Editorial

Re-defining Neurological Syndromes: The Genotype Meets the Phenotype

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Since time immemorial, generations of medical students and physicians have always been taught that a thorough and detailed history and examination is the foundation of the practice of good clinical medicine. This is particularly so in Neurology, in which the detection of an absent reflex or of focal weakness may assist in localisation of the lesion and, ultimately, in fixing the clinical diagnosis. While this age-old maxim still holds true and continues to play a vital role in our practice, recent advances in molecular science have threatened to challenge the classification of neurological syndromes based on clinical symptoms and signs, and to influence treatment options and patient management.

Recognising the immense role that advances in molecular science, in particular human genetics, have played in the diagnosis and treatment of diseases, the Human Genetics Subcommittee of the Bioethics Advisory Committee published guidelines addressing a wide spectrum of pertinent issues in genetic testing and research. In this light, I would like to highlight how recent advances in genetics have challenged the conventional classification of some neurodegenerative diseases, and the potential impact and challenges these discoveries have on clinical practice in this region.

Most of us would have no problem in recognising a patient with cerebellar dysfunction, characterised by an unsteady gait, incoordination, dysmetria, dysarthria, and ocular movement abnormalities. For years, the diagnosis and categorisation of so-called idiopathic spinocerebellar ataxias (SCAs) have been based initially on Holmes’s neuropathological classification and later Harding’s clinical classification. The discovery of an abnormal nucleotide repeat expansion (e.g. trinucleotide or pentanucleotide) as a genetic cause for these familial (and also apparently sporadic) SCAs has changed clinical classifications and allowed “marriage” of clinical syndromes previously thought to be of separate entities (such as Machado-Joseph disease and SCA3). The discovery of an abnormal nucleotide repeat expansion (e.g. trinucleotide or pentanucleotide) as a genetic cause for these familial (and also apparently sporadic) SCAs has changed clinical classifications and allowed “marriage” of clinical syndromes previously thought to be of separate entities (such as Machado-Joseph disease and SCA3). The repeat size expansion in these non-ataxia patients is generally lower than those patients with ataxia, and this result should provide the basis for research to unravel the underlying pathophysiology.

Fragile X syndrome is due to a trinucleotide repeat expansion in the fragile X mental retardation 1 gene (FMR1). The full mutation of >200 CGG repeats results in methylation, transcriptional silencing, and a deficiency of the FMR1 protein (FMRP). It is the single most common neurological diseases, such as multiple system atrophy. Hence genetic testing for SCA in patients with ataxia alone or ataxia in combination with other neurological signs would enable us to confirm the exact diagnosis and may allow the early institution of genetic counseling. It can also assist in the selection of specific patients for pharmaceutical treatment trials, and ultimately could elucidate the pathogenesis and prognosis of the disease.

While it is reasonable to consider sending a patient with ataxia for a genetic test for one of the SCA genes, who would have thought that mutations of these genes could be responsible for a group of well defined neurological diseases with no ataxia? Parkinson’s disease (PD), a neurodegenerative disease characterised by rest tremor, bradykinesia and rigidity is clearly distinct clinically from SCA. Ataxia or other atypical signs (such as hyperreflexia) are recognised exclusion criteria for the diagnosis. There was great disbelief amongst the scientific community when patients who presented with typical signs and symptoms of PD were found to harbour the CAG repeat expansion of SCA2. The mutation segregates with the abnormal phenotype in the family, supporting the causal relationship. Subsequently, many more families and sporadic PD cases were described, and these patients could not be differentiated from other PD patients without the mutation, based on their clinical signs and treatment response. Positron emission tomography scanning in one family showed a reduced fluorodopa uptake and normal to increased raclopride binding with a rostro-caudal gradient similar to that found in idiopathic PD. The phenotype which has SCA2 positive cases has even expanded to include motor neurone disease and postural tremor. The repeat size expansion in these non-ataxia patients is generally lower than those patients with ataxia, and this result should provide the basis for research to unravel the underlying pathophysiology.

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inherited cause of mental impairment. Testing for fragile X is considered for any child with otherwise unexplained developmental delay or mental retardation. Male carriers with 55 to 100 CGG repeats have FMR1 mRNA levels that are two to four times higher than normal, with slightly reduced FMRP levels. Recently, it has been highlighted that these adult male carriers may present with features similar to essential tremor, sporadic progressive cerebellar ataxia, atypical parkinsonism and multiple system atrophy, the so-called Fragile X tremor/ataxia syndrome (FXTAS).8,9

In fact, in countries where the prevalence of carrier status is high, some of these patients have been wrongly diagnosed to have other neurological diseases.10 This is another illustration of the significant overlap of what was previously thought to be distinct neurologically diseases.

Mutations in a number of disease-causing genes have been described in both familial and sporadic PD patients.11-13 As mutations only account for only about 10% of all PD cases, it has been argued that these genetic forms may be phenotypically different from idiopathic PD, as they present much earlier in life and frequently have other associated features such as dystonia or psychiatric manifestations.11 Interestingly, mutation of one of the PD genes is also responsible for some patients with dementia of Lewy bodies, which is clinically and pathologically different from PD.11 Recently, the identification of a common LRRK2 (G2019S) mutation across populations in both familial and sporadic PD patients suggests that genetic forms of PD may present late and may be totally indistinguishable from non-genetic forms.11,14 Interestingly, post-mortem studies of LRRK2 positive PD patients revealed a wide spectrum of pathologies which simulate Alzheimer disease and progressive supranuclear palsy, two diseases that are distinctly different from PD.14 Some of these LRRK2 mutations can also present initially as benign essential tremor.15

Thus, molecular genetics has strikingly changed the clinical definition of disease phenotype, and suggests significant overlap of the various neurodegenerative diseases. One major problem for us is that most of these studies have been conducted in white Europeans (Caucasians), and the results may not be entirely relevant to our local or regional patients.15 It is possible that there are ethnicity-specific effects or geographical differences for the prevalence of these diseases.11 Relative to the West, there is generally a paucity of information on the prevalence and genetic testing of some of these neurological disorders in Asian countries. One of the major reasons is the lack of facilities and expertise for many countries in this region. The absence of an effective curative treatment for these neurodegenerative diseases does not provide impetus for health authorities to grant priority to develop diagnostic genetic services in places where provision of basic healthcare is more important. Whether it is for clinical or research genetic testing, cultural beliefs and practice amongst some ethnic populations could be a hindrance. The recent difficulties encountered by investigators in getting our local people to participate in large scale clinical and genetic studies are an illustration.16 It appears that Asians may be more reserved, reticent and volunteering for clinical or research test is not part of our upbringing or culture. Like many of my colleagues, I have encountered difficulties in getting at-risk relatives and family members of patients with neurological problems to come forward for an examination and to undergo genetic testing. In some instances, patients have falsely given a negative family history. For potentially disabling or disfiguring diseases with no cure, the perception of a curse to the family or of ancestral misdeeds is not uncommon. Some patients try to avoid the truth through denial, or hide their condition from friends and relatives. This pattern of behaviour and thinking of many of our patients apparently contrasts significantly with that of Western patients. Public education is important, but I suspect the problem is more deep rooted and cannot be solved overnight. Any measures to encourage participation would have to be broad based, and educational measures may have to target the schools, and our social fabric would have to be re-examined. Perhaps changes in thinking and perception would evolve in tandem with changes in our society.

In conclusion, advances in molecular genetics are likely to re-define many of the traditional neurological syndromes and offers quicker and better diagnosis and potential therapeutic opportunities. However, we need greater information on the effect of these advances in our local and regional patients, for us to provide a value-added service. This can only be successfully carried out through improved clinical care and research, with support from patients and healthcare institutions. While guidelines and recommendations for genetic screening and testing, supply of genetic test devices and genetic counseling have recently been proposed locally, it is worth emphasising that we need to better equip ourselves with the appropriate sensitivity and knowledge of the ethical, social, legal and psychological issues regarding genetic testing in our population. Hopefully more widely embracing and cooperative efforts to examine the manpower, infrastructure, cost-effectiveness, and scientific issues related to genetic testing for specific diseases will soon be realised.

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REFERENCES