Clinical neurophysiology: Evolution and prospects

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In the diagnostic armamentarium of neurological disorders, clinical neurophysiology has attained a critical role as it provides useful information on the functional integrity of the central and peripheral nervous system and localization of the lesion. With sophistication of instrumentation, major advances in electronics and computer technology have been translated into clinical application, facilitating a more precise understanding of the functional state of the nervous system. The noninvasive approach of many of the electrophysiological procedures, like electroencephalography, electromyography, nerve conduction and evoked potential studies, has made them acceptable in routine clinical practice for evaluating the functional status of brain, special sensory, motor and somatic sensory pathways, peripheral nerves, neuromuscular junction and muscle in various states of health and disease. In the recent years, for studying the central motor pathways, electrical stimulation has been replaced by magnetic stimulation. Another new development, still under evaluation, is magnetoencephalography, which recognizes a tangentially oriented electrical source and may become a complementary tool to the conventional electroencephalography. In the Indian context, there is an urgent need for a closer interaction of the scientists in the fields of basic physical sciences and neurosciences to foster mutual growth and promote new developments in clinical neurophysiology.

CLINICAL neurophysiology, in the current practice of neurology, has become an invaluable tool for diagnosis, localization of the lesion in the neuraxis, monitoring of its functional status during drug therapy, intervention and neurosurgical procedures as well as determination of brain death crucial for transplant surgery. Better understanding of the physiology of the central and the peripheral nervous system has been possible because of concomitant developments in the fields of electronics and computers, leading to sophisticated instrumentation. Functional evaluation of muscle, neuromuscular junction, peripheral nerves (motor, sensory, autonomic), plexus, roots, spinal cord and cerebrum has now become a routine practice in clinical neurology using techniques of electromyography (EMG), nerve conduction, electroencephalography (EEG) and evoked potentials. In the recent years, attempts have been made to overcome the limitations of the traditional methods, which are chiefly qualitative, by quantitative analysis of data. Recording of EEG at a distance (telemetry), electric and magnetic stimulation of the brain for determining central motor conduction, expert systems in EMG and magneto-electroencephalography are some new additions in the field of electrophysiology.

History

The emergence of clinical neurophysiology as a distinct discipline in the last 50 years owes its origin to the epoch-making researches of Galvani in 1791 when the first claims for intrinsic animal electricity were made as a culmination of years of experimentation. Nearly 80 years later, in a landmark paper in 1875, Caton[1] reported electrical currents of the brain in animals, thus laying the foundation of electroencephalography (EEG). His astute observation of the changes in cerebral potentials evoked by sensory stimulation is the concept basic to the current use of evoked potentials in clinical practice. At the turn of the century, Hans Berger confirmed the observations of Caton and further demonstrated similar electrical activity in human brain and hoped that it may be possible to learn the physical basis of consciousness. He introduced electro-encephalogram (EEG) as a diagnostic tool in clinical neurology.

Almost paralleling the development of EEG, Galvani's famous experiments demonstrating twitching of frog legs and Du Bois–Reymond's observation of electrical potentials from the surface of muscle on contraction in man laid the foundation for electromyography (EMG). Development of induction coil by Du Bois–Reymonds sensitive enough to detect the changes in potential when an impulse passes along a nerve and the instrument designed by Helmholtz in 1850 for measuring conduction velocity led to its practical application in the diagnosis of peripheral neuropathies.

Electroencephalography

EEG is a noninvasive method recording the space- and time-varying patterns of brain electrical activity by surface electrodes applied over the scalp. The activity thus recorded is of cortical origin, reflecting the extracellular current flow associated with excitatory and inhibitory postsynaptic potentials[2,3] of chiefly the pyramidal neurons, which are vertically oriented with a large apical dendrite projecting towards the surface of the brain. In the spherical model of the head, though the EEG sees the electrical sources in the brain oriented radially and located in the gyri as also the tangential dipole located in sulci, it is dominated by the radial source. The contribution from tangential source (from horizontally oriented cortical cells) is negligible[4]. The rhythmicity of cortical activity depends on the functional integrity of thalamic nuclei, which have an inherent rhythmic activity (facultative pacemaker theory) and which impose upon the cortex in a pattern determined by the specific thalamocortical projections from the relay and association nuclei[5]. This thalamic rhythmicity is under the influence of inputs from the brainstem[6] and afferent spinal pathways[7]. Cortical spike is the abnormal waveform characteristic of epileptiform discharge and is associated with synchronous paroxysmal depolarizing burst followed by prolonged after-hyperpolarization resulting in a slow wave[8].

In clinical practice EEG is very useful in the investigation and management of epilepsy, coma, metabolic and infective disorders, in particular, herpes simplex, subacute sclerosing pan-encephalitis and localizing in structural lesions. It is also used in determination of cerebral death and is helpful in the study of sleep and its disorders. In the recent years EEG is being increasingly utilized for evaluation of the new born and premature infants. It has now become possible, with reasonable confidence, to assess the level of brain maturation by analysis of ontogenesis of electrical activity and correlate it with behavioural development[9].

In evaluation of intractable epilepsy long-term monitoring with video-EEG has been found to be a valuable asset in determining the need for neurosurgical intervention. Introduction of ambulatory cassette EEG and telemetric EEG has provided a means to study brain electrical activity under various physiological states and normal daily activities.

Electromyography and nerve conduction

The recording of electrical activity of muscles (electromyography – EMG) provides a tool for determining the status of motor unit in health and disease states. In combination with nerve conduction studies, EMG permits localization of the disease process to muscle, neuromuscular junction, peripheral nerve, plexus, roots and anterior horn cell. By the conventional technique of concentric needle EMG (CNEMG) 10–15 muscle fibres of a motor unit in a 1 mm radius can be evaluated. Analysis of muscle activity at rest, on weak and strong voluntary effort, along with analysis of the morphology of motor unit potential, provides evidence for either a primary lesion of muscle (myopathic process) or secondary to disease of lower motor neuron and peripheral nerve (neurogenic process). The laborious manual process of characterizing the motor unit by the duration, amplitude, spike area, phases, and the number of satellites has now been replaced by quick automatic analysis. The frequency spectrum of action potential and the recruitment pattern have also been automated.

Introduction of single-fibre EMG (SFEMG) using a needle with lead-off area of 25 μm has permitted the recording of electrical activity derived from a single muscle fibre and the area covered is about 300 μm radius. With SFEMG, muscle fibre density, a measure of the clustering of fibres within a motor unit, can be determined, which was not possible with CNEMG. Fibre density provides valuable information regarding reinnervation of muscles[10]. Using SFEMG technique, 'jitter' – as determined by the latency variability following repetitive nerve stimulation – provides a sensitive index of transmission defect at neuromuscular junction and also conduction defects of nerve and muscle[11].

The CNEMG and SFEMG do not reflect the electrical activity of an entire motor unit since the motor unit territory ranges from 5–10 mm and the radius of electrical activity recorded by these techniques is much smaller. Using a special needle, macro-EMG and averaging techniques, it is possible to extract the electrical activity from all muscle fibres belonging to one motor unit. The three techniques, concentric, single fibre and macro-electromyography, are complementary and provide comprehensive information about the motor unit.

The physiological basis of nerve conduction is the generation of action potential following electrical stimulation. Essentially, there are two phases; the subthreshold event is the local current produced due to changes in transmembrane potential. When the depolarization reaches the threshold, an action potential occurs[12]. This is an all or none response, a resultant of complex energy-dependent processes involving molecular changes of sodium and potassium channels which affect sodium and potassium conductance across the membrane. The predominant localization of sodium channels to the nodes of Ranvier and the distribution of potassium channels along the internodes has been delineated by voltage clamp experiments[13,14]. Motor and sensory functions of a peripheral nerve are assessed by nerve conduction studies and were first described for clinical use in 1948 to 1949 (refs. 15, 16). Electrical stimulation of nerve initiates an impulse, the conduction characteristics being dependent on the integrity of the nerve and determined by analysing evoked response elicited from the muscle which it innervates for motor conduction and the nerve itself for sensory conduction studies. Detection of signals within the expected noise level of the system, which was not possible by conventional techniques of photographic superimposition, has now been achieved by digital averaging. Any peripheral nerve accessible for electrical stimulation can be examined and be stimulated at multiple sites along its course to determine focal lesions due to compressive or demyelinating pathology. The choice of nerves for conduction studies is dictated by the clinical condition. In leprosy, sensory conduction of the greater auricular nerve and dorsal cutaneous branch of the ulnar nerve were found to be particularly useful and provided evidence of nerve dysfunction[17–19]. In Guillain–Barre syndrome, phrenic nerve conduction time was found to be a more sensitive parameter than vital capacity or median nerve motor conduction velocity in assessing the severity of the disease and predicting impending ventilatory failure[20].

The parameters derived from conventional nerve conduction studies do not reflect faithfully the early abnormality of the excitability cycle of the axon since a diseased nerve may conduct at normal velocity but not at normal frequency[21]. Refractory period assessment has been demonstrated to be a sensitive parameter for study of axon excitability[22]. Following the initiation and propagation of a nerve impulse, the nerve is inexcitable to a second impulse for a period of time which is termed as the refractory period. The techniques of assessment of the refractory period have found clinical application in the study of peripheral neuropathy[23, 24].

Evoked potentials

In addition to spontaneous electrical activity of the brain (EEG), potentials can be evoked in specific regions of the brain by sensory stimuli such as visual, auditory and somatic stimuli. The technique of recording evoked potentials allows assessment of the function of less accessible regions of the brain and in case of somatosensory evoked potentials the proximal portion of the peripheral nerve can also be studied[25, 26]. A special application of this technique is in monitoring of evoked potentials during neurosurgical procedures so as to avoid or minimize the damage to the nervous system. Brainstem auditory evoked response studies, in addition to EEG, are useful for evaluation of coma and brain death. The evoked potential occurs at short latency after the stimulus and is very brief, necessitating rapid acquisition and storage and also requires averaging technique to improve the signal-to-noise ratio.

Somatosensory evoked potential studies provided information of the afferent pathway and till recently there were no techniques available to examine the integrity of central motor pathways and the proximal segments of peripheral motor pathways. Electrical or magnetic stimuli applied to the intact surface of the scalp, spinal cord and lumbosacral enlargement have been shown to evoke a compound muscle action potential from the hand or leg muscles[27–29]. Since discomfort is experienced with electrical stimulation, magnetic stimulation is now preferred. The central motor conduction time can be determined by subtracting the peripheral latency from the total conduction time, which is the latency to the scalp evoked muscle action potential. Motor evoked potential studies have been found useful in the diagnosis of multiple sclerosis, cerebral infarct, degenerative disorders and spinal cord compression.

Computers in EEG and evoked potentials

Analysis of EEG and evoked potentials using computers is now slowly replacing the traditional methods of visual interpretation, which is often qualitative and subjective. Digitizing the continuous analog EEG signal, spectral analysis, signal averaging, identification of transient activity such as spike, minimizing and rejecting artefacts have increased the precision in analysis and correlation of time with events and in following the time course of different components of the signal. Frequency domain analysis, sequential and three-dimensional mapping with topographic display of several EEG channels allows a better understanding of the spatial relationship. Computers have also replaced the tedious and expensive traditional long-term monitoring of EEG in epilepsy or automatic sleep staging.

Magnetoencephalography

Magnetoencephalography (MEG), a noninvasive tool, is a new addition to the armamentarium of neurophysiological techniques, but its clinical application is yet to be proved[30]. The electrical currents produced from the brain also produce a magnetic field, termed as 'neuromagnetic field' and recording this has been used to determine the location of activity in terms of dipole[31]. Although, superficially, MEG resembles EEG, it provides different information about the electrical activity from the EEG and is, therefore, complementary to EEG[4]. MEG recognizes electrical sources oriented tangentially unlike EEG, which sees both radial and tangential sources, preferentially the former ones. The cost of MEG at present is prohibitive and requires a magnetically shielded room. MEG and MEG–EEG combination have a future for accurate dipole localization of epileptogenic area and need to be compared with intracranial recordings.

Status in India

It is heartening to note from the recent exhaustive review of the status of clinical neurophysiology in India that most of the techniques discussed in the present paper are being routinely used in clinical neurological practice in the country[32]. What seems to be lacking is a close interaction of scientists in the fields of electronics, computers and allied disciplines with clinical neuroscientists, which is crucial for the emergence of new developments in the field of clinical neurophysiology. Mechanisms need to be evolved to promote and foster such interactions in the country.

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Nuclear magnetic resonance: Molecules, cells and animals

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Since its discovery in 1945, nuclear magnetic resonance (NMR) has developed into one of the most important techniques utilized in almost all branches of science. In the field of life sciences itself, NMR applications cover problems at almost all levels: structure and function of biological molecules, cellular metabolism, morphology and chemistry of intact organs such as brain, heart and liver, microscopy of tissues, and as a diagnostic tool in medicine. I propose to give some information on the current status of the developments in diverse areas of biological NMR, with particular attention to interests of neuroscientists. The future trends in biological NMR will also be presented. For those interested in details, several general references have been appended.

What is NMR, MRI and MRS?

The principle of NMR is based on the fact that nuclei having non-zero spins I (e.g. ^{1}H, ^{31}P and ^{13}C, which have $I = 1/2$) act like tiny magnets with magnetic moments (μ_n) and have nondegenerate energy states in