

Genetic Chameleons; remember the relapsing disorders

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Our genetic code is satisfyingly reliable. It does not suffer circadian fluctuations - there is no need for an 'early morning' or 'fasting' DNA test. It does not transmute over time – there is no need to resample, or compare results with an aged-matched sample. It does not suffer the vagaries of the test-retest variation seen with an ESRs or a CK. The famous twisted-ladder of the double helix structure provides great physical and chemical stability. This inherent steadfastness is the tenet on which Michael Crichton's *Jurassic Park* is based, as well as countless real and fictionalised courtroom dramas. These features may predicate the optics through which we view a genetic disorder; indelible, inevitable, fixed and inert. In reality no branch of medicine is as straight-forward as we were initially taught– and medical genetics is unrecognisable from the undergraduate lectures of only a couple of decades ago. Somatic variation, mosaicism and heteroplasmy are but some of the mechanisms that undermine the superficial but false impression of genetic constancy.

Consider the gamut of genetic disorders that break from this archetype, such as the paroxysmal conditions. There are the familial hemiplegic migraine disorders (*CACNA1A*, *ATP1A2*, *SCN1A*, *PRRT2*) that produce spells on a spectrum from episodic migraine to fulminant encephalopathy. There are startle disorders such as the neonatal-onset hyperekplexias (*GLRA1*, *SLC6A6*, *GLRB*) that produce easily-elicited startle responses that do not readily habituate. There are febrile seizure genes (*SCN1A*, *GABRG2*) – that not only produce self-limiting seizures, but intriguingly need the secondary stimulus of the febrile illness. In many ways these are similar to the paroxysmal kinesigenic dystonias in so much as the genetic fault (*PRRT2*, again) needs a secondary trigger.

There are genetic disorders that are associated with relapsing and remitting episodes that persist for days or weeks. In Newcastle we'd perhaps first think of the encephalopathy and seizure-related strokes of MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; m.3243A>G) as a great example of these inherently unstable and fluctuating genetic disorders. MELAS illustrates two trajectories well – the chronic and the acute. There is a steady inexorable decline over decades as demonstrated by dementia clinically, and progressive atrophy on MRI brain; both of which are exacerbated by the encephalopathic focal-seizures of MELAS.

The painless sub-acute visual loss in Leber's Hereditary Optic Neuropathy (mitochondrial DNA point mutations at 11778, 14484, and 3460) is often diagnosed late because of the broad range in age of onset (primary school to retirement age). A proportion of the variability in the age of onset pertains to an environmental trigger and asymptomatic carriers are prompted to live a virtuous life. Smoking

tobacco and, to a lesser extent, imbibing alcohol are established provoking factors; similarly, smoking cessation reduces the severity of symptoms.

The prototypic epileptic encephalopathy, Dravet syndrome (*SCN1A*, again) has a *gestalt* that varies depending on when you meet the patient. The first phase (6 to 18 months) is of frequent and unusual febrile seizures, the second (12 months to teenage years) consists of developmental slowing, regression, and multiple drug-refractory seizure types, and the third phase (adult) has fewer recognisable features. There are patterns of gait change, loss of bladder control and the fever-sensitivity may remain, but the myoclonus may no longer predominate and the EEG may not be characteristic. I would wager that the majority of clinical diagnoses of Dravet in adult medicine are made with the 20/20 hindsight of having a definitive genetic result available. The test is now trivial to commission because it should be on every epilepsy gene panel. The flood gates are now open. Neurologists who commission genetic testing now must forge closer links with clinical genetics, and where available, neurogenetic MDTs because the challenge is now primarily around variant interpretation rather than access to gene panels or 'hypothesis free' testing such as sequencing the entire exome or genome. As always if you know that you should test, but not what to test – ask for DNA to be extracted and stored and speak to your local clinical genetics team.

When considering a case at grand round, if you have correctly localised the pathology and have an understanding of the chronology of the disease, you won't be far wrong. Neurology has an abundance of these words for describing the time-course: acute, chronic, fatigable, fixed, fluctuant, inconsistent, progressive, relapsing, remitting, stuttering, sub-acute and more. Some of these words will directly narrow down the field of enquiry – so it is worth remembering the genetic chameleons. Particularly the conditions that initially impersonate an inflammatory or infectious illness. In this edition of Practical Neurology we have a case that very much fits that paradigm; acute necrotising encephalopathy (*RANBP2*).[1]

In this genetic disorder the children (primarily) have no hallmarks of an illness until they are exposed to an acute infection, often influenza. This triggers a rapidly progressive encephalopathy that would be readily attributed to 'post infectious' causes and not aggressively investigated further were it not that this pattern can, tragically, recur in siblings. The most striking feature that separates this from isolated acute necrotising encephalopathy is that it can also recur in the proband so that it may broadly mimic a relapsing-remitting disorder. Features that suggest this genetic disorder include a later (teenage and older) age of onset, without abnormal liver function tests, with thalamic and pontine involvement on MRI.

Consider the genetic chameleons, including those that have environmental triggers, as we evolve our paradigm of what constitutes a genetic disease. As more children with complex neurological disorders survive into adulthood we will be caring for more young adults with genetic disorders – with and without a diagnosis.

References

1. Case report. Practical Neurology 2019 This Edition