Epilepsy & Behavior 32 (2014) 1–8

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

The concept of symptomatic epilepsy and the complexities of assigning cause in epilepsy

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ARTICLE INFO

Article history:
Received 2 November 2013
Revised 16 December 2013
Accepted 21 December 2013
Available online 22 January 2014

Keywords:
Symptomatic epilepsy
Idiopathic epilepsy
Provoked epilepsy
Causes of epilepsy

ABSTRACT

The concept of symptomatic epilepsy and the difficulties in assigning cause in epilepsy are described. A historical review is given, emphasizing aspects of the history which are relevant today. The historical review is divided into three approximately semicentenial periods (1860–1910, 1910–1960, 1960–present). A definition of symptomatic epilepsy and this is followed by listing of causes of symptomatic epilepsy. The fact that not all the causes of idiopathic epilepsy are genetic is discussed. A category of provoked epilepsy is proposed. The complexities in assigning cause include the following: the multifactorial nature of epilepsy, the distinction between remote and proximate causes, the role of nongenetic factors in idiopathic epilepsy, the role of investigation in determining the range of causes, the fact that not all symptomatic epilepsy is acquired, the nosological position of provoked epilepsy and the view of epilepsy as a process, and the differentiation of new-onset and established epilepsy. The newly proposed ILAE classification of epilepsy and its changes in terminologies and the difficulties in the concept of acute symptomatic epilepsy are discussed, including the inconsistencies and gray areas and the distinction between idiopathic, symptomatic, and provoked epilepsies. Points to be considered in future work are listed.

This paper reviews several aspects of the concept of 'symptomatic epilepsy' and more broadly the issues of attributing cause in epilepsy. A historical overview will first be given, listing areas which are important to our current understanding of 'causation' in epilepsy. The listing of causes and the problems of classification will then be covered. The question of the nosological position of provoking factors will be discussed. Finally, a critique of the concept of acute symptomatic epilepsy will be given. The concept of symptomatic epilepsy is not as simple as at first sight it might appear, and the purpose of this paper is to draw attention to the inherent complexities inherent in assigning causation in epilepsy.

1. Historical perspective

The modern history of symptomatic epilepsy can be divided conveniently into three periods.

1.1. 1860–1910

Many concepts of etiology of epilepsy were formulated between about 1860 and 1910, and several are worthy of special mention for their insights which are relevant to us today.

1.1.1. The distinction between predisposing and exciting causes

All authors of the period, without exception, considered epileptic seizures to have two distinct causal components: an innate predisposition (a predisposing cause; a diathesis) and a precipitating (exciting) cause. Although different authors used the terms differently, the predisposition was considered by most to be largely inherited and the exciting causes to be external or provoking factors (the position of structural and congenital causes was ambiguous). This dichotomy has been arguably unjustly neglected in recent times. The analogy of gunpowder and the match was often used (for instance, by Sieveking [1]), even before Jackson's famous definition of the epileptic seizure as a 'discharge'. Spratling [2], the doyen of American epileptologists, even attempted to explain the contributions of the exciting and predisposing causes mathematically, writing that: if it took 100 points to induce a seizure in an individual, a predisposition could contribute 60 points and an exciting cause 40 points, whereas if the predisposition contributed only 40 points, it would require an exciting cause to have 60 points in order to reach the 'seizure point'. This concept is also the basis of the 'seizure threshold' widely referred to today.

1.1.2. The introduction of the term 'symptomatic epilepsy'

The first use of the term 'symptomatic epilepsy' that I find was by John Russell Reynolds in 1861 [3], who classified epilepsy into 4 categories (idiopathic, eccentric (syn: sympathetic), diathetic, and symptomatic). Symptomatic epilepsy was defined as epilepsy in which convulsions are due to "*more or less contiguous structural disease of the brain. Thus, an intracranial tumour, a chronic inflammatory condition of*

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http://dx.doi.org/10.1016/j.yebeh.2013.12.025

the meninges, softening or disintegration of the brain substance, or any other structural change in the nervous centres … may set up that peculiar interstitial or molecular change which is the immediate cause of convulsion." This is a definition which is the basis of that used today although the eccentric and diathetic epilepsies would now be included within the symptomatic category. It should be pointed out too that Reynolds did not fall into the mistake of considering all symptomatic epilepsies to be acquired epilepsy, a mistake still sometimes perpetrated today.

1.1.3. The distinction between proximate and remote causes

In the 19th century, a distinction was sometimes made between proximate and remote causes. This important distinction was expounded in its fullest form by Hughlings Jackson in 1874 (see Taylor [4]), who in this was following the lead of his mentor Russell Reynolds. He considered the proximate cause to be the actual cellular disturbance at the epileptic focus, and the remote causes to be those which triggered this disturbance (such as brain tumors, stroke, and infection). He viewed the epileptic seizure as the explosive release of abnormal energy (just as gunpowder can store energy that is liberated when firing the gun). He considered that the reason for the abnormal levels of stored energy was 'abnormal nutrition', and it was this physiological abnormality which he considered the *proximate cause*. It is worth quoting him at length:

> '*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*.'

Jackson defined abnormal *physiology* in the narrow and specific meaning of: '*the departure of the healthy function of nerve tissue. That function is to store up and to expend force … in epilepsy, the cells store up large quantities and discharge abundantly on very slight provocation: there is what I call instability or what is otherwise spoken of as increased excitability*'.

Our present concepts of cause currently to an extent fail fully to appreciate this very important insight. Causal classifications of epilepsy would be very different if we thought in terms of physiological causal mechanisms, rather than pathologies.

1.1.4. The concept of the neurological trait

Another most interesting aspect of the concept of 'cause' in the late nineteenth century, but one which is very relevant, is the concept of the neurological trait (syn: neurological taint, neuropathic trait). This concept was almost universally accepted at the time (although interestingly not by Jackson). According to this theory, a range of conditions including epilepsy were inherited together, and linked to this was the view that as the 'trait' was passed from generation to generation, and that the inherited tendency became more severe (the theory of 'degeneration'). Gowers, for instance, in 1888, wrote that 40% of his 2400 cases showed evidence of the neuropathic trait [5]. This concept has been effectively reinvented today with the recognition of neuropsychiatric 'comorbidities' and their bidirectional nature. In the nineteenth century, the conditions were not seen as 'comorbidities' but as manifestations of the same underlying causes. It seems likely that this is in fact the case, with perhaps similar defects in biochemical or developmental pathways resulting in a variety of different disorders. This too reflects an orientation towards causal mechanism (proximate) rather than downstream (remote) causal pathologies.

1.1.5. The theory that 'seizures beget seizures': epilepsy as a process

Another unique contribution made by Gowers [6] to "cause" in epilepsy is worthy of mention, and his theory was as follows:

> '*The malady is self-perpetuating; when one attack has occurred, whether as the result of an immediate excitant or not, others follow either without any immediate cause, or after some very trifling disturbance. The search for the causes of epilepsy must thus be chiefly an investigation into the conditions with precede the occurrence of the first fit.*'

This concept ("seizures beget seizures") was also widely accepted in the time of Gowers. Gowers and others, therefore, made a major distinction between new-onset epilepsy (which was reversible with active therapy) and chronic epilepsy (which was largely incurable). Epilepsy was seen as a process, and the cause of the seizures was the maturation of this process. The molecular science has demonstrated a range of changes which might underlie this process, and this topic continues to excite debate.

Of course, other concepts of cause in this early period have not stood the test of time — including concepts of reflex causation, autointoxication, constipation, masturbation, and so on.

1.2. 1910–1960

This was a period when much work focused for the first time on the symptomatic causes of epilepsy.

1.2.1. The dependence of cause on investigatory methods

At the start of this period, there was far more interest in the heredity of epilepsy than in the symptomatic causes, but this was to change as the century advanced. This was partly due to the catastrophic consequences of hereditarian theories which lead to eugenics and then to the sterilization and then mass extermination of people with mental handicap and epilepsy, which were based on and justified by contemporary hereditarian science and medicine. A second reason of course for the refocusing of interest towards symptomatic epilepsy was the advent of new investigatory modalities such as neuroimaging, electroencephalography, and advances in neuropathology, which all helped uncover cerebral structural defects associated with epilepsy. Advances in neuroimaging included the application of X-ray (discovered in 1898 but utilized in neurology widely only after 1910) and then ventriculography (1918), and cerebral angiography (1927). These techniques were strongly developed in the early postwar years and especially for the detection of vascular and tumoral lesions. One of the first to write in detail about the impact of the early changes was Walter Dandy, who wrote in 1932 [7]:

> '*Epilepsy is always regarded as an idiopathic disease. The theories of its causation are indeed so numerous as to reflect seriously upon any exclusive stand concerning its etiology or pathology. However, the writer is confident that there is now assembled from experimental, pathologic, clinical and surgical studies a sufficient number of unquestioned facts to place epilepsy unequivocally upon a pathologic instead of idiopathic basis …. the fundamental conception that in every case of epilepsy there is a lesion of the brain can no longer admit of doubt ….*'

Dandy recognized 17 categories of brain lesions causing epilepsy (Table 1), a list which seems peculiar today but which, nevertheless, put symptomatic epilepsy back into focus.

In the early postwar years, the major methodological advance in the field of epilepsy was of course the EEG (introduced into clinical practice in 1940). In terms of etiology, EEG was used to detect structural abnormalities, such as brain tumor or infection, a role now completely superseded by modern neuroimaging. It was EEG too which led to the recognition of the importance of hippocampal sclerosis as a prominent cause of epilepsy and the underlying pathology in many cases of