GENETICS & NEUROLOGY

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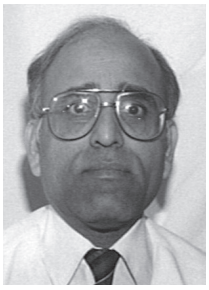

There has been tremendous progress in understanding the genetic basis of many neurological disorders during the past several decades, paving the way for better insight into their molecular bases and rational management. Major advances in transforming basic research into clinical science have finally led to the availability of gene therapy for a handful of serious neurological diseases. Establishment of clinics and fellowships for specialty training in major universities has propelled *neurogenetics* into an attractive subspeciality.

The genetic basis of many diseases has been assumed based on the presence of positive family history and study of the inheritance patterns. During my training days, many decades ago, the only neurological disorder with known specific chromosomal abnormality was Down syndrome, which could actually be confirmed by karyotyping. In sharp contrast, I recently saw two cases of what appeared to be Charcot Marie Tooth (CMT) disease (commonest form of inherited neuropathy) with subtle differences in phenotype. It was fascinating to figure out that one had mutation in the peripheral myelin protein (PMP) 22 gene, while the other had it in the myelin protein zero (MPZ) gene.

Let us look at some of the neurological disorders where the precise genetic basis has been confirmed and then explore the exciting and long-awaited advances in therapy, which are finally starting to give a ray of hope to patients.

ROLE IN DIAGNOSIS & PROGNOSIS:

Multiple diseases that afflict different parts of the central and the peripheral nervous system, including muscles, have been proven to have a specific genetic abnormality, thanks to discoveries in the 1980-90s. Here are some examples where the gain in genetic insight has been quite impressive.

The most well-known muscle disease ***Duchenne muscular dystrophy (DMD)*** which is inherited as a X-linked recessive disorder, has been found to be due to mutations in the dystrophin gene (it has the distinction of being the largest gene, containing a whopping 79 exons) located in the X chromosome. This gene is responsible for production of dystrophin, a large cytoskeletal protein located at the surface of the sarcolemma, necessary for maintaining healthy muscle. Lack of dystrophin is considered to be the underlying cause of muscle loss in DMD. Deletion of one or more exons has been found to be the most common mutation, usually among exons 44-55 leading to a defective reading frame (A reading frame is a sequence of nucleotide triplets that is potentially translatable into a polypeptide). A milder form of the disease is Becker dystrophy, in which some dystrophin is still produced; this results from in-frame deletions that do not alter the overall reading frame. Another form of muscular dystrophy, ***myotonic muscular dystrophy*** has been found to be due to abnormal repetition of nucleotide bases in the DMPK (myotonic dystrophy protein kinase) gene located in chromosome 19. The severity of disease depends on the number of the abnormal trinucleotide repeats, useful information to share with the patient while discussing prognosis.

Another disease that has been the focus of many recent studies is ***spinal muscular atrophy (SMA)*** which is a leading cause of death from neurogenetic disease in the first year of life. It is a form of motor neuron disease that results from mutations in the SMN

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gene located in chromosome 5, which codes for a protein essential for survival of the spinal motor neurons (survival motor neuron protein). In the absence of the SMN 1 gene, a backup gene called SMN 2 can produce the protein to a small extent. With lack of the SMN 1 gene, the babies fail to achieve motor milestones and often die in the first year; however, if there are several copies of the SMN 2 gene, the disease is milder as some amount of the survival motor neuron protein is still produced. Thus, the study of the genetic profile in SMA is not only diagnostic, but also gives a hint at the prognosis. With the recent availability of targeted gene therapy, newborn screening for SMN has become routine in many states.

Genetic knowledge about the hitherto untreatable neurological disorder, ***Huntington's disease (HD)*** is giving hope for novel treatment. HD is a monogenic disorder caused by mutations in the HTT gene, located in chromosome 4, coding for a protein called huntingtin. There are excessive nucleotide repeats and the greater the number of repeats, the earlier the onset of disease.

GENE THERAPY

Let us look at the more exciting topic of gene therapy. The basic goal is to treat diseases at the genetic level by adding new genes to replace faulty or absent genes or by editing the faulty gene in vivo.

Gene addition is a logical step in genetic diseases, in which there is a single faulty gene, which is replaced with a healthy functioning gene. While the principle is simple, there are many hurdles in effectively getting the gene into the affected cells with the faulty gene. The healthy gene is often sent through a harmless virus or special compounds such as polymers.

Gene editing is aimed at either disrupting or inactivating the part of the malfunctioning gene, or correcting it, or inserting genetic material. A number of techniques like CRISPR-CAS9 are being tried to achieve this.

There are two neurologic diseases with currently FDA-approved gene therapies. Three pharmaceuticals have been approved for ***SMA***. The first was nusinersen, an oligonucleotide to correct the loss of 7th exon during RNA splicing of the SMN 2 gene, and make it function like the SMN 1 gene. It has to be given intrathecally, repeatedly and treatment has to be started early to stop progressive loss of motor neurons; newborn screening for SMN 1 is crucial in this regard. The second drug, onasemnogene abeparvovec, delivers a working copy of the SMN gene to the motor neurons via a virus vector. It is given IV and the expectation is that a single treatment should give lasting relief. A third drug, risdiplam, is an oral form of SMN 2 splicing modifier, approved for use in 2020.

DMD is the other condition where genetic therapy has been approved. Exon skipping antisense oligonucleotidses (ASO) are effective in increasing dystrophin production; genetic analysis is done to locate the faulty exon and use specific ASO to skip it. Eteplirsen was the first drug to be approved for gene therapy in DMD; it specifically skips faulty exon 51. Exon 53 has been the main target of further development resulting in golodirsen and viltolarsen being approved by FDA in 2019 and 2020. Casimersen was approved in 2021 for skipping exon 45. It looks like the flood gates are open for exon skipping therapy, an exemplary example of personalized precise medicine.

The next in line is oligonucleotide for Huntington's disease, trials of which are underway. Gene therapy for certain forms of CMT are also being tested. It is likely that many similar disorders will have genetic therapy in the near future. However, the three "Darth Vaders" of neurology, ALS (amyotrophic lateral sclerosis), Alzheimer's disease and Parkinson's disease show familial transmission only in a tiny percentage of patients. Hence, they may not be candidates for genetic therapy anytime soon. Nevertheless, extensive study of familial forms of these disorders is already yielding genetic data which may open up new therapeutic options.

The spectacular advances in molecular genetics and the increasing sophistication in gene sequencing techniques is posing a unique challenge to practicing physicians in every field of medicine, including neurology. It is becoming quite difficult to keep up with the fast pace at which the genetic basis of a given disorder is being uncovered. For the neurologist, akin to all other specialties, faced with the barrage of new developments in every disorder (not to mention the new drugs appearing almost every few weeks for multiple sclerosis and epilepsy), it is challenging to learn in depth about the ongoing advances in neurogenetics. It is also frustrating and embarrassing when one cannot quickly recall the causative genetic defect of a clinical syndrome at the bedside.

Neurologists are trained to aske four questions at the end of patient evaluation: Where is the lesion? What is the lesion? What is the prognosis? What is the best treatment? Perhaps we should add a fifth question: What is the genetic basis? Fortunately, there are so many resources readily available at the click of a key to provide the answer to the last question. Periodic assimilation of genetic knowledge from published data, plus using it effectively at the bedside while evaluating each patient, should make the process easier. In this context I am reminded of Osler's famous advice: "To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not go to sea at all." ⚜

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