empowering the neurogenetic testing services in developing countries: use the basic skills with speed and scale

Although genetic and inherited disorders are individually rare, they collectively affect about one in 17 individuals in Western population[1]. Genetic abnormalities at conception are more common and many of them become incompatible for embryo survival. In fact, chromosome abnormalities in embryo account for about 50% first trimester pregnancy losses. Most of these genetic abnormalities are numerical chromosome aberrations and recurrence risk of numerical chromosome abnormalities in subsequent pregnancy is low. However, neurological developmental abnormality among survivals with chromosomal aberrations, such as trisomy 21 (Down syndrome), is almost universal.

Neurogenetic diseases aren't that rare: informing the lawmakers

Despite the fact that genetic disorders are not less frequent in developing countries than the Western population genetic tests continue to be under prescribed for poor patients or referred to private labs. Deeper analysis shows that public hospitals have not taken the initiative in launching these services in developing countries such as India. Those which are running these facilities do not receive patients as these get lost to private labs. While it is true that the spectrum of diseases in developing countries mainly comprise of infectious diseases and malnutrition which is exacerbated with poverty and limited access to health care, it is equally true that the most diseases are the result of variable environment-gene interactions. The fact that other scourges (like poverty, malnutrition, tuberculosis, malaria, and HIV) in developing countries have made genetic diseases appear invisible, data thus far, does not suggest that the health system in developing countries should neglect them.

Chromosomal abnormalities and monogenic diseases occur in over 1% of the population anywhere in the world. Polygenetic and multifactorial contribution to human diseases is far more common. Chromosomal and Mendelian hereditary disorders affect central and peripheral nervous system disproportionately morein frequency and severity than it affects other organ systems. This is partly because of the large spectrum and complexity of motor, sensory, autonomic and other neuronal systems; over half of the gene pool in human genome is transcribed and expressed in the nervous system. For example, the most common chromosomal abnormality - trisomy 21 (Down syndrome) affects nervous system and causes the most common syndromic mental retardation. Incidence of trisomy 21 progressively increases with maternal age, from approximately 1 in 250 at 35 year-age to 1 in 20 at 45 year-age. For this reason, the anti-natal screening for trisomy 21 is a standard of care for all pregnant women age 35 or more. However, 80% of babies with Down syndrome are born to mothers below 35 year-age due to higher fertility rate among younger women. Despite preventive efforts in place there are currently over 400,000 people with Down syndrome in the Unites States. The prevalence of Down syndrome is likely higher in the developing countries.

Aside from common intellectual and developmental impairment in chromosomal disorders, neurological diseases are also common both in children and adults in monogenic genetic disorders. Most frequent monogenic neurological disorders include a variety of dementias, movement disorders, ataxias, spastic paraplegias, spinal muscular atrophies (SMA), polyneuropathies, muscular dystrophies, and visual and hearing impairments. Hereditary polyneuropathy (Charcot-Marie-Tooth disease) alone occurs 1 in 1250 to 2500 individuals in the western population[2]. For these diseases no genetic testing services exist in public hospitals in India which is unfortunate.

Among monogenic recessive neurological diseases, carrier frequency of many mutant alleles is relatively high in populations world-wide. For example, the carrier frequency for spinal muscular atrophy in Caucasian population is estimated to be approximately 1 in 40. Autosomal recessive neurological disorders are more frequent in populations where consanguineous marriages are common (Middle East, Pakistan, Indonesia, Muslim community in India), as also in small in-bred ethnic populations (Ashkenazi Jews). Gene panel screening is now feasible and indeed is being practiced in efforts to prevent autosomal recessive diseases in small affluent ethnic populations. One example is neonatal screening for Tay Sachs (1:30 in Ashkenazi and 1:300 in Sephardic and Mizrahi Jews) and Canavan (1:48) and SMA (1:40) gene mutations in Ashkenazi Jews. A public health policy addressing population screening and prevention of these incurable, disabling and often fatal neurological diseases is expected to pay rich dividends in future especially when complex genetic neurological diseases can be efficiently analysed by cost-effective DNA sequencing.

Genetic and congenital neurological diseases contribute significantly to economic, social and human-resource development because they are often severe in their manifestations, the stigmatization they engender is long-lasting, costing enormously for their treatment and care. The identification of specific genetic variant in patient's DNA sample which is responsible for an inherited disease can establish or confirm a clinical diagnosis, guide personalized approach to medical management, and if the disorder is frequent, it can help institute population screening programs to manage and prevent neurological disease burden in communities. Genetic information can also facilitate risk assessment for affected individuals and families and enable effective reproductive decision-making.

Where will the poor patients go for neurogenetic tests?

Following the first draft sequencing of human genome in 2001 and the ensuing technological advances, medical genetics has ushered in an era where DNA-based genetic testing has become routine in developed nations, and also in small wealthiest sections of many developing countries. A panoply of DNA-based tests, including tests for single targeted gene, panel of genes and even whole exome (protein-coding sequence) or genome sequencing (WES and WGS), also called next generation sequencing (NGS) platforms[2], are now available for genetic diagno-

ses. In developing countries, in sourced commercial genetic testing services have emerged because many such countries do not publicly support medical genetic services. The private sector then begins to provide testing in response to demand from the wealthier sections of the society, and the service provision is generally driven by profit. Thus, the more commercially profitable services, such as prenatal diagnosis and genetic and sex analysis for example are typically the first tests to be provided, followed by more sophisticated DNA-based molecular genetic tests.

From the public health perspective, care and management of complex and chronic hereditary neurological disorders are expensive and they require a good deal of human, technical and economic resources. However, prevention of the occurrence of genetic diseases by effective counseling at individual, family and community levels reduces the number of affected individuals and thereby frees the resources for the care of smaller number of individuals with genetic diseases. Furthermore, care of patients with these conditions is not just an ethical obligation based on the right to health, but it also increases the trust of the population in the goals of the country's public health system. A national policy of equitable and accessible genetic services should be available to the entire population, not just a small wealthier section in the developing world.

Historically, only major hospitals in large urban centers established clinical genetic services in both developed and developing countries in orderto provide diagnosis and counseling to patients with, or at risk for, genetic diseases and congenital anomalies. In developing countries, the major roadblocks in increasing access to genetic services have been fundamentally the scarcity of funding, the lack of appropriate technology and facilities, the shortage of trained specialists and under utilization of existing basic scientists, and the lack of links of specialty centers with the point of primary health service. As the importance of genetic component of diseases is recognized widely and the price of genetic evaluation falls, the responsibilities of clinical genetics centers is likely to expand from dealing with rare genetic diseases to dealing with the genetic components of common diseases, such as genetic susceptibility to fetal loss, congenital anomalies, mental retardation, cancer, etc.

The challenge of change: empowering basic sciences in public medical institutions

Another major challenge for developing countries is to define the type of genetic neurological services needed in concert with the prevalence of genetic diseases and limited resources. The development and implementation of initial services with a base in primary health care that follow sustainable cost-efficiency model may be crucial. For example, prenatal genetic services at primary health centers are essential and most cost-effective component of all public health programs. These services should be aimed at detecting genetic reproductive risks, through programs such as carrier screening for prevention of autosomal conditions and prenatal screening for neural tube defects and chromosomal abnormalities, common causes of genetic neurological disorders. For more advanced DNA-based tests these health centers require to be linked with regional specialty centers. Experience shows that these programs can only be successful when people identified as at risk have access to diagnostic tests, free access to genetic counseling and the option to terminate affected pregnancies in appropriate cases. In a large developing country like India, these services should be adequately regionalized with linkage of basic science departments with clinical services and primary to tertiary care centers in order to ensure equity, cost-efficiency and quality of service. Genetic screening program should be implemented in a manner that is sensitive to the population's economic hardships and affordability. The major goal of public health applications of genetics is to reduce the impact of genetic disorders on health and well-being, through primary and secondary prevention and prevention through reproductive options. However, this is not possible until the poor patients are not provided the luxury of cheap genetic testing service in publically funded medical institutes.

India has enacted legislation regulating the use of prenatal diagnosis[3]. These laws permit prenatal testing only to detect chromosomal abnormalities, genetic metabolic diseases, hemoglobinopathies, congenital anomalies, sex-linked genetic diseases and any other abnormalities or diseases as may be specified by the Central Supervisory Board[3]. The regulations also include requirement that informed consent be obtained from the affected party. The diagnostic and therapeutic services outside prenatal genetic services are largely unregulated in India. Within the existing prenatal regulations and emerging unmet genetic neurological services, these issues need to be urgently addressed for effective and worthwhile national genetic services.

Personnel and training

Genetic services require highly skilled professionals and good quality genetic diagnostic facilities mandated by NABL, the Indian accreditation board. Both of them are currently in short supply in the developing world. It is generally felt that the skills of geneticists or basic scientists that work in these Institutions are grossly underutilized. In order to achieve genetic services' legitimate mission, it is essential that the dialogue and cooperation between government bodies, health professionals and patients and families, basic scientists, policy makers and other stakeholders - to maximizes the health benefit - is in place.

Genetic counseling

Ensuring good quality genetic counseling should go hand-in-hand with genetic testing and genetic screening programs. Counselors should be adequately trained in accordance with available resources. Key national organizations must be entrusted to establishas well as modify guidelines on the minimum skills required for genetic counselors and assist in designing training courses in genetic counseling to cater the demand for services. Patient support organizations should also be encouraged to work alongside medical professionals and genetic counselors to reduce genetic disease burden in communities.

Quality assurance and patient safety

Fostering patient well-being through implementation of quality assurance standards for genetic tests, and screening and appropriate enforcement mechanisms are necessary for effective genetic services. As mentioned above, unregulated commercial genetic testing services may pose problems in developing countries until supervised by skilled scientists. Specific concerns relate to the test accuracy and test utility in profit-driven commercial environment. India is reported to have a record of questionable and coercive reproductive health policies under some political doctrine in the past. Lower level of education, lack of regulation in private labs and absence of fully informed con-

sent may make genetic testing potentially harmful in developing countries.

Legal measures to protect patients' interests

Stigmatization of, and discrimination against, people with genetic disorders and carriers of recessive genetic conditions result in direct harm to patients and regardless of their economic background this must be protected at all costs. It is, therefore, imperative to implement legal measures to protect patient privacy and confidentiality and to safeguard patients against discrimination and stigmatization on the basis of genetic information. The professional community should aid capacity building in relevant public policy and legislation-drafting skills to support this endeavor.

Conclusion

Compared with the developed nations, developing countries are still burdened by high levels of communicable diseases, poverty and structural deficiencies and resource constraints which overshadow a rampant undetected neurogeneticand congenital anomalies. Facing this hard reality, developing countries must carefully assess their disease burden and set their priorities, making sure that the prevention and care of genetic and congenital neurological conditions are not neglected at the cost of profit-driven private centres. Public hospitals must engage the basic scientists to develop cost effective genetic testing services in the service of poor patients and curb these tests from being referred to private centres.

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