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Heredity in epilepsy – An historical overview

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Abstract

This paper provides an overview of the concepts of the genetic causation of epilepsy from 1860 to the present day, and an appreciation of the impact of these concepts today. The paper is a summary of part of the Masakawa Seino Memorial Lecture given at the AOEC meeting in Melbourne in October 2010.

It has been realized since the time of Hippocrates that epilepsy is often 'an inherited disease' but it was only really around 1860 that modern discourse on this topic was initiated.[1] In this paper, the main lines of thought about heredity in epilepsy from 1860 are summarized in three 50 year periods.

1860-1910

In 1860, there were no investigatory facilities and the description and classification of neurological disease was only just taking on a modern shape. The only confirmation of cause could come from pathology, and there was also no idea how heredity 'worked'. Darwin's origin of the species was published only a year before and Mendel had not yet devised his laws. The words genetic or gene were not yet conceived.

However, epilepsy was widely considered to be an inherited diseases and four concepts particularly developed in this period which have resonance today: (a) The division of causes into predisposing and exciting causes. Sieveking[2] used the analogy of gunpowder and the match: the level of flammability was set genetically (the predisposing cause), and this influenced the chance of a flame (the exciting cause) resulting in the explosion (the seizure). The predisposing cause was considered to be largely heredity, and the inherited predisposition was known as the 'Epileptic Diathesis' (very similar to our concept of the epilepsy threshold). (b) The view that epilepsy was a term which should be largely confined to the 'idiopathic' disease and that 'cause' was equivalent to 'causal mechanism'. As Jackson put it: *"The confusion of two things physiology and pathology under one (pathology) leads to confusion in considering "causes". Thus, for example, we hear it epigrammatically said that chorea is "only a symptom" and may depend on many causes. This is possibly true of pathological causation; in other words it may be granted that various abnormal nutritive processes may lead to that functional change in grey matter which, when established, admits occasional excessive discharge. But physiologically, that is to say, from the point of view of Function, there is but one cause of chorea - viz. instability of nerve tissue. Similarly in any epilepsy, there is but "one cause' physiologically speaking - viz. the instability of the grey matter, but an unknown number of causes if we mean pathological processes leading to that instability".*[3] (c) The 'Neurological trait'. This interesting idea originated earlier in the 19th century and by Gowers' time was universally accepted.[4] According to this theory, individuals inherit together a propensity for a range of neurological conditions, of which epilepsy was only one. The linked inherited propensity was known as the neurological trait. The trait encompassed a variety of conditions, the exact range of which varied according to different authors, but usually included insanity, psychiatric disorders of various types, mental retardation; and personality or behavioural degeneration evinced by sexual excess, masturbation and perversion. (d) 'Degeneration'. This was also an immensely influential concept, and almost universally held by the end of the century, in parallel to the concept of the neuropathic trait. It originated in the French literature.[5-8] Epilepsy was at the core of the 'degenerative endowment'. According to the concepts of degeneration and the neurological trait, the inherited endowment became progressively more severe from generation to generation, eventually ending in the extinction of the line. Thus, for instance, it might cause mild hysteria in one generation, then a more serious epilepsy in the next, and dementia or idiocy in the next.

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Degeneration was thought to bring out atavistic traits, primitive often ape-like traits, which had disappeared during evolution. This view of the biological basis of epilepsy reached a zenith with the work of Cesare Lombroso. He conceived the notion of the 'Born Criminal' - one whose criminality is based in heredity. His experimental method was the study of physiognomy and of psychological attributes. He held that two thirds of dangerous criminal individuals were 'born criminals' who inherited a criminal trait and possessed 'anomalies (physical and psychological) resembling the traits of primitive man and animals (and even plants). Thus criminals were *atavistic throwbacks* to a primitive stage in human evolution. He proposed too that epilepsy itself was an atavistic characteristic and a fundamental component of the criminal type.[9] Overall, he wrote that 26.9% of all epileptic men and 25% of all epileptic women have a 'full criminal type'.

1910-1960

Two concepts are of interest from this period:

(a) Eugenics: By far the most important development in this period in this field was Eugenics. This became a predominant branch of science around the turn of the century. It was based on Mendelian genetics which were 'discovered' at this time. The first publication on epilepsy was that of Davenport and Weeks[10] from the newly created Eugenic Record Office at Woods Hole. The scientific method was that of pedigree analysis and physical measurement, very much in the Lombrosian and Galtonian tradition. According to eugenic theory, epilepsy was inherited by Mendelian mechanisms as a recessive trait. The concern of Davenport and the American eugenecists was that the population of epileptics was increasing rapidly. The Eugenics movement thus sought ways of preventing the production of epileptic offspring, including segregation, prohibition of marriage, then voluntary and then mandatory enforced sterilisation. In Nazi Germany, eugenic theory was taken further. Using eugenics as a justification, the mass murder of the unfit (including epileptics) was sanctioned under the guise that this was mercy killing to improve the population stock. It has been estimated that up to 700,000 mentally and physically handicapped persons were murdered from 1939 to 1945 under the *Action T4* and other 'euthanasia' programmes.[11]

(b) The multifactorial nature of epilepsy inheritance. For several decades after this, genetics was rather ignored by the scientific community, but again became topical with the work of William Lennox.[12] An important contribution was his emphasis on the multifactorial nature of epilepsy. He conceived of epilepsy as being the result of complex interactions between gene and environment and perceived these contributing to the seizure threshold, a concept remains influential today. He was one of the early researchers to study the difference between monozygotic and dizygotic twins as a method of exploring hereditability. In his 225 twin pairs, he found concordance rates of 62% for monozygotic and 14% for dizygotic twins.

1960-2010

This is the age of molecular genetics. There have been profound advances in the understanding of human genetic disease. These include: the methodology of linkage studies, the mapping of the human genome, the development of sequencing methods, karyotype analysis, methods of DNA amplification and analysis, biometrics, the HapMap project and array technology.[13] The genetic basis of almost all the single gene disorders which have epilepsy within their phenotype, of which there are over 200, has been identified. A few of these are rare familial pure epilepsies (currently 15 genes in total). Other work with copy number variations has recently identified microdeletions, rearrangements and duplications which also underpin a number of cases and may also be involved in psychiatric co-morbidity.

GENERAL POINTS FROM THIS HISTORY

A number of general points arise from this historical survey. First is the importance of social influences on theories of epilepsy genetics. The concerns about degeneration at the end of the nineteenth century for instance were reflected in the degenerative theories of the etiology of epilepsy, as were theories of criminality. Eugenic research in epilepsy was primarily driven by economic, political and social forces. Science has a social responsibility and is never neutral or objective, a fact often forgotten in the laboratory, and the results can be disastrous, as was the case in the 1930s.

Although the genetic basis of epilepsy has been the focus of much recent work, the results have been generally somewhat disappointing. Highlights are the recognition of the role of ion channel defects and the identification of the

genetic defect in single gene disorders (over 200) in which epilepsy is part of the phenotype and even of genes in rare families where epilepsy is the only condition. Taking a broad view though, genetic research has not illuminated causation in many cases, and the genetic basis of the vast majority of idiopathic cases remains obscure. This is sometimes referred to as the missing hereditability of epilepsy.[14] The lack of advance in epilepsy is in great contrast to the major advances in immunological disease and cancer for instance, and the reason may reside in the fact that epilepsy and other neuropsychiatric disorders have their origins in neurodevelopment, and where epigenetic and epistatic mechanisms, or even chance, play a much greater role (this is discussed elsewhere).[15]

Today we make the distinction between the 'mechanisms' of epileptogenesis (increased excitation, defects in ion channels etc) and the causes of epilepsy, whereas in Jackson's time this was not the case. There is much to commend in Jackson's approach, and exactly how causal lesions translate into epilepsy is still largely unknown, and it is surely time to reconsider the concept of etiology as mechanism. In the genetics of epilepsy, this will require a focus away from gene-identification towards neuro-development and epistasis and epigenetics processes.

The concept of the predisposing and exciting causes is another concept worth re-evaluation as more emphasis is placed on provoking factors for epilepsy. Linked to this is the need for aetiology to be more accounted for in modern classifications of epilepsy.[16]

Finally, the concept of the neurological trait is again of some current interest, for exactly the same neuropsychiatric co-morbidities reported in the trait are found in contemporary statistical surveys of patients with epilepsy. These are considered usually to be co-morbidities, but it seems quite possible that there are mechanistic links between cryptogenic epilepsy and other neurological diseases, or links between epilepsy and cerebral degenerative mechanisms. Studies with copy number variations have provided some interesting evidence on this point, and the uncovering of common mechanisms that may give a clue to the genetic basis of epilepsy and these other conditions. A warning from history though; in the early twentieth century, the link of epilepsy to degeneration and to mental disorder resulted in enormous stigma and resulted in eugenic measures to restrict reproduction and culminated in the murder of handicapped persons. The very power of modern molecular genetics carries grave risks. People with epilepsy are very vulnerable particularly if the flavor of research moves to looking at epilepsy within the wider neuropsychiatric context – for it was exactly from this basis that eugenic theories in relation to epilepsy developed. We must therefore be exceptionally vigilant in this area. Science has a responsibility and is never morally neutral - least of all genetics – a lesson from history that should not be forgotten.

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