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# Subacute sclerosing panencephalitis in Northern Ireland: twenty years' experience

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## SUMMARY

*Subacute sclerosing panencephalitis (SSPE) is a rare degenerative disease of the central nervous system that affects primarily children and adolescents. It is a late manifestation of measles virus infection. In a 20-year period (1965-85) there have been 26 cases of SSPE in Northern Ireland, a frequency of approximately one case per 1.2 million population per year. Males were affected more frequently than females. In other parts of the world the incidence of this disease has been dramatically reduced following effective measles immunisation programmes. The vaccination rate in Northern Ireland probably remains too low to have a similar effect.*


## INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) was first recognised as a sporadic encephalitis with a subacute course in the early part of the 20th century. In 1933 Dawson described intranuclear inclusions and postulated a viral aetiology.[1] The term 'subacute sclerosing panencephalitis' was first used by Van Bogaert following careful studies of the white matter lesions.[2] In 1967 the role of the measles virus was postulated by Connolly, Allen, Hurwitz and Millar when they demonstrated measles antigen in brain cells and high titres of measles antibody in serum and CSF.[3] The first cases in Northern Ireland, also reported by Connolly, Allen, Hurwitz and Millar, were three patients who all became ill within a six-month period in 1965.[4]

SSPE is now recognised as a worldwide disease with an incidence in most studies of about one per million population per year.[5] However, even in North America where most epidemiological studies have been carried out, there has been some variation in incidence from state to state. This paper presents a retrospective study of all cases of SSPE known to the Regional Neurological Unit and the Regional Virus Laboratory at the Royal Victoria Hospital where all such cases would be expected to be referred.

## CLINICAL FEATURES

During the period 1965-85 there were 26 documented cases of SSPE in Northern Ireland giving an overall incidence of 1.2 cases per million population per year. The disease had a definite predilection for males, boys being affected

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eight times more frequently than girls (23 males, three females). This male predominance has been a consistent finding in all reported series.

It has been stated that measles infection at an early age is a risk factor for the development of SSPE.[6] In this series, the age of measles infection was known in 19 cases. Three patients had measles under the age of two years, 13 between the ages of two and four years and only three over the age of four years, the average age of measles infection being 2.9 years. None of the cases had a history of measles vaccination. The age of onset of the encephalitis varied from three to 19 years with a mean of 10.8 years and there was a mean latent period between measles infection and the development of SSPE of 8.0 years, range two to 15 years. (Fig 1).

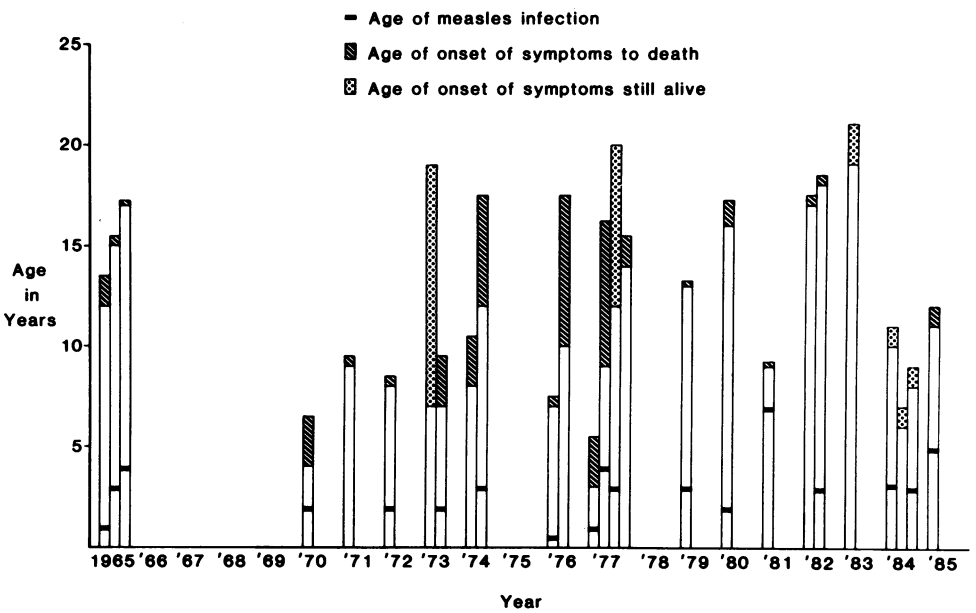


Fig 1. The age of onset of the encephalitis, and the age of measles infection in 26 patients with SSPE from 1965 to 1985.

The clinical course of the disease can be divided into four characteristic stages but there is no sharp demarcation between the stages, and the speed at which one merges into the next is variable. These stages are summarised in Table I. In this series, the first stage was most frequently characterised by intellectual impairment and changes in behaviour. The onset was often very gradual so that it was difficult to be specific about the exact time of onset of the illness. In several cases, signs were first detected by school teachers who noticed impaired intellectual performance. Deterioration in writing and school work was thought to be due, in six children, to difficulty in performing fine movements with the hands, and, in five others to some visual disturbance. Impaired powers of concentration and decreased intellectual ability followed in most cases, while 12 patients were noted to undergo personality change, most often becoming emotionally withdrawn.

Frequent falls were another common early symptom, and a history of trauma was obtained in 25% of cases. Although this was probably an effect of the disease,

the trauma was frequently cited by patient's relatives as the cause of the child's symptoms. In all cases the trauma was minor and on admission 21 of the 26 patients were noted to have unsteadiness of gait.

TABLE I

*Clinical features of SSPE, in 26 patients, during the progress of the disease*

| | | |
|---|---|---|
| *STAGE 1 :* | *MENTAL DISTURBANCES* | |
| | Intellectual deterioration | 24 |
| | Personality or behaviour changes | 12 |
| | Slurred speech | 11 |
| | Poor concentration | 9 |
| | Dressing dyspraxia | 5 |
| *STAGE 2 :* | *MOTOR DISTURBANCES* | |
| | Frequent falls/Unsteadiness of gait | 21 |
| | Myoclonic jerks | 21 |
| | Generalised/focal seizures | 10 |
| | Cortical blindness | 8 |
| | Difficulty performing fine movements with hands | 6 |
| | Other visual loss | 5 |
| | Urinary incontinence | 7 |
| | Choreform movements | 2 |
| | Facial weakness | 1 |
| *STAGES 3 AND 4 :* | *HYPERTONIA AND DECEREBRATION* | |
| | Absent speech | 22 |
| | Extrapyramidal rigidity | 13 |
| | Decerebrate rigidity | 12 |
| | Difficulty in swallowing | 11 |
| | Laryngeal spasms | 3 |

The second stage was characterised by motor disturbances: myoclonic jerking occurred in 21 patients and generalised seizures in 10. At this stage the virus is thought to have spread to the white matter and focal deficits such as cortical blindness were sometimes apparent. This second stage lasted for a variable length of time, but in all cases the disease followed a progressive downhill course, and during the later stages there was further loss of higher cortical function with increasing lower limb spasticity. This progressed to severe extrapyramidal rigidity and finally complete loss of cerebral cortex function and akinetic mutism.

Twenty of the patients have died, usually from terminal lung infections. Six are still alive, at least three of whom appear to have gone into a state of remission, a previously recognised feature of the condition,[7] sometimes resulting in survival for many years despite severe disablement.

## INVESTIGATIONS

*EEG*

All 26 cases had an electroencephalogram. The typical tracing of SSPE is a slow background activity of 4 – 8 c/s with periodic outbursts of high amplitude slow waves at approximately 3 c/s occurring at intervals of 10 – 15 seconds, which may be accompanied by generalised myoclonic jerking.[8] This type of tracing was seen in 25 of the 26 cases, but the timing of the investigation is important as in many cases the initial EEG was non-specific showing a generalised abnormality or even, as in three cases, a focal abnormality. (Table II).

TABLE II

*Investigations*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | *Measles Ab Titre* | | *Typical* |
| | | *Typical* | *Cerebrospinal fluid* | | | | | *histological* |
| *Patient* | *Sex* | *EEG* | *Protein* | *WCC* | *Lange* | *Serum* | *CSF* | *findings* |
| 1 | M | Yes | N | N | P | 2048 | 128 | Yes |
| 2 | M | Yes | N | N | N | 1024 | 128 | Yes |
| 3 | M | Yes | N | N | N | 128 | 32 | Yes |
| 4 | F | Yes | N | 7 | P | 2560 | 256 | Yes |
| 5 | M | Yes | .80 | 6 | N | 320 | 40 | — |
| 6 | M | Yes | — | — | — | 640 | 80 | Yes |
| 7 | M | Yes | N | N | P | 640 | 16 | No |
| 8 | M | Yes | N | N | N | 2560 | — | Yes |
| 9 | F | Yes | N | N | ? | 640 | 32 | Yes |
| 10 | M | Yes | N | N | N | 2560 | 64 | — |
| 11 | M | Yes | N | N | P | 5120 | 128 | — |
| 12 | M | Yes | N | 7 | P | 5120 | 32 | |
| 13 | M | Yes | N | N | N | 2560 | 64 | — |
| 14 | M | Yes | N | N | P | 5120 | 64 | — |
| 15 | M | Yes | N | N | N | 2560 | 64 | — |
| 16 | M | Yes | N | N | N | 640 | 32 | Yes |
| 17 | M | Yes | N | N | — | 320 | 32 | Yes |
| 18 | M | Yes | N | N | N | >10240 | 64 | — |
| 19 | M | Yes | N | N | — | >10240 | 256 | Yes |
| 20 | M | Yes | 1.14 | N | P | >10240 | 512 | Yes |
| 21 | M | No | N | N | — | 2560 | 16 | — |
| 22 | M | Yes | (1) 0.94 | 20 | N | 160 | 16 | — |
| | | | (2) 0.68 | 5 | P | | | |
| 23 | M | Yes | N | 8 | — | 2560 | 128 | — |
| 24 | M | Yes | N | N | P | 320 | 64 | — |
| 25 | F | Yes | N | N | P | 2560 | 64 | — |
| 26 | M | Yes | N | N | — | 1280 | 64 | — |

Protein N = < .45 g/l
WCC N = < 4 cells/µl
Lange P = Paretic

*CSF*

Every patient had CSF analysis carried out. In 19 the protein and cell count was within normal limits. A raised protein value was recorded in four cases, in five cases there was a modest lymphocytosis of 6 – 8 cells/μl, and a further case had 20 lymphocytes/μl on the first of two occasions when lumbar puncture was carried out. A paretic Lange curve was another relatively common finding (in 11 out of 21 cases measured).

An elevated CSF measles antibody titre at greater than 1:8 was found in 25 of the patients (in the other case the CSF antibody titre was not measured). It has been shown in these cases that measles virus antibody in the CSF is specifically raised when compared with polio type 2 antibody, indicating either a selective permeability of measles virus antibody through the blood brain barrier or measles virus antibody production within the CNS.[9]

## HISTOLOGY

Six of the patients had a brain biopsy performed and nine had a post-mortem examination. Three of the biopsies showed features of encephalitis with congestion of the brain. In the later stages there was nerve cell degeneration with loss of nerve fibres and glial replacement. Two cases were more specific in demonstrating inclusion bodies or measles antigen using immunofluorescence. The final case demonstrated only slight congestion of the cortex but was otherwise normal.

Post-mortem examination was performed in nine cases. While the brains appeared macroscopically normal, on microscopy extensive perivascular infiltration in both grey and white matter was found, together with degeneration and loss of neurones. In all but one case, intranuclear inclusion bodies and/or measles antigen were demonstrated. The neuronal loss was accompanied by gliosis, but with little destruction of myelin, both of which features are characteristic of this condition. (Fig 2).

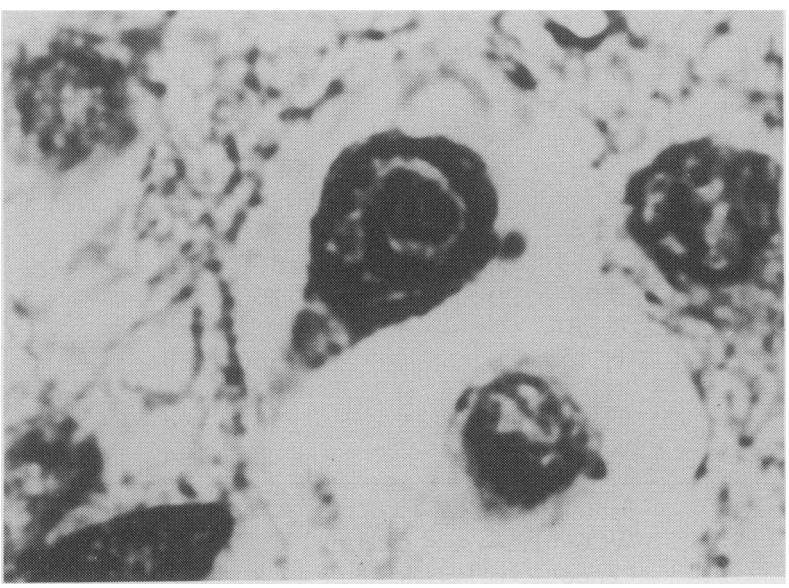

Fig 2.
Neurone with intranuclear inclusion body in SSPE, ×400. (Courtesy of Professor I V Allen).

## TREATMENT

A small group of patients survived for several years and spontaneous remissions have been reported.[7] Over the last 20 years, several agents have been advocated to treat SSPE: steroids were used in two cases with little or no affect. Anti-viral therapy with amantadine (two cases), vidarabine (one case) and interferon (three cases, administered in the Hospital for Sick Children, Great Ormond Street, London), did not prove helpful in our cases although there have been reports of their efficacy from other centres.[10]

Following an observation in-vitro that the measles virus is susceptible to heat,[11] hyperpyrexial therapy was administered to five patients. This was performed by raising the body temperature to 40.5C for 18 hours on two occasions one week apart and then for 24 hours two weeks later. There was no apparent benefit. It has been suggested that patients with SSPE have a deficiency of cellular immunity and that this might be restored by small amounts of transfer factor;[12] also that plasmaphoresis might reduce the high titres of measles antibody. One of our cases therefore underwent a combination of these proposed therapies, but there was no beneficial effect.

Two of our patients received isoprinosine, a drug which is thought to have an immunomodulating effect, and which current research suggests may be more effective than any other form of therapy in reducing the mortality and morbidity of SSPE.[10] It did not alter the outcome. Palliative measures continue to have an important part to play in management, particularly the use of anticonvulsants, nutritional supplements, physical aids and good nursing care.

## CONCLUSION

SSPE remains a distressing condition. It runs a progressive course with a high mortality rate and those that survive do so with profound neurological deficits. Although the measles virus has long been held to be responsible for the disease, only recently has it been more fully understood how the virus produces its effect so late after the acute infection. It is suggested that the virus enters the host at a vulnerable immunological period, then appears to escape the natural host reaction and enters the central nervous system. The CNS being a relatively protected site immunologically, the virus survives. For some still poorly understood reason the virus is defective and cannot mature into complete virions in the brain. This failure to produce virion progeny by the persistently infected cells distinguishes SSPE from acute measles virus infection and, as a result, virus antigen is not exposed to the extra-cellular space where it may be recognised and destroyed by the host immune response. Only when the cell dies and the virus is extruded does an antibody response occur.

There is so far no effective therapy. In the United States of America a decline in measles infection occurred between 1964 and 1968, and this was reflected by a similar fall in SSPE from 1971 onwards.[5] These changes appeared to correlate with the measles immunisation programme which began in 1964. Although a small number of cases of SSPE have been reported in previously immunised individuals, it has not been shown that the vaccine was responsible and the risk of developing SSPE after measles infection is 10 times greater than after vaccination.[13] To date, there does not appear to have been a similar reduction in the incidence of the disease in Northern Ireland and this is probably a reflection of our low vaccination rate which is currently around 15%. The best hope for control of the disease locally lies in achieving high levels of vaccination against measles.

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