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A short history of the long and productive search for the cause of *subacute sclerosing panencephalitis*

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Abstract

This brief historical review recounts the efforts of the discovery of the cause of subacute sclerosing panencephalitis from its initial pathological descriptions, through the identification of measles virus as its pathogen, to the current conceptual framework of its pathogenesis. It is presented as an example of what was once considered an "unconventional" infection, but is now the subject of speculation according to the modern principles of molecular biology.

Key words: *subacute sclerosing panencephalitis, Gajdusek, SSPE, measles virus.*

Introduction

The original concept of slow virus infections, promoted by Bjorn Sigurdsson, offered D. Carleton Gajdusek a platform on which he pivoted infections of an unusual sort, the ones to which he applied the term "unconventional." This was a very useful concept, because it suggested that the traditional criteria by which one evaluated infections did not always fit. In this there was some prescient ideation that the customary manner of searching for infectious agents by culturing specimens, or by inoculating animals, did not always work. Indeed, it seems that on this basis alone, by far the largest part of the microbiome is not detectible by conventional methods. Even now, as we relegate the concept of slow virus infections to an historic niche, we have to account for the prions, which lack nucleic acids and therefore by the traditional cognition are not even alive; we know of biofilms within which the organisms that remain undetectable multiply and survive environmental assaults, and we detect other ones by metagenomics, because we are unable to offer them an *in vitro* environment in which they can thrive.

So a conceptional inclusion of *subacute sclerosing panencephalitis* within the unconventional infections prompted a number of laboratories to begin searching for its causative agent by unconventional methods. The heuristic value of this concept led to the eventual recognition of the pathogenic agent and ultimately, but still incompletely understood, its pathogenesis. This then is the subject of the following essay. We now know, of course, that the agent is the measles virus, in a form sufficient to cause continuous harm, yet being too defective to sustain its replication *in vitro*.

Evolution of the current point of view

Primacy of discoveries is always difficult to establish. Each new finding can be traced to an individual and an attribution to only one often provokes a frantic res-

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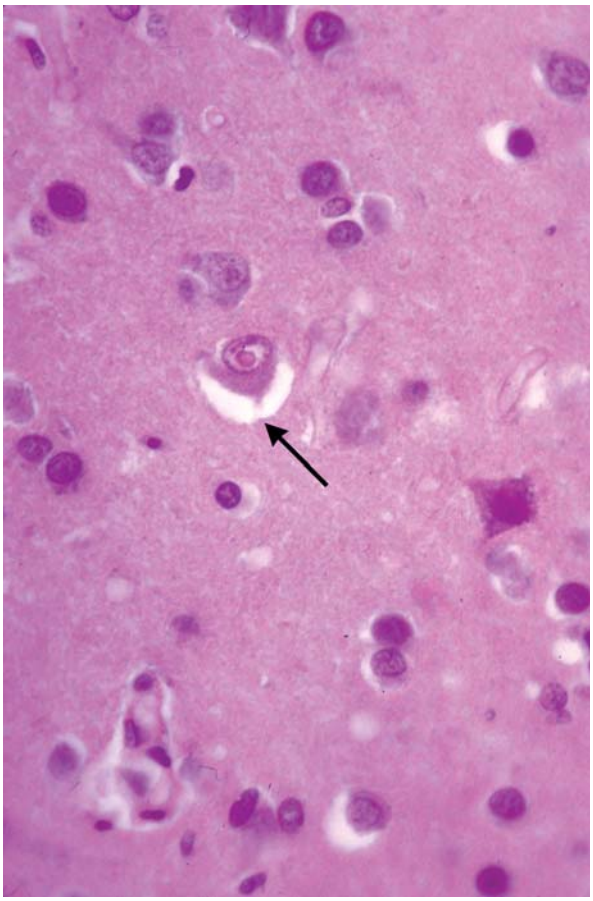

Fig. 1. Cortical neuron (in the center of the field) containing type A intranuclear inclusion body (arrow). Section comes from one of Dawson's two cases dating back to 1931; these two cases were called 'Dawson's inclusion body encephalitis'. H & E × 400.

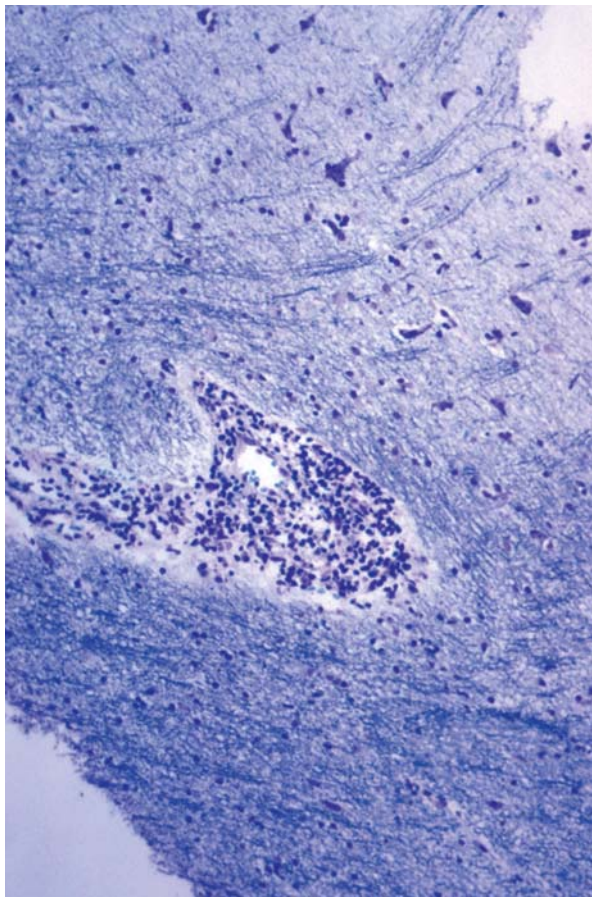

Fig. 2. White matter of a girl with SSPE showing replacement of normal morphology of white matter by macrophages and large fiber-forming astrocytes. H & E × 100.

ponse that an earlier source was the original one. Few discoveries remain singular. Most are products of partial observations whose ultimate coherence becomes a whole; so it was with the subacute sclerosing panencephalitis (SSPE.) One early report by Dawson in 1933 [7] described it as "inclusion body encephalitis." It was a case history of a child who died after several years of slow deterioration that ended in a vegetative state and then demise. Dawson's pathological description of the case identified intranuclear eosinophilic inclusion bodies, which reminded Dawson of viral inclusions (Fig. 1). No etiologic cause was identified.

In 1945 van Bogaert [20], working in Antwerp, described a case of a child who had a clinical history resembling that of Dawson's case, but whose pathological findings were noted in the white matter as sclerosing lesions, and van Bogaert applied to it the name of "sclerosing panencephalitis" (Fig. 2). Dawson's name tended to predominate and clinicians began to identify these cases as Dawson's encephalitis. The clinical course of their disease was similar and they all died. Their brains contained both the inclusion bodies and the sclerosing lesions. This fusion of observations then lead to the ultimate acceptance of the common name, SSPE, apparently first suggested by Greenfield [8].

Electron microscopic observation by Boutellie et al. [3] of structures resembling nucleocapsids of a paramyxovirus was an important clue to the possible

cause, and it led Connolly et al. [5] to search for antibodies to paramyxoviruses. He hit pay dirt when he noted that the children so afflicted not only had antibodies to the measles virus but that those antibodies appeared in astronomical concentrations, not just in the blood, but also in the cerebrospinal fluid. From this point on the search for the cause began in earnest.

Obvious ordinary efforts to culture the measles virus failed, although it was possible to identify measles antigen within the inclusions by using fluorescence microscopy. Epidemiological analysis of the case histories gave some clues to the process. It appeared that the victims of this encephalitis tended to have clinical measles at a rather early age by contrast with matched comparison groups. Other possible clues did not turn out to be helpful, such as rural domicile, which suggested the possibility of a zoonotic paramyxovirus, i.e. distemper or rinderpest as the root cause of the disease.

Efforts to culture the virus from the brains of patients with SSPE were initially unsuccessful, although it was possible to establish explant cell cultures from the brain tissues [2], which contained antigens reacting with the measles antibody in a fluorescence test and structures resembling nucleocapsids [17] on electron microcopy. Yet efforts to culture the virus in the traditional manner failed. Finally, with the use of helper cells or viruses, measles virus was rescued from these cultures [1,9,18], but it was interesting that this rescue could be accomplished at will, over and over again from cultured cells derived from some cases, or not at all from others, no matter how effortful the attempts were. Yet all of the cultures contained measles antigens. The conclusion that followed was that the viruses were defective and that the degree of the defectiveness determined whether they could be rescued [11].

Once the connection to the measles virus was established, two questions remained: why were only certain children so affected, and what was the nature of the aberrant relationship between the defective virus and the host?

These questions are still being answered by conjectures. With respect to the first, there are the following considerations. The events seem to be random. Even SSPE in one of monozygotic twins does not necessarily have a parallel in the other. The second question can be answered by another conjecture that a rare coincidence of another factor, for example transient immune failure [6], perhaps caused by a coincident infection [10,19], suppresses – but does not abolish – the measles infection. This forces the measles virus to remain intracellular and continually leak its antigen, which results in sustenance of the high concentration of antibodies, but the infection remains intracellular.

Efforts to develop animal models of SSPE have not been wholly successful either. In the earlier days of those studies, before transgenic mice could be created, various animals were inoculated either with measles virus, or with the measles viruses rescued from SSPE patients or with the antigen-rich cells explanted from the patients.

Injection of chimpanzees resulted in seroconversion in some, but no discernable clinical disease. Injection of ferrets with the rescued SSPE viruses failed to cause a disease. However, when the ferrets were injected with cells containing the SSPE measles antigen they developed subacute encephalitis, but one that was not a wholly typical human clinical picture of SSPE [12-15].

Newer technology permitted creation of a mouse model that is closest to the human disease. It was developed by an infection with an altered measles virus in which the M gene of the Edmonston strain was replaced by a hypermutated M gene from an isolate derived from an SSPE patient. This resulted in a progressive, but slower case of encephalitis with the mice remaining alive for several months [16].

The irony remains that SSPE has been essentially abolished in the wake of the elimination of measles by the widespread use of the vaccine [4]. Thus the clinical stimulus of the persistence of this fatal disease has been removed. What remains is the intellectual challenge to discern its pathogenesis. This could be important for two reasons. It may point a way to a novel mechanism of viral persistence that may also characterize other virus-host relationships; it is also possible that by discerning such a mechanism one would be able to resolve pathogenic mechanisms of other viral infections whose abolition by preventing the root infection may not yet be possible.

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References

1. Barbanti Brodano G, Oyanagi S, Katz M, Koprowski H. Presence of two different viral agents in brain cells of patients with su-

bacute sclerosing panencephalitis (SSPE). Proc Soc Exp Biol 1970; 134: 230-236.
2. Baublis JV, Payne FE: Measles antigen and syncytium formation in brain cell cultures from subacute sclerosing panencephalitis (SSPE). Proc Soc Exp Biol 1968; 129: 593-597.
3. Boutellie M, Fontaine C, Vedrenne CL. Sur un cas d'encephalite subaigue a inclusions. Etude anatomoclinique et ultrstructurale. Rev Neurol 1965; 113: 454-458.
4. Campbell H, Andrews N, Brown KE, Miller E. Review of the effect of measles vaccination on the epidemiology of SSPE. Int J Epidemiol 2007; 36: 1334-1348.
5. Connolly JH, Allen IV, Hurwitz LJ, Millar JH. Measles virus antibody and antigen in subacute sclerosing panencephalitis. Lancet 1967; 1: 542-544.
6. Coulter JB, Balch N, Best PV. Subacute sclerosing panencephalitis after drug-induced immunosuppression. Arch Dis Child 1979; 54: 640-642.
7. Dawson JR Jr. Cellular inclusions in cerebral lesions of lethargic encephalitis. Am J Pathol 1933; 9: 7-15.
8. Greenfield JG. Encephalitis and encephalomyelitis in England and Wales during the last decade. Brain 1950; 73: 141-166.
9. Horta-Barbosa L, Fuccillo DA, London WT, Jabbour JT, Zeman W, Sever JL. Isolation of measles virus from brain cell cultures of two patients with subacute sclerosing panencephalitis. Proc Soc Exp Biol 1969; 132: 272-277.
10. Katz M: Measles and central nervous system disease, a critical appraisal. Med Microbiol Immunol 1974; 160: 247-250.
11. Katz M, Koprowski H. The significance of failure to isolate infectious viruses in cases of subacute sclerosing panencephalitis. Arch Ges Virusforsch 1973; 41: 390-393.
12. Katz M, Koprowski H, Tucker SH. Transmission of encephalitogenic agents from brains of patients with subacute sclerosing encephalitis to ferrets. New Engl J Med 1968; 279: 793-798.
13. Katz M, Rorke LB, Masland WS, Brodano GB, Koprowski H. Isolation of a virus encephalitogenic for ferrets. J Inf Dis 1970; 121: 188-195.
14. Lehrich JR, Katz M, Rorke LB, Barbanti-Brodano G, Koprowski H. Subacute sclerosing panencephalitis. Encephalitis in hamsters produced by viral agents isolated from human brain cells. Arch Neurol Psychiat (Chi.) 1970; 23: 97-102.
15. Mehta PD, Thormar H. Immunological studies of subacute measles encephalitis in ferrets: similarities to human subacute sclerosing panencephalitis. J Clin Microbiol 1979; 9: 601-604.
16. Oldstone MB, Lewicki H, Thomas D, Tishon A, Dales S, Patterson J, Manchester M, Homann D, Naniche D, Holz A. Measles virus infection in a transgenic model: virus induced central nervous system disease and immunosuppression. Cell 1999; 98: 629-640.
17. Oyanagi S, Muller D, Katz M, Koprowski H. Electron Microscopic observations in subacute sclerosing panencephalitis brain cell cultures: their correlation with cytochemical and immunocytological findings. J Virol 1970; 6: 370-379.
18. Payne FE, Baublis JV, Itabashi HH. Isolation of measles virus from cell cultures of brain from a patient with subacute sclerosing panencephalitis. New Engl J Med 1969; 281: 585-589.
19. Sevilla N, Kunz S, Holz A, Lewicki H, Homann D, Yamada H, Campbell KP, de La Torre JC, Oldstone MB. Immunosuppression and resultant viral persistence by specific viral targeting of dendritic cells. J Exp Med 2000; 192: 1249-1260.
20. van Bogaert L: Une leucoencephalite sclerosante subaigue. J Neurol Neurosurg Psych 1945; 8: 101-120.