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Saad Shafqat
Agha Khan University, saad.shafqat@aku.edu

Mohammad Wasay
Aga Khan University, mohammad.wasay@aku.edu

Neurology in the 21st Century: Contemporary state of Diagnostics and Therapeutics

S. Shafqat (Section of Neurology, Department of Medicine, Aga Khan University Medical College, Karachi.)
M. Wasay (Section of Neurology, Department of Medicine, Aga Khan University Medical College, Karachi.)

Although neurological disease has been recognized since antiquity, neurology as a systematic clinical discipline is less than 130 years old. Neurological practice has traditionally been constrained by the complexity of the human nervous system, which has been slow to yield its secrets. Over the last three decades, however, clinical neurology has been transformed in terms of both diagnostics and therapeutics and now marches in lockstep with the cutting edge of medicine. Efficacious treatments are now available for the majority of neurological diseases, including epilepsy, migraine, Guillain-Barre syndrome, Parkinson's disease, multiple sclerosis, and ischemic stroke. This neurological revolution has been enabled by advances in neuroimaging and through the integrated application of basic research, drug development, biotechnology and clinical trial methodology. Neurology in the 21st century is a dynamic specialty offering relief and benefit to many patients, and holding the promise for one day conquering neurological disease in all its manifestations.

Introduction

Neurological diseases are common and often devastating illnesses. As a result, the global burden of neurological disease is daunting. Stroke is the leading cause of physical handicap worldwide and projected to be the 2nd commonest cause of death after heart disease by 2025.1 Epilepsy has a worldwide prevalence of up to 3%, and the lifetime risk of a single seizure approaches 5%.2 The population prevalence of migraine is 3.5-7% and the lifetime prevalence of any severe disabling headache exceeds 30%.3 Parkinson's disease afflicts 1 million people in the United States alone and is estimated to affect tens of millions around the world.4 Dementia affects 20 million people worldwide and, as the population of elderly people increases in both developed and developing countries, this burden is expected to nearly double by 2025.5 The collective human burden of neurological illness is thus enormous.

Neurological problems have been recognized since antiquity, but neurology as a systematic clinical discipline is less than 130 years old. In 1882, Jean-Martin Charcot became professor of neurology at the University of Paris, in recognition of clinical investigation and scholarship devoted to neurological signs and symptoms.6 Neurology as an institutionalized medical specialty can be said to have been born in Charcot's ward at the Salpetriere Hospital, where the clinical neurological examination was developed and neurological diseases subjected for the first time to clinico-pathologic study. Neurology has continued to be blessed with eminent and gifted physician-scientists through the 19th and 20th centuries, but the practice of neurology has traditionally been constrained by the complexity of the human nervous system.

In the latter half of the 20th century, a number of landmark advances from different areas of biomedical science converged to transform the science and practice of medicine in far-reaching and fundamental ways. The neurological applications of these advances - including developments in imaging technology, molecular biology, drug development and epidemiology - have transformed the care of neurological diseases into a rigorous clinical discipline with powerful diagnostic tools and an increasingly larger array of therapeutic options. Neurology in the 21st century is a robust and dynamic specialty offering relief and benefit to many patients, and holding the promise for one day conquering neurological disease in all its manifestations.

Diagnostic Advances

Most of the bedrock tools of diagnostic neurology - lumbar puncture (LP), electroencephalography (EEG), electromyography and nerve conduction studies (EMG/NCS), and evoked potentials (EP) - have been available for the greater part of the last century.7 The true revolution in diagnostic neurology did not come until the 1970s and 80s, when it became possible to visualize the brain and spinal cord during life. Contemporary clinicians will find it hard to imagine that neurological practice was once conducted without computed tomography (CT) or magnetic resonance imaging (MRI), yet prior to the mid-1970s (when CT scanning became widely available), the living brain could not be imaged at all and brain structure was assessed only indirectly, by studying calcified pineal glands on plain skull X-rays, distorted ventricular contours on pneumoencephalography, or abnormal vascular anatomy on invasive cerebral angiography.8 The latter two procedures were fraught with great discomfort and risk of complications, involving injection of air into the subarachnoid space by lumbar puncture (pneumoencephalography) and direct arterial puncture of the carotid artery in the neck (angiography).

CT and MRI:

Modern neuroimaging allows visualization of the living brain, spinal cord and associated vasculature with great sophistication and detail; as a consequence the practice of neurology has been transformed. CT and MRI both permit high-quality anatomic resolution of all pathologic processes involving the neuraxis, including infarction, hemorrhage, inflammation, infection, neoplasia and congenital.9 Novel MRI sequences have been customized for specific abnormalities10, including diffusion-perfusion for ischemia; gradient-recalled echo for early and remote hemorrhage; fat-suppression for enhanced visualization in the skull base, neck and spinal canal; fluid attenuation inversion recovery (FLAIR) for exquisite detection of parenchymal abnormalities; and magnetization transfer contrast for conspicuous visualization of multiple sclerosis plaques or metastatic deposits in the brain.
Vascular imaging has also greatly advanced through CT and particularly MRI. Magnetic resonance angiography (MRA) uses no extraneous contrast and identifies stenoses in the intracranial and cervical vasculature with sufficient resolution for routine clinical use. Although MRA tends to overestimate the degree of stenosis, its clinical value as a screening angiographic procedure remains paramount.11 CT angiography requires intravenous iodinated contrast and uses a helical scanning technique to reconstruct vascular anatomy, allowing detailed two-dimensional as well as three-dimensional reconstruction of the carotid system.12 Helical CT also enables realistic three-dimensional reconstructions of complex anatomic regions, such as the orbit or the skull base, that are becoming indispensable to surgical management.

Functional neuroimaging:

While the standard clinical use of CT and MRI involves structural imaging, functional brain imaging promises to mark the dawn of a new era in understanding and diagnosing neurological disease. For decades, the only diagnostic tool for functional study of the brain was EEG, in which patterned electrical activity from the cortical mantle is recorded by surface electrodes on the scalp. Functional neuroimaging technology relies on the ability to measure minute differences in regional cerebral blood flow, as in PET (positron emission tomography)13, SPECT (single photon emission computed tomography)14 and functional MRI (fMRI).15 A parallel technique is magnetic resonance spectroscopy (MRS), in which local concentrations of biological chemicals can be measured in vivo and expressed as an imaging signal.16 Magnetoencephalography is another functional imaging technique that takes the functional signals of standard EEG and maps them on to two-dimensional axial brain anatomy.17 The excitement surrounding functional neuroimaging comes from the greater mechanistic understanding of neurological disease that this technology has enabled. At present, clinical applications are limited to specialized situations, such as identification of seizure foci in patients being considered for epilepsy surgery. With improved technology, lowered cost, and advances in research, it is only a matter of time before functional

neuroimaging pushes back the frontiers of neurology through clinical applications as well.

Molecular diagnostics:

As in other clinical fields, textbooks in neurology have also been rewritten with the molecular biology revolution that has taken place over the last two decades. The genetic defects underlying a vast number of neurological diseases have been discovered, contributing to a refined nosology and promising a hitherto unimagined level of mechanistic understanding. The genetic abnormalities range from point mutations and deletions to gene duplications and triplet repeat expansions - all conveniently assayed through modern DNA diagnostic technology and providing 100% diagnostic accuracy for several confusing and complex, albeit uncommon, neurodegenerative disorders.18 With the success of the Human Genome Project, these molecular advances promise not only to make DNA diagnostics commonplace but also to create remarkable new research possibilities that will one day hopefully lead to rational therapies for many or all of the neurodegenerative and neurogenetic conditions that remain unconquered today.

Advances in Therapeutics

Long considered a field dominated by therapeutic nihilism, neurology in the 21st century has begun to march in lockstep with the rest of clinical medicine. Although many devastating neurodegenerative diseases remain for which no efficacious treatment exists, modern neurologists are equipped with sufficient treatment options to make a difference to disease manifestation or outcome in most of their patients.

Ischemic stroke

In 1996, the first scientifically proven treatment for acute ischemic stroke appeared in the form of the intravenous thrombolytic drug tissue plasminogen activator (tPA). When administered to ischemic stroke patients within 3 hours of symptom onset, this drug is associated with a 30% greater likelihood of eventually being able to walk unaided, compared to placebo.19 The intra-arterial agent pro-urokinase has also been studied in a carefully conducted clinical trial and found efficacious in improving functional outcome in patients with middle cerebral artery infarction due to local arterial thrombus.20 The possibility of limiting acute stroke damage by neuroprotective drugs - agents that block the cellular and biochemical effects of ischemia - has also emerged in recent years. Although this strategy remains unproven in human clinical trials, the large amount of exciting animal model data and sound theoretical foundations of this approach, indicate that it is almost certainly a treatment of the future.21 The availability of urgent interventions for acute ischemic stroke has changed the very landscape of stroke care, which comprises the bulk of acute emergency neurology.
Rational and efficacious secondary prevention strategies are now also available for every ischemic stroke patient. Patients with ipsilateral 70-99% stenosis of the internal carotid artery can achieve significant stroke risk reduction with carotid endarterectomy.22 In selected patients, a less invasive option is carotid angioplasty with stenting, whose precise safety and efficacy is currently under investigation.23 Patients with atrial fibrillation, prosthetic heart valves or hypokinetic left ventricles are at particularly increased risk for cerebral thromboembolism and can be protected with oral warfarin titrated to an INR of 2.0 - 3.0.24 All other ischemic stroke patients are able to reduce their recurrence risk with anti-platelet therapy. Currently the most efficacious combination is aspirin and extended-release dipyridamole; the combination of aspirin and clopidogrel may be more effective and is under investigation.25
Epilepsy. With judicious use of anticonvulsants, the great majority (>80%) of patients with epilepsy can be made seizure-free or almost seizure-free and are able to lead normal and productive lives.26 Although phenobarbital has been available since 1912 and phenytoin has been available since 1938, as recently as the 1960s satisfactory seizure control was possible in less than two-thirds of epilepsy patients. Both phenobarbital and phenytoin are associated with

potentially limiting side-effects. Carbamazepine is structurally related to tricyclic antidepressants and first appeared in the 1950s as a treatment for trigeminal neuralgia; its anticonvulsant properties were soon recognized. Valproic acid, developed in the 1970s and appearing on the market in 1978, was another important addition and remains one of the most efficacious anticonvulsants for primary generalized seizures. Beginning in the 1990s, however, a very wide selection of new anticonvulsants became available, including gabapentin, tiagabine, levetiracetam, oxcarbazepine, lamotrigine, topiramate and vigabatrin.26 This vast addition to the neurologist's therapeutic repertoire represents the combined triumph of industrial drug development and clinical trial methodology.

While the classical anticonvulsants - phenytoin, carbamazepine and valproic acid - remain the most commonly prescribed anti-epileptic drugs, clinical indications for the newer agents are increasingly being defined. Most of these agents are used as adjunctive therapy and are effective in significantly reducing seizure frequency in patients only partially controlled with the classical agents. Because of almost nonexistent cognitive side-effects and proven efficacy against partial as well as generalized seizures, lamotrigine is emerging as the drug of first choice in the first-line management of uncomplicated epilepsy.27 Gabapentin, though a relatively weak anticonvulsant, has no major side-effects and no significant drug interactions, making it an excellent choice for managing seizures in medically complex patients, such as critically ill patients with multi-organ dysfunction.28 Epilepsy in the 21st century is completely compatible not only with a normal and productive life, but also with pregnancy and motherhood. Although all anticonvulsants are potentially teratogenic, lamotrigine has the safest record of use during pregnancy. Since pre-conception seizure control predicts seizure risk during pregnancy, an epileptic woman well controlled on lamotrigine can expect nearly the same pregnancy outcomes as healthy women.29 An important caveat is that the available anti-epileptic agents represent symptomatic control only - they are effective seizure suppressants but have no effect on epileptogenesis, the pathologic process(es) responsible for seizure generation in the first place. With ongoing exponential advances in neuropharmacology and in our understanding of synaptic plasticity and associated phenomena, there is every reason to hope that the next generation of anti-epileptic agents will be able to modulate epileptogenesis as well, rendering epilepsy curable.

Parkinson's disease

The use of dopamine supplementation in the form of oral levodopa for the control of Parkinsonian symptoms represented a revolutionary therapeutic advance in neurology, and one of the most dramatic treatment advances in all of clinical medicine. First discovered in 1967, the efficacy of levodopa in ameliorating the parkinsonian features of rigidity, bradykinesia and tremor remains unsurpassed today, making it the cornerstone of Parkinson's disease management.30 The drug is not a panacea, however, and limiting side-effects (most notably motor fluctuations such as on-off periods and dyskinesias) develop in nearly all patients after a variable period of use. Strategies for reducing the risk of developing dyskinesias - such as delayed initiation of levodopa or the use of dopamine agonists - have traditionally failed. In recent years, however, two new selective dopamine agonists - ropinirole and pramipexole - have become available whose initial use in Parkinson's disease significantly delays the onset of dyskinesias, improving and prolonging quality of life.31 The concurrent use of catechol-O-methyltransferase (COMT) inhibitors reduces time spent in the off-period, presumably by stabilizing dopamine availability at the remaining nigrostriatal nerve terminals.32 Although mortality in Parkinson's disease remains unchanged and several unmet symptomatic needs also persist, these therapeutic advances doubtless offer the chance of enhanced quality of life to many parkinsonian patients.

Multiple sclerosis

The classic nihilistic image of multiple sclerosis (MS) as an untreatable neurodegenerative disorder has been radically altered in the face of disease-modifying immunomodulatory therapy made available in the 1990s through intensive basic research, clinical experimentation and cutting-edge biotechnology. The use of beta-interferon33 or glatiramer acetate34 results in an approximately 30% lower annual relapse rate in multiple sclerosis patients compared to placebo.

The benefit is also detectable in terms of reduced plaque burden on MRI as well as better clinical scores on scales of functional performance such as the Extended Disability Status Scale. The use of beta-interferon after an initial attack of central demyelination (optic neuritis, incomplete transverse myelitis, or a brainstem or cerebellar syndrome) also reduces the subsequent likelihood of developing MS.35 Despite these advances, however, the effectiveness of treatment for MS remains limited and efforts to develop better agents remain intense. Mitoxantrone (an antineoplastic agent)36 and natalizumab (a monoclonal antibody directed against the adhesion molecule alpha-4 integrin)37 have been promising in clinical trials.

Migraine

One of the commonest neurological afflictions, migraine attacks are capable of producing excruciating, incapacitating craniofacial pain. Traditionally, the management of acute migraine attacks has relied on nonsteroidal analgesics, which often provide only partial relief and may require combination with barbiturate or opiate agents that are likely to produce addiction and habituation. With the help of new insights into the pathophysiology of migraine, abortive therapy for acute migraine attacks has been revolutionized. The 'triptans', a group of serotonin receptor 5-HT 1B/1D agonists, are capable of producing quick and dramatic relief in 70-90% of migraine attacks.38 Following the availability of sumatriptan in 1991, a wide selection of these agents has been developed, including rizatriptan, zolmitriptan, naratriptan, almotriptan, frovatriptan and eletriptan. Because over 70% of migraine attacks are associated with nausea and vomiting, many of these agents are available in non-oral formulations, including subcutaneous injection, intranasal spray and rectal suppositories.39

Alzheimer's Disease

Dementia, perhaps the most dehumanizing of the neurological illnesses, is the quintessential neurodegenerative disease. Alzheimer's disease (AD) - the commonest form of dementia - was recognized as a distinct pathologic entity in 1907, but mechanistic insights into the condition did not emerge until the 1980s. One of the best characterized abnormalities in the brains of AD patients is a cholinergic deficit in the cerebral cortex resulting from degeneration of the nucleus basalis of Meynert in the basal forebrain, which represents the major source of cortical cholinergic projections.40 Although by no means a revolutionary or dramatic treatment, attempts to replace the cholinergic deficit in AD patients does result in measurable improvement in the rate of cognitive decline compared to placebo, as assessed by validated scales of cognitive performance and activities of daily living.41 The medications that are effective in this role - tacrine, rivastigmine, donepezil and galantamine - all act by inhibiting acetylcholinesterase to enhance cholinergic neurotransmission. There is great expectation that insights into the other well recognized abnormalities in AD, including deposition of beta-amyloid in the brain and the association with apolipoprotein E4, will yield therapeutic dividends as well.

Guillain-Barre Syndrome

With the global decline in poliomyelitis, Guillain-Barre syndrome is now the leading cause of acute flaccid paralysis worldwide. The disorder is uncommon though not rare, and has been associated with a small but significant mortality as well as risk of chronic disability.42 Although questions about etiology, prognosis and outcome predictors in GBS remain incompletely answered, the immunomodulatory treatments of plasma exchange (PE) and intravenous immunoglobulin (IVIg) have proven efficacy in clinical trials.43 Compared to supportive care alone, GBS patients receiving either PE or IVIg are at least 50% less likely to be on a ventilator after 4 weeks, and up to 25% more likely to have full motor strength recovery after 1 year.43 GBS is being increasingly recognized as an autoimmune attack on peripheral nerves, possibly triggered by antecedent infection. Epidemiological insights, such as the strong association of Campylobacter jejuni infection with the axonal form of GBS, may hold the key to understanding the ultimate immunological basis of GBS and creating opportunities for more efficacious therapy.44

The Future

Modern neurology is a transformed discipline. As recently as three decades ago, neurological practice was based on a small repertoire of poorly tolerated drugs and, without the ability to see the brain in vivo, largely on blind diagnostics. In remarkable contrast, neurologists in the 21st century are at the center of a dynamic, vibrant clinical specialty with high diagnostic certainty and an ever-expanding choice of efficacious therapeutic options.

The future holds great promise for further landmark achievements in neuroimaging as well as in neurological therapeutics. There is no theoretical upper limit to the anatomic resolution possible through MRI, so an ever greater degree of detail can be expected with advancing magnetic resonance technology. Functional neuroimaging, while it continues to unlock the great secrets of brain function, can also be expected to enter routine clinical use for indications involving epilepsy, tumors and possibly dementias. With fundamental discoveries in genomics, proteomics and cellular pathophysiology, the mechanistic bases of many untreatable neurodegenerative conditions - entities like motor neuron disease, Huntington's disease, advanced dementias, advanced Parkinson's disease and crippling neurogenetic disorders - will become known, creating hope for effective treatment. Even in the absence of such mechanistic leads, powerful biotechnology tools such as gene therapy and monoclonal antibody technology can be expected to keep expanding the neurologist's therapeutic armamentarium.

Undoubtedly, the changed character of neurological practice will bring about new perceptions about the field among patients, prospective trainees, clinicians from other specialties, and the public at large. The ultimate reward is what these advances have already enabled, and will continue to enable, in terms of better care of patients with neurological illnesses. For neurology and for the patients it serves, the future is bright.

Comments

The analysis shows that Jinnah Postgraduate Medical Centre facilities are mostly being utilized for investigation purposes. Basic drugs (analgesics, antacids and multivitamins) are being provided to the patients while specific drugs like antibiotics, anti ulcers oral hypoglycemics and seizure controlling drugs etc are not provided and the patients have to purchase them on their own.

In order to improve the health delivery system, efforts should be directed to shorten the time spent by the patient in the OPD's along with reduction in the number of visits made by the patients.

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