

This Week's Citation Classic

Connolly J H, Allen I V, Hurwitz L J & Millar J H D. Measles-virus antibody and antigen in subacute sclerosing panencephalitis. *Lancet* 1:542-4, 1967. [Depts. Microbiology and Pathology, Queen's Univ., and Royal Victoria Hospital, Belfast, Northern Ireland]

Measles antibody was found in serum and cerebrospinal fluid of three boys with subacute sclerosing panencephalitis and serum/CSF antibody ratios were low. Serum titres were high in two boys while in one the titre increased 16-fold during the illness. Measles virus antigen was present in the brain. [The **SC[®]** indicates that this paper has been cited over 285 times since 1967.]

John H. Connolly
Department of Microbiology
and Immunobiology
Queen's University
Belfast BT12 6BN
Northern Ireland

February 10, 1981

"Subacute sclerosing panencephalitis (SSPE) is a very rare disease yet in 1965 within a three month period, three boys from different areas of Northern Ireland were diagnosed by the Royal Victoria Hospital neurologists, Lewis Hurwitz and Harold Millar. Northern Ireland had a population of only 1.5 million people so this was an unusual event. I was doing diagnostic virology in the Queen's University, department of microbiology, and Hurwitz, whom I knew well, encouraged me to examine the patients. Seeing the boys with this devastating disease was a powerful stimulus to do some investigative work. We asked the parents about the boys' childhood illnesses, animal contacts, and whether they had been in contact with each other. No clues emerged. The success of this project owed much to the enthusiasm of Hurwitz, who ensured that all specimens asked for were delivered and who encouraged us during the whole investigation.

"Serum and cerebrospinal fluid (CSF) specimens taken on the same day were tested against several viral complement fixing antigens including a recently

acquired measles antigen. When I saw the first measles antibody titrations I was surprised at the height of the titres, then doubts appeared because we knew the boys had had measles 11 to 13 years previously. The results were confirmed using the haemagglutination-inhibition test. It seemed contradictory that childhood measles, which was then a universal illness, should be associated with this rare disease.

"We were anxious to isolate measles virus from the brain although numerous attempts with CSF were unsuccessful. When the three boys died, the neuropathologist Ingrid Allen from Queen's University, department of pathology, carried out the post-mortems within a few hours of death, so that any virus present would still be viable. Two post-mortems were done in the middle of the night. However, all attempts at virus isolation were unsuccessful. The histological features of SSPE including the virus-like type A inclusions first described by Dawson¹ were seen.

"Shortly after this, Kenneth Fraser came to the department of microbiology. He was experienced in the immunofluorescence technique and we discussed the possibility of using it to detect measles antigen in the brains. Measles antisera were labelled with fluorescein isothiocyanate. Brain sections stained with these antisera showed intranuclear and intracytoplasmic measles antigen. Subsequent work^{2,3} extended these observations and showed the production of immunoglobulins within the central nervous system. There is still, however, an incomplete understanding of the pathogenic mechanisms involved in SSPE.

"I think this paper is often cited because it was the first to show measles antibody in serum and CSF and measles antigen in the brain in SSPE and there was widespread interest in slow and persistent viral infections of the central nervous system."

1. Dawson J R. Cellular inclusions in cerebral lesions of lethargic encephalitis. *Amer. J. Pathol.* 9:7-15, 1933.
2. Connolly J H, Allen I V, Hurwitz L J & Millar J H D. Subacute sclerosing panencephalitis: clinical, pathological, epidemiological and virological findings in three patients. *Quart. J. Med.* 37:625-44, 1968.
3. Thomson D, Connolly J H, Underwood B O & Brown F. A study of immunoglobulin M antibody to measles, canine distemper and rinderpest viruses in sera of patients with subacute sclerosing panencephalitis. *J. Clin. Pathol.* 28:543-6, 1975.