed for individuals with binaural low-frequency hearing and severe-to-profound high-frequency hearing loss.

Indications

Electro-acoustic stimulation is the latest strategy conceptualized for residual hearing preservation in the implanted ear, in order to provide combined electrical stimulation and acoustic hearing for candidates with bilateral high-frequency, severe-to-profound sensorineural hearing loss. The addition of the electrical stimulation to such patients, with existing residual low frequency hearing, can provide clear speech recognition in background noise and better appreciation of musical notes. Low-frequency thresholds generally can range from 20 dB HL to 60 dB HL through 750 Hz, and thresholds at 1000 Hz and above must generally exceed 60–70 dB HL Preoperative speech perception criteria require that aided consonant nucleus consonant (CNC) monosyllabic word recognition score in the ear to be implanted cannot exceed 50–60%. Individuals with binaural high frequency hearing loss may not gain significant benefit from traditional hearing amplification. Their relatively good low-frequency hearing may disqualify them from conventional cochlear implant (CI) candidacy. As a result, individuals with good low-frequency hearing and severe-to-profound high-frequency hearing loss can experience significant difficulty in everyday communication, particularly in noisy backgrounds, where low-frequency information alone is not sufficient to allow high levels of speech understanding.

In recent times, implant surgeons are employing soft surgical techniques

which include a smaller cochleostomy or round window insertion, performed gently with thinner electrode arrays and/or perimodiolar electrodes (atraumatic cochlear insertion) which contribute to hearing preservation with standard cochlear implants. The hybrid device uses a shortened CI electrode array that is inserted just 10-20 mm into the cochlea (versus 20-30 mm for a conventional implant), covering the basal two third of the cochlea. A successful surgical outcome allows for monaural electric stimulation of the basal cochlea for high-frequency information without damaging apical cochlear structures that transmit low-frequency acoustic information. This combination allows for the integration of electric and acoustic perception in the same ear.

Components of Hybrid Implant

The EAS system consists of two parts: a CI with a soft and flexible electrode array for preservation of residual low frequency hearing, and a speech processor which combines the CI component with conventional acoustic stimulation in one comfortable and compact device. EAS patients wear an in-the-ear (ITE) hearing aid in the implanted ear (which can amplify sound signals up to 43 dB acoustical gain) in combination with an external ear-level or body-worn speech processor or an integrated hearing aid/speech processor on the implanted side. Surgery for EAS is very similar to conventional cochlear implantation, and round window insertion is often preferred for optimal hearing preservation. The hybrid implant has a specialized microphone competent for parallel processing of sounds. The acoustic and electric digital sound processing components of the EAS processor receive sound signals from this single microphone. The parallel processing of these signals is performed separately and optimized for both acoustic stimulation (focusing on low-frequency hearing) and CI stimulation (focusing on high-frequency hearing). This microphone automatically adjusts to incoming sounds in order to capture all the vital cues necessary for understanding speech clearly without requiring special programming or the use of a switch to shuffle between the two modes of hearing.

Enhanced music perception is one of the major benefits reported by candidates who receive EAS implants.

Auditory Brainstem Implants

Auditory brainstem implantation (ABI) is a safe and effective means of hearing rehabilitation in patients with retrocochlear disorders, such as neurofibromatosis type 2 (NF2) or congenital cochlear nerve hypoplasia/aplasia, wherein the cochlear nerve is damaged or absent on both sides and hence, a cochlear implant (CI) would be ineffective. In such patients, the brainstem implant bypasses the damaged / absent cochlear nerves and directly stimulates the cochlear nucleus in the

brainstem(7).

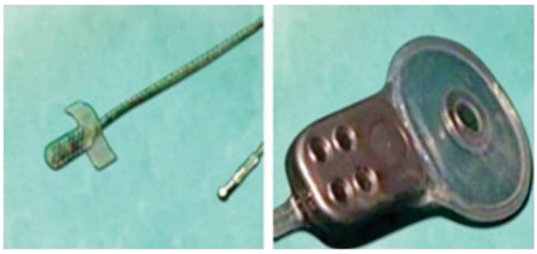

Fig. 6: Two ends of the auditory brainstem implant

Indications For Auditory Brainstem Implantation

Multichannel ABI are USFDA approved for adult patients with NF2 tumors involving both vestibule-cochlear nerves. The implant is usually placed in the lateral recess of the fourth ventricle after tumor resection(8). (Fig.6)

The indications for ABI have expanded onto non-tumoral (NT) cases, such as congenital bilateral cochlear nerve aplasia(9). In such cases, the pediatric ABI helps bypass the non-functioning hypoplastic or absent cochlear nerves and stimulates the cochlear nucleus directly, thereby restoring auditory sensation in children. Other indications for ABI include bilateral totally ossified cochleae in which a CI cannot be used, bilateral auditory neuropathy, bilateral temporal bone fractures and demyelinating diseases affecting the eight cranial nerves, but sparing at least one cochlear nucleus. Contraindications to ABI include previous stereotactic radiotherapy which has the risk of radiation necrosis of the cochlear nucleus region, and anatomic distortion and fibrosis. ABI may not be possible in very large tumors which cause distortion of the brainstem.

A multidisciplinary collaboration between neurotologist, neurosurgeon, implant audiologist and neuro-anesthetist is required in order to perform this intricate and sophisticated surgery. Most patients with the implant have good auditory awareness with appreciation of environmental sounds, but obtain more modest benefit with regard to speech perception. Majority of ABI patients use the implant, in order to facilitate lip reading while some can, in varying degrees, comprehend speech directly. It has been demonstrated that the ABI with surface electrodes may provide sufficient stimulation of the central auditory system in adults for open-set speech recognition. These favorable results motivated the clinicians to extend ABI indications onto children with profound hearing loss who are not candidates for CI.

The incidence of cochlear nerve aplasia in the overall population world over is very low, estimated at one in every 100,000 newly born babies wherein ABI is indicated. Auditory brainstem implantation appears to be more effective in non-tumor diseases of the auditory nerve or cochlea than in patients with NF2 tumors.

Clinical Assessment for Auditory Brainstem Implantation

A meticulous work up – audiology & electrophysiology and high resolution radio-imaging with computed tomography (CT)/magnetic resonance imaging (MRI) of the brain and inner ear is mandatory.

In children, a detailed genetic study, neurological and psychomotor assessment is necessary apart from the routine work up as done for cochlear implantation.

Operative Procedure for Auditory Brainstem Implantation

For successful ABI surgery, a few important issues such as patient selection, choice of device, choice of approach, technique of tumor removal, knowledge of microanatomical variations, intraoperative identification of the cochlear nucleus and prevention of complications have to be considered. The procedure is done under intensive neuroanesthesia with intraoperative cranial nerve monitoring. Translabyrinthine approach or lateral suboccipital approach is used. Craniotomy exposes the transverse sinus superiorly and sigmoid sinus laterally. Dura needs to be opened by a vertical incision 1 cm away from the sigmoid sinus, and is reflected laterally. Cerebrospinal fluid (CSF) is let out from the basal cisterns to make the cerebellum lax. Cerebellum is retracted medially to reach the cerebellopontine (CP) angle where the VII and VIII nerve complex is identified. Inferiorly, the lower cranial nerves are seen and followed medially onto the foramen of Luschka where the choroids plexus is identified. Further dissection is done to reach the floor of the IV ventricle, where a constant vein called the straight vein is present, which leads to the site of the cochlear nucleus. In tumoral cases as in NF2, tumor excision via the same approach precedes the implantation. After tumor excision, the landmarks (VII, VIII and IX cranial nerves, choroid plexus) for the foramen of Luschka are identified. Location of the lateral recess can be confirmed by noting the egress of

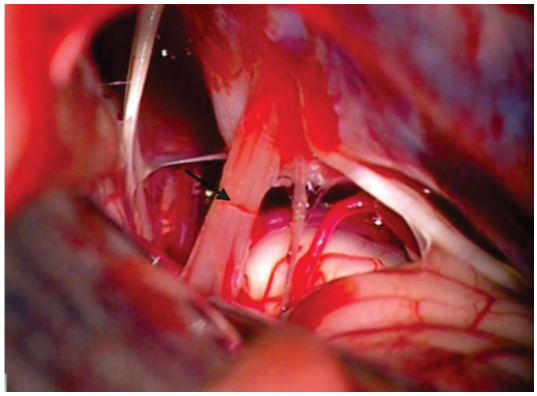

Fig. 7: Hypoplastic VIII N

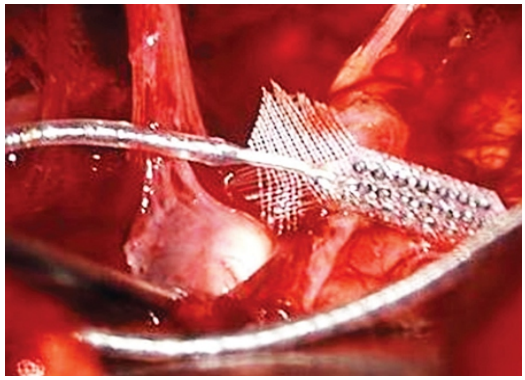

Fig. 8: Insertion of electrodes in brainstem

CSF during valsalva maneuver. The ABI electrode array is then inserted into the lateral recess and positioned once the cochlear nucleus is well delineated. Initially, temporary electrodes are placed on it and electrically evoked auditory brainstem responses (EABR), early mid-latency responses (EMLR), and device telemetry (DT) are performed to check the optimal positioning and functioning of the electrodes. Once integrity is confirmed, the permanent electrodes are then placed onto the cochlear nucleus and positioned with fibrin glue and surgicel. (Fig. 7 & 8)

The receiver-stimulator coil is placed in a bed created in the area posterosuperior to the craniotomy. It is placed at least 10 mm behind the edge of the auricle and above the canthomeatal line, and is angled 30–45° posterosuperiorly. Tie-down holes are made on either side of the receiver-stimulator for securing the implant. Reconfirmation of implant function is done with electrophysiological tests. The stimulus to ABI is delivered by an external component comprising of a microphone, a signal processor and a transmitter coil very similar to the CI. Dura is closed primarily in a water-tight fashion. Postoperative neurointensive care is necessary with cranial nerve monitoring.

Habilitation After Auditory Brainstem Implantation

The device is switched on 2 months after implantation, providing sufficient time for wound healing and full recovery. Switch on needs to be done in the operation theater with neuro monitoring and adequate preparation for active CPR, as there may be inadvertent stimulation of other brainstem nuclei and the possibility of non-auditory stimulation of vital centers. The stimulus threshold and comfort level on each electrode is ascertained. Postoperative CT scan and X-ray of skull confirm the position of the ABI in situ. (Fig. 9)Habilitation of ABI patients requires intense dedication and skill on the part of the auditory habilitationist and audiologist, along with adequate motivation and family support from the patient's side.

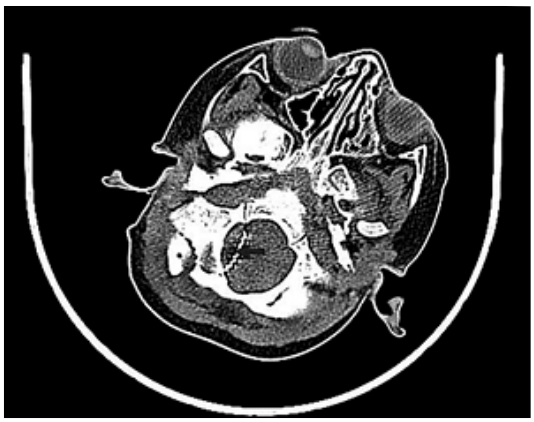

Fig. 9: CT scan image showing brainstem implant in situ

Outcomes of Auditory Brainstem Implantation

Intensive auditory verbal habilitation is then initiated and continues for a minimum period of 1 year (as advocated for CI) with periodical EABR and EMLR - tests done during the follow-up for confirmation of device integrity and

assessment of optimal performance of the implantee. Most implantees develop very good sound awareness and good gross auditory discrimination with appropriate habilitation. Achievement of lucid environmental sound perception with pitch discrimination for closed set speech is often the culmination of the habilitation process.

MERF Experience

Of the seven candidates who underwent ABI, one patient was post-lingual and had neurofibromatosis type II and six were pre-lingual with bilateral cochlear and cochlear nerve aplasia. The outcome assessment is by habilitation scores (CAP, SIR, MUSS, MAIS), electrically evoked auditory brainstem response and cortical auditory evoked potentials.

Auditory Midbrain Implant

The auditory midbrain implant (AMI) has been designed for stimulation of the auditory midbrain, particularly the central nucleus of inferior colliculus (ICC).

Cochlear implantation (CI) is ineffective for those without an implantable cochlea or an absent, thin non-functional or tumor of the vestibulo-cochlear nerve. These patients can be implanted with the auditory brainstem implant (ABI), which directly stimulates the surface of the cochlear nucleus. Unfortunately, ABI has achieved limited success in providing environmental awareness and auditory sensations, especially in patients with large neurofibromatosis type 2 (NF2) wherein tumor induced damage to the brain-stem/cochlear nucleus often co-exists. The midbrain is a target, is more surgically accessible than the cochlear nucleus in the lateral recess and hence AMI has today emerged as a valuable alternative to the ABI. The central nucleus of ICC is tonotopically well organized like the cochlea and accesses all ascending auditory impulses from the peripheral pathways(10). AMI offers advantage over the ABI in that it can be surgically implanted under direct visual exposure of the target ICC region, with less risk of damaging critical brainstem structures and cranial nerves. Stimulation of the ICC site helps in enhancing the lip-reading capabilities and also provides environmental awareness with improvement in speech perception performance.

Conclusion

Advances in biomedical engineering have led to the development of auditory neural prostheses such as cochlear implants and auditory brainstem implants which have helped habilitate patients with severe – profound hearing loss. Their efficacy and safety are well proven. Advancements in technology will enhance the benefit provided by these prostheses.

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