The Era of Pediatric Neurogenetics

Mustafa Abdalla M. Salih
Professor, Division of Pediatric Neurology, Department of Pediatrics, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Following the successful implementation of the Expanded Program on Immunization worldwide, and with the improvement in childhood nutrition, genetic diseases emerged as a significant health problem causing significant mortality and life-long morbidity. The majority of these genetic disorders manifest in childhood with either neurobehavioural impairment or as degenerative neurological disorders.

The high incidence of consanguineous marriages in North Africa, including Sudan, and the Arabian Peninsula is reflected on the high prevalence of autosomal recessive (AR) disorders, in contrast to the situation in North America and Europe. The magnitude of neuromuscular disorders, mostly inherited as AR, is apparently large. The prevalence rate of anterior horn cell diseases, including Werdnig-Hoffman disease, was 133 and 177 per million in two studies, compared to 12 per million from the World Survey. A severe childhood autosomal recessive muscular dystrophy (SCARMD) resembling Duchenne MD was first noted in families from Sudan and Tunisia. Subsequently, the disease was identified in other Maghreb countries and in the Arabian Peninsula. The frequency of this form of MD was found to be equivalent to, and higher than, Duchenne MD in Tunisia and Saudi Arabia, respectively. The corresponding genes were identified including alpha-sarcoglycan (or Adhalin gene, from the Arabic word Adhal for muscle). The same founder mutation of one form of congenital muscular dystrophy (MDC1A) was detected in families from Saudi Arabia and Sudan.

Utilizing the power of family-based genetic studies combined with emerging DNA technology, new syndromes and diseases were identified. Those with gene / locus identification included:

1. Salih myopathy: Autosomal recessive titinopathy causing early onset myopathy/dystrophy with dilated cardiomyopathy. (http://www.ncbi.nlm.nih.gov/books/NBK83297/).
2. Charcot-Marie-Tooth Disease Type 4B1 (OMIM 601382).
3. A new form of childhood-onset, autosomal recessive spinocerebellar ataxia and epilepsy. (http://brain.oxfordjournals.org/cgi/content/full/130/7/1921). (http://www.ncbi.nlm.nih.gov/pubmed/24369382).

4. Spinocerebellar ataxia with axonal neuropathy (SCAN1; OMIM 607250); http://www.ncbi.nlm.nih.gov/books/NBK1105/).
5. Horizontal gaze palsy and progressive scoliosis (OMIM 607313).
6. Bosley-Salih-Alorainy syndrome (OMIM 601536).
7. Salih ataxia: (http://brain.oxfordjournals.org/content/133/8/2439.full.pdf+html) (http://www.ncbi.nlm.nih.gov/pubmed/23728897).
8. A new form of childhood-onset autosomal recessive hereditary spastic paraplegia (SPG49) caused by a novel gene (CYP2U1) mutations. (http://www.cell.com/AJHG/abstract/S0002-9297%2812%2900579-4).
9. A novel form of congenital myasthenic syndrome due to AL2G2 gene mutations (http://brain.oxfordjournals.org/content/136/3/944.long).
10. A novel form of congenital muscular dystrophy due to B3GALNT2 gene mutations (http://www.cell.com/AJHG/retrieve/pii/S0002929713000694).
11. 11. A newly recognized autosomal recessive syndrome affecting neurologic function and vision. (http://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.35850/abstract;jsessionid=57FC0B56AA5ACBFD4CD5CEFA85862B3C.d01t01).
12. A novel gene for migrating partial seizures in infancy. (http://www.ncbi.nlm.nih.gov/pubmed/24596948).

These advances of pediatric neurogenetics helped in refashioning the prognosis and differential diagnosis of these diseases. It also made possible the choice of life-saving drugs in congenital myasthenic syndromes, and made possible presymptomatic, prenatal, and pre-implantation genetic diagnoses for affected families.