Molecular Diagnosis of Neurological Disorders in India

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Abstract: The last decade has seen remarkable advances in sequencing the human genes. There are more genes expressed in the brain than any other organ. The knowledge regarding the genome has led to tremendous progress in molecular characterization of the genes responsible for neurological disorders. The present review covers the molecular diagnosis of Duchenne muscular dystrophy, spinal muscular atrophy, and fragile X syndrome. These are three neurologic disorders common in India for which facilities of molecular diagnosis are currently available in the country. As a result of funding by the Department of Biotechnology of the Government of India, a number of molecular diagnostic centers are being established. It is hoped that molecular diagnosis of many more neurological disorders will soon become available in India. (Indian J Pediatr 1996; 64: 661-666).

Key words: Molecular diagnosis in India; Prenatal diagnosis; Duchenne muscular dystrophy; Spinal muscular atrophy; Fragile X syndrome

This is the decade of the brain. It has coincided with the initiation of the Human Genome Project which aims to sequence all the human genes by the year 2005. These activities have led to rapid and even spectacular advances in the knowledge of molecular mechanisms underlying neurological disease. This has resulted in highly accurate diagnostic methods. An immediate spin-off has been the ability to provide prenatal diagnosis of these incurable disorders, so as to prevent their recurrence in future offspring, and thus helping to reduce their burden.

Molecular diagnostic technologies are currently available in India in only a few centers. The Department of Biotechnology of the Government of India has made a heavy investment to develop genetic centers in different parts of the country, with a focus on molecular technologies. It is hoped that in the coming years the benefits of these centers will accrue to the Indian patients with neurological disorders. This paper examines molecular diagnostic techniques for three common neurologic disorders encountered in India, and briefly mentions those disorders for which diagnostic facilities will be established in the near future.

Duchenne Muscular Dystrophy (DMD)

This is the commonest muscular dystrophy in all countries with an incidence of 1:5000 male births. There has been a suggestion that DMD is more common in Indians as
compared with other ethnic groups. It is estimated that there are about 52,000 cases of Duchenne MD, while about 2300 new cases are born each year. It is an X-linked disorder which means that the sons of a carrier female have a 50% chance of being affected, while the daughters have a 50% chance of being a carrier. As presently there is no definitive cure for this disorder, prevention deserves a high priority.

**Diagnosis**

It is important to make an early diagnosis, as a delay may result in the parents not realizing that they have a risk of recurrence and having another affected child. Any child who has delay in walking, or has difficulty in going up the stairs, or walks on tip toes should be carefully examined and evaluated to exclude this disorder. **Hyper trophy** of the calf muscles, brachioradialis, deltoid, infraspinatus and **atrophy** of quadriceps, biceps and sternal head of pectoralis major muscle are quite characteristic. It is to the credit of an Indian scientist who pointed out that there is a hypertrophy of the infraspinatus muscle. Gower’s signs is characteristically present. There is a gradual worsening so that by the age of 12 years or so the child becomes wheel-chair bound, progressing inexorably towards death by the age of 20-25 years. Becker muscular dystrophy is a milder form of the same disease as the mutations are present in the dystrophin gene which is also involved in DMD. The affected persons remain mobile beyond 16 years and even upto 30-40 years in age.

**Laboratory Tests**

The creatine phospho-kinase (the current term is creatine kinase) values are very high, although as the muscles become atrophic the values come down. This is often incorrectly interpreted by the parents that the child is improving. An EMG should be done and shows a myopathic pattern. A muscle biopsy can be diagnostic provided dystrophin staining has been done. Unfortunately this specialized staining is available in only a few places in India.

**Molecular Diagnosis**

With the ease in molecular diagnosis, current practice in most centers is to go ahead for a molecular diagnosis instead of the muscle biopsy, provided the clinical picture is consistent with the diagnosis of DMD. Interesting at the molecular level, the disease is characterized by the presence of deletions. At our centre at Ganga Ram Hospital we screen for deletions of 27 exons in the dystrophin gene, although many centers rely on screening for 18 exons. This not only confirms the diagnosis but also provides us the knowledge to carry out an accurate prenatal diagnosis in a future pregnancy in this family. It would also help to analyze carrier status in other female members of the family. Deletions are detected in about 70% of the cases. Based on studies in about 300 cases of DMD we found that the hot spot for deletions is exons 44 to 51. Similar observations were reported by Mittal and colleagues.

**Prenatal Diagnosis**

Prenatal diagnosis by molecular techniques is straightforward if deletions are present, by looking for the same deletions in the male fetus. If no deletions are detectable in